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Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Avalglucosidase alfa for treating Pompe disease

ERRATUM

Post factual accuracy check version with corrections

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Inês Souto-Ribeiro, Senior Research Assistant, Health Economics Emma Maund, Research Fellow, Evidence Synthesis Keith Cooper, Senior Research Fellow, Health Economics Karen Pickett, Senior Research Fellow, Evidence Synthesis Marcia Tomie Takahashi, Research Fellow, Health Economics David Alexander Scott, Principal Research Fellow, Statistics Jonathan Shepherd, Principal Research Fellow, Evidence Synthesis
Correspondence to	Dr Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS, UK www.southampton.ac.uk/shtac
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Declared competing interests of the authors and advisors

- The authors declare none.
- Dr Broomfield has been a member of a Sanofi Genzyme Advisory Board for Pompe disease, though not specifically in relation to alglucosidase alfa or avalglucosidase alfa. He is a co-investigator of the Mini-COMET and Baby Comet trials. He has led the drafting of a standard operating procedure (SOP) for the NHS on Infantile Pompe disease in the UK, which makes a recommendation for a higher dose of Myozyme (alglucosidase alfa).
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- ERG report figures 1, 2, 3, 4

- Text quoted in ERG report sections and pages: section 1.4 on p16, section 2.2.1.4 on p29, section 2.2.2 on p30, section 2.2.3 on p33, section 2.3.1 on p32 - p34, section 3.1 on p40, section 3.2.5.2 on p64, section 3.2.6 on p74, and Table 56 in Appendix 1.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Inês Souto-Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Emma Maund critically appraised the clinical effectiveness systematic review, and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Karen Pickett critically appraised the clinical effectiveness systematic review, and drafted the report; Marcia Tomie Takahashi critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the economic evaluation and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
ALGLU	Alglucosidase alfa
AVAL	Avalglucosidase alfa
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CRIM	Cross-reactive immunological material
CSR	Clinical study report
DICE	Discretely Integrated Condition Event (DICE)
DSU	Decision Support Unit
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EPOC	European Pompe Consortium
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
ETP	Extended treatment period
FVC	Forced vital capacity
GAA	Acid alpha-glucosidase
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
IOPD	Infantile-onset Pompe disease

ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intent to treat
IVFS	Invasive ventilation-free survival
LOPD	Late-onset Pompe disease
LSD	Lysosomal storage disorder
mITT	Modified intent to treat
MMRM	Mixed-effects Model with Repeated Measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
PAP	Primary analysis phase
PAS	Patient Access Scheme
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
qow	Every other week
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VFS	Ventilation-free survival
6MWT	Six-minute walk test

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG'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, health technology, evidence and information on the issues are in the main ERG report, starting at Section 2.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1 lists the key issues for technical engagement proposed by the ERG in this report. Sections 1.3 to 1.5 of this executive summary describes each key issue in turn, cross-referring to the relevant section(s) of this report where further detail can be found.

As will become evident below, Pompe disease comprises two distinct patient populations: Infantile-onset Pompe disease (IOPD) and Late-onset Pompe disease (LOPD). Some key issues are relevant to just one of these populations, and some issues apply to both. We have denoted the relevant population parentheses, at the end of each key issue headline description '(IOPD)' or '(LOPD)' or (IOPD and LOPD)'.

Table 1 Summary of key issues

Issue number	Headline description	ERG report sections
1	The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty (IOPD and LOPD)	2.3, 4, 5
2	It is unclear if all relevant clinical effectiveness evidence has been included in the company submission (IOPD and LOPD)	3.1

3	Studies with a sample size of <100 people, conducted outside the UK and the Netherlands, were not selected for data extraction in the company submission (LOPD)	3.1
4	The limited available evidence on the efficacy and safety of AVAL in the IOPD population is a major uncertainty in the economic evaluation	4.2.6.1
5	The duration of the AVAL treatment effect is very uncertain (LOPD)	4.2.6.2
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9	The option for ERT dose escalation is excluded from the company's cost utility models. The impact on cost effectiveness of different dose escalation approaches is unknown. (IOPD)	2.2.2; 4.2.8.1
ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT Enzyme replacement therapy; IOPD Infantile-onset Pompe disease; LOPD Late-onset Pompe disease.		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new health technology extends length of life and improves health-related quality of life in comparison to existing health technologies. This is expressed in terms of incremental quality-adjusted life years (QALYs) gained. An ICER is the ratio of the additional cost of the new technology for every QALY gained.

Table 2 reports the company's cost effectiveness base case results for the IOPD population, updated in response to ERG clarification questions (B4, B14-B16). The results show that avalglucosidase alfa (hereafter referred to as AVAL) is [redacted] and [redacted] to alglucosidase alfa (hereafter referred to as ALGLU) in clinical efficacy (incremental QALYs), making it a dominant treatment in cost effectiveness terms. The model results were most sensitive to changes in the unit cost of AVAL and the relative treatment effect for OS.

Table 2 Company's updated base-case results for IOPD (discounted, PAS price for AVAL)

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental, AVAL vs. ALGLU			
				Costs (£)	LY	QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: reproduced from company clarification responses, Table 14.
ICER, incremental cost-effectiveness ratio; LY, life-years; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 3 reports the company's base case results for LOPD, updated in response to clarification questions (B12-B16). The updated results show that AVAL yields [redacted] versus ALGLU and is therefore dominant. Treatment discontinuation and adverse effects leading to discontinuation are the key drivers of the model results.

Table 3 Company's updated base case results for LOPD (discounted, PAS price for AVAL)

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental, AVAL vs.			
				Costs (£)	LY	QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: reproduced from company clarification responses, Table 18.
ICER, incremental cost-effectiveness ratio; LY, life-years; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALYs, quality-adjusted life years.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty (IOPD and LOPD)

Report section	ERG report section 2.3 (Critique of the company's definition of the decision problem); 4.2.1 (Cost effectiveness; NICE reference case checklist); section 5 (Cost effectiveness results).
Description of issue and why the ERG has identified it as important	The company's decision problem states cost-comparison analysis as their preferred approach to economic evaluation, for both the IOPD and LOPD populations. • The ERG considers the phase 2 trial evidence in the IOPD population is too limited to justify the assumption that the two drug treatments are necessarily equivalent in efficacy and safety in this patient population. • For LOPD, the company highlights phase 3 randomised trial evidence showing AVAL to be non-inferior to ALGLU at improving lung function (FVC% predicted), and in addition they state their intention to offer [redacted]. However, as we will report below (see Issue 6), an ERG scenario analysis suggests a possible incremental lifetime survival advantage for AVAL impacting cost effectiveness. The ERG concludes, therefore, that cost-comparison is not adequately justified at present. Furthermore, cost comparison does not meet the NICE reference case criteria for single technology appraisals health benefits are not included.
What alternative approach has the ERG suggested?	In this appraisal cost-utility analysis is a more appropriate approach to economic evaluation given uncertainty about the degree to which AVAL and ALGLU are equivalent in efficacy, safety and costs. The ERG therefore focus on a cost-utility analysis reported by the company "for reference" in CS Appendix L. The remaining key issues in this report apply to this cost-utility analysis.

What is the expected effect on the cost-effectiveness estimates?	Use of cost-utility analyses means that AVAL could change from being cost-saving (as per the cost comparison analysis), or dominant (i.e. [redacted] than ALGLU and [redacted] in efficacy and safety), to cost-effective (an ICER below a willingness-to-pay threshold of £20,000-£30,000 per QALY) to not cost-effective (i.e. an ICER exceeding a willingness-to-pay threshold of £30,000 per QALY). Differences in assumptions about benefits and costs affect which of the above judgments apply.
What additional evidence or analyses might help to resolve this key issue?	Although the company present a cost-utility analysis there is uncertainty for some of the input parameters due to limited available data. We outline additional evidence and analyses with the potential to resolve uncertainty in the key issues below.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 It is unclear if all relevant clinical effectiveness evidence has been included in the company submission (IOPD and LOPD)

Report section	ERG report section 3.1 (Critique of the methods of review)
Description of issue and why the ERG has identified it as important	The company included 103 studies (clinical trials / observational studies) in their systematic review of clinical effectiveness. Of these, four studies were included in the CS. Reference details of 40 of the 103 studies were not provided. The ERG was therefore unable to independently assess the relevance of these 40 studies to the company's selection criteria. It is unclear whether all relevant clinical effectiveness studies have been included in the CS, raising the possibility of a biased selection of evidence.
What alternative approach has the ERG suggested?	Provision of the reference details of the 40 studies and for each the stated reason for exclusion from the CS.
What is the expected effect on the cost-	Unknown; there is a risk that not all relevant clinical effectiveness data has been identified, which potentially could have bearing on the clinical efficacy assumptions in the economic modelling.

effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	As stated above, provision of the reference details of the 40 studies and for each the stated reason for exclusion from the CS. This would enable the ERG to independently check study eligibility status in order to rule out any potential bias in selection of studies.

Issue 3 Studies with a sample size of <100 people, conducted outside the UK and the Netherlands, were not selected for data extraction in the company submission (LOPD)

Report section	ERG report section 3.1 (Critique of the methods of review)
Description of issue and why the ERG has identified it as important	The company stated that "LOPD studies with a sample <100, conducted outside the UK and the Netherlands, and without humanistic outcomes [which the ERG discerns to mean HRQoL outcomes]" (CS Appendix D, section D.1.1) were not selected for data extraction (i.e. they were excluded from the CS). Seventeen studies were excluded for this reason. It is unclear from the CS, however, which studies these were, so the ERG has been unable to check them for relevance. The company also has not explained their reason for excluding studies with these characteristics from data extraction. It is therefore unclear if these exclusions were appropriate. Given that Pompe disease is a rare condition, the ERG's initial impression, without explanation from the company, is that it is not reasonable to exclude studies with a sample size <100 people.
What alternative approach has the ERG suggested?	That the company could have given their reasoning for excluding studies conducted outside the UK and Netherlands, with a sample size of <100 people and made it clear which studies were excluded for this reason.
What is the expected effect on the cost-effectiveness estimates?	Unknown; there is a risk that not all relevant clinical effectiveness data has been identified, which potentially could have bearing on the clinical efficacy assumptions in the economic modelling.
What additional evidence or	Provision of a list of the 17 studies identified in CS Appendix D, Figure 1, as not being selected for data extraction (i.e. excluded

analyses might help to resolve this key issue?	from the CS) for this reason. We suggest the company detail the populations, interventions, comparators, outcomes and designs of these studies, and explain why each study was not considered relevant. We also suggest the company provide their reason for not selecting studies conducted outside the UK and the Netherlands with a sample size <100 for data extraction and therefore the reason for the exclusion of these from the CS.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 4 The limited available evidence on the efficacy and safety of AVAL in the IOPD population is a major uncertainty in the economic evaluation

Report section	ERG report section 4.2.6.1 (Treatment effectiveness and extrapolation; IOPD model); section 6.2.1 (ERG's preferred assumptions; IOPD results)
Description of issue and why the ERG has identified it as important	The only available comparative evidence for the clinical effectiveness of AVAL in the IOPD population is the phase 2 mini-COMET trial (Cohort 3). However, with a sample size of n=11 participants the results are highly uncertain. A further limitation is that the study included ERT experienced participants (who demonstrated clinical decline or sub-optimal response to ALGLU) but no ERT naïve participants were enrolled. It is unclear whether treatment response to AVAL would necessarily be similar according to previous treatment status. For the purposes of economic evaluation, the company assumes that AVAL and ALGLU in the IOPD population are similar in treatment effect. The ERG considers it unclear whether the effects of AVAL would necessarily be similar to ALGLU in IOPD over the 50-year model's time horizon.
What alternative approach has the ERG suggested?	The ERG tested the assumption of similar effectiveness for AVAL vs ALGLU in a set of scenario analyses. We reduced the hazard ratio for AVAL vs ALGLU to illustrate the impact of incremental increases in overall survival (OS) estimates favouring AVAL: (A) HR OS of 0.98 (incremental survival of one month) (B) HR OS of 0.95 (incremental survival of three months)

	(C) HR OS of 0.90 (incremental survival of six months)
What is the expected effect on the cost-effectiveness estimates?	The company's assumption of similar treatment effects in terms of OS (i.e., HR of 1 for AVAL versus ALGLU) yields an [redacted] for AVAL with the ERG's base case assumptions. The ERG's scenario analyses show that ICERs are significantly higher if a survival benefit for AVAL is assumed (due to longer time on treatment and therefore higher treatment costs). (A) £1,006,487 per QALY for AVAL versus ALGLU (B) £744,901 per QALY for AVAL versus ALGLU (C) £716,567 per QALY for AVAL versus ALGLU
What additional evidence or analyses might help to resolve this key issue?	Evidence on the comparative efficacy of AVAL in the IOPD population, based on larger samples and with long-term follow-up (> 5 years) is needed. The lack of evidence of AVAL in treatment naïve IOPD will be addressed by an ongoing single-arm open-label study, Baby-COMET. However, there is no comparator arm to inform estimates of relative efficacy and safety. The study is due to be completed in December 2026.

Issue 5 The duration of the AVAL treatment effect is very uncertain (LOPD)

Report section	ERG report section 4.2.6.2 (Treatment effectiveness and extrapolation; LOPD model); section 5.3.4 (ERG summary of key issues and additional analyses)
Description of issue and why the ERG has identified it as important	The ERG considers that there is limited evidence showing the duration of the treatment effect of AVAL. Therefore, there is uncertainty around the assumption that the treatment effect of AVAL lasts longer than that of ALGLU.
What alternative approach has the ERG suggested?	The ERG base case assumes the [redacted] duration of treatment effect between AVAL and ALGLU: [redacted] for FVC% predicted and [redacted] for 6MWT. This appears a more plausible estimate, given the available evidence.
What is the expected effect on the cost-effectiveness estimates?	The ERG base case ICER (which includes the [redacted] duration of treatment effect between arms) is £398,367 per QALY for AVAL versus ALGLU. Assuming the company's assumption (duration of 5 years for FVC% predicted and 6MWT) changes the ICER to £266,950 per QALY.

What additional evidence or analyses might help to resolve this key issue?	Longer-term data (e.g., five years or more) showing the duration of the treatment effect of AVAL.

Issue 6 The lifetime incremental survival advantage for AVAL is likely to be underestimated (LOPD)

Report section	ERG report section 4.2.6.2.1 (Treatment effectiveness and extrapolation; LOPD model; Overall survival); section 5.3.4 (ERG summary of key issues and additional analyses)
Description of issue and why the ERG has identified it as important	The ERG considers that a lifetime survival gain of [redacted] for AVAL compared to ALGLU is likely to be an underestimate. This is in view of the short-term benefits demonstrated by AVAL compared to ALGLU in the COMET trial (FVC% predicted and 6MWT).
What alternative approach has the ERG suggested?	The ERG base case assumes an OS HR of 0.85 for AVAL versus ALGLU, which equates to an incremental lifetime survival gain of three months. This appears a more plausible estimate, given the available evidence.
What is the expected effect on the cost-effectiveness estimates?	The ERG base case ICER (which includes the OS HR of 0.85) is £398,367 per QALY for AVAL versus ALGLU. Assuming the company's HR of 1 for AVAL versus ALGLU changes the ICER to £319,612 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Longer-term data (e.g. five years or more) showing how the short-term benefits of AVAL on lung function and mobility translate into long-term survival.

Issue 7 The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs (IOPD) and LOPD)

Report section	ERG report section 4.2.8 (Resources and costs)
Description of issue and why the ERG has identified it as important	The company's calculation of drug acquisition costs assumes vial sharing of leftover medication. The ERG considers this is unrealistic and therefore underestimates the cost of ERT.
What alternative approach has the ERG suggested?	The ERG considers that vial sharing should not be assumed in the calculation of the drug acquisition costs. Instead, the number of vials used should be estimated by rounding up to the nearest whole number, as suggested by clinical experts to the ERG.
What is the expected effect on the cost-effectiveness estimates?	Changing the assumption of vial sharing (company base case) to no vial sharing (ERG's preferred assumption) in the IOPD model, the ICER for AVAL vs ALGLU changes from being [redacted] to an incremental cost per QALY of £15,029. Changing the assumption of vial sharing (company base case) to no vial sharing (ERG's preferred assumption) in the LOPD model, the ICER for AVAL vs ALGLU changes from being [redacted] to an incremental cost per QALY of £398,367.
What additional evidence or analyses might help to resolve this key issue?	In the absence of data on the use or non-use of vial sharing, additional expert clinical opinion may provide more clarity.

Issue 8 The increased dosing frequency for the comparator treatment ALGLU during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment (IOPD)

Report section	ERG report section 3.2.1.1 (Study characteristics); 4.2.8.1 (Drug acquisition); section 4.2.8.2 (Drug administration)
Description of issue and why the ERG has identified it as important	When commencing ERT with ALGLU, for the first 12 weeks ALGU is administered weekly, and thereafter every other week. AVAL is to be administered every other week during this period. Expert clinical advice to the ERG suggests that during the initial three months of ERT they would expect the dose of AVAL to match that of ALGLU.
What alternative approach has the ERG suggested?	We changed the dose frequency of AVAL from every other week to weekly during the first 12 weeks, to match the dosing frequency of ALGLU.
What is the expected effect on the cost-effectiveness estimates?	Assuming weekly dosing for AVAL in the first 12 weeks makes AVAL less cost-saving in relation to ALGLU, changing the incremental cost [redacted]. AVAL is still the dominant treatment in terms of cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional expert clinical opinion may be informative to assess consensus.

Issue 9 The option for ERT dose escalation is excluded from the company's cost utility models. The impact on cost effectiveness of different dose escalation approaches is unknown. (IOPD)

Report section	ERG report section 3.3.2.1 (4.2.8.1 (Drug acquisition); section 4.2.8.2 (Drug administration)
Description of issue and why the ERG has identified it as important	The anticipated licence for AVAL permits dose escalations for IOPD patients, to 40 mg/kg qow (every other week) if there is an inadequate clinical response to the standard 20 mg/kg qow dose. Escalations of the ALGLU dose are done off-label. The company excludes dose escalation of both drugs from their IOPD cost-utility model assuming that their equivalent efficacy means the proportion of patients requiring dose escalation is not anticipated to differ between these treatments. As we

	commented above, equivalence cannot necessarily be assumed based on current available data (see Issue 1 and 4 above). In turn, it is unreasonable to assume no differences between AVAL and ALGLU in the proportion of patients requiring a dose increase.
What alternative approach has the ERG suggested?	Dose escalation of both AVAL and ALGLU should be included in economic modelling of IOPD patients (NB. clinical experts were of the opinion that dose escalation would not be performed in the LOPD population, and it is not included in the anticipated licence indication for this population). The ERG notes at least three different approaches to the timing of ALGLU dose escalation in clinical practice: 1. **Initiation of ERT.** Where permitted, clinician preference is to initiate ALGLU in new patients at the higher dose of 40 mg/kg qow (or 20mg/kg weekly), to be maintained indefinitely (ERG clinical expert). 2. **Onset of clinical decline**. ALGLU dose may be increased from 20mg/kg to 40mg/kg qow when the level of response begins to attenuate (CS page 32). 3. **Inadequate treatment response.** Dose escalation from 20mg/kg to 40mg/kg qow may be required where an adequate treatment response is lacking (subject to individual patient funding requests) (CS page 156). It is not clear whether the above approaches would necessarily be applicable to AVAL dosing (though the proposed licence indication does allow for the third approach). Total drug acquisition costs per patient will vary according to the timing and duration of dose escalation, and any differences in approach to dose escalation between AVAL and ALGLU will influence incremental cost effectiveness estimates. Economic modelling should explore the above approaches in terms of base case / scenario analyses.
What is the expected effect on the cost-effectiveness estimates?	At present this is uncertain. If AVAL and ALGLU are assumed to be equivalent in efficacy the proportion of patients requiring dose escalation may be similar with little resulting impact on incremental cost effectiveness. If AVAL achieves superior

	treatment response at standard dose compared to ALGLU at standard dose, it could be assumed that, all other things being equal, fewer AVAL patients will require dose escalation / AVAL would have a longer time to dose escalation, thus reducing AVAL's costs. However, any such cost savings may be offset by the additional costs of treating AVAL patients who live longer.
What additional evidence or analyses might help to resolve this key issue?	Definitive evidence is needed on the clinical effectiveness of AVAL vs ALGLU in the IOPD population to confirm clinical equivalence (see Issues 1 and 4 above). Further expert clinical opinion / consensus would be informative for modelling of different dose escalation approaches. For the approaches 2 and 3 listed above, data / assumptions are needed on the average time to onset of clinical decline and the average time period over which an adequate treatment response would be expected, respectively. Sources relevant evidence such as the Pompe Registry and long-term clinical studies of AVAL and ALGLU could be informative.

The following issues identified by the ERG in the cost effectiveness evidence are not considered as key issues as they only have a small impact on the model results:

IOPD model

- **Extrapolation of OS**: the ERG notes the uncertainty in estimating OS and therefore prefers the exponential parametric curve for OS instead of the Weibull (company base case).
- **Health state utility values:** we prefer to use the values estimated from the Pompe registry instead of the values from Simon et al.[1]
- **Age-adjusted utilities:** This has been incorrectly implemented in the company model. The ERG prefers to remove age-adjusted utility as utility values have been specified for three age groups (infant, children and adult).
- **Disease-related costs from Clinical Practice Research Datalink (CPRD):** The company use incorrect values for disease related costs. The ERG corrects these values.

LOPD model

- **Utility values for caregivers:** we suggest that the disutility values from the mild state should be used for the not dependent on ventilator or wheelchair state and the

moderate state should be used for the non-invasive ventilation dependent health state (see section 4.2.7.3).

- **Disutilities for patients using both a ventilator and wheelchair:** the ERG prefer to use a multiplicative method instead of adding the disutilities applied for each health state separately (see section 4.2.7.3). As we are unclear on how to implement this change in the model, we have not included it in the ERG base case.
- **Duration of treatment effect for FVC% predicted / 6MWT**: we assume the [redacted] duration of treatment effect for AVAL and ALGLU ([redacted] for FVC% predicted and [redacted] for 6MWT) while the company have assumed [redacted] duration for AVAL.
- **Decline rate for 6MWT for no treatment:** the ERG assumes a faster decline rate of 6MWT for those patients on no treatment ([redacted] per year) than for patients treated with ERT therapies, instead of the [redacted] decline rate.

1.6 Other key issues: summary of the ERG's view

None at present

1.7 Summary of ERG's preferred assumptions and resulting ICER

Based on the ERG's critique of the company's cost-utility model (discussed in section 4.2), we have identified the following aspects of the company base case with which we disagree. Our preferred assumptions are the following:

IOPD model

- **Double dosing for AVAL for the first 12 weeks:** we consider the dosing for AVAL should be the same as for ALGLU;
- **No vial sharing:** we consider that the calculated number of vials should be rounded up to the nearest whole number;
- **Extrapolation of OS**: the ERG notes the uncertainty in estimating OS and therefore prefers the exponential parametric curve for OS instead of the Weibull (company base case).
- **Health state utility values:** we prefer to use the values estimated from the Pompe registry instead of the values from Simon et al.[1]
- **Age-adjusted utilities:** This has been incorrectly implemented in the company model. The ERG prefers to remove age-adjusted utility as utility values have been specified for three age groups (infant, children and adult).
- **Disease-related costs from CPRD:** The company use incorrect values for disease related costs. The ERG corrects these values.

Modelling errors identified and corrected by the ERG for the IOPD model are described in Table 42. Table 4 reports the ERG preferred base case results for the IOPD model for AVAL vs ALGLU. According to the ERG's preferred base case assumptions, AVAL changes from being [redacted] than ALGLU, [redacted].

Table 4 Cumulative change from the corrected company base case to the ERG preferred base case for the IOPD model

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Company base-case (corrected)	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
Double dosing for AVAL for first 12 weeks	ALGLU	[redacted]	[redacted]		Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
No vial sharing	ALGLU	[redacted]	[redacted]		Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
OS, exponential	ALGLU	[redacted]	[redacted]		Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
Utility values from Pompe registry	ALGLU	[redacted]	[redacted]		Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
No age adjusted utilities	ALGLU	[redacted]	[redacted]		Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
Corrected disease related costs	ALGLU	[redacted]	[redacted]		Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
ERG base case	ALGLU	[redacted]	[redacted]		Dominated
	AVAL	[redacted]	[redacted]	[redacted]	

LOPD model

- **No vial sharing:** we consider that the calculated number of vials should be rounded up to the nearest whole number.
- **Utility values for caregivers:** we suggest that the disutility values from the mild state should be used for the not dependent on ventilator or wheelchair state and the moderate state should be used for the non-invasive ventilation dependent health state (see section 4.2.7.3).
- **Disutilities for patients using both a ventilator and wheelchair:** the ERG prefer to use a multiplicative method instead of adding the disutilities applied for each health state separately (see section 4.2.7.3). As we are unclear on how to implement this change in the model, we have not included it in the ERG base case.
- **Duration of treatment effect for FVC / 6MWT**: we assume the [redacted] of treatment effect for AVAL and ALGLU ([redacted] for FVC% predicted and [redacted] for 6MWT) while the company have assumed [redacted] for AVAL.

- **Decline rate for 6MWT for no treatment:** the ERG assumes a faster decline rate of 6MWT for those patients on no treatment ([redacted] per year) than for patients treated with ERT therapies, instead of the [redacted] decline rate as for ALGLU and AVAL.
- **OS survival:** we assume a HR for OS of 0.85 for AVAL vs. ALGLU, instead of a HR of 1.

Modelling errors identified and corrected by the ERG for the LOPD model are described in later in this report (see Table 43)

Table 5 reports the ERG preferred base case results for the LOPD model for AVAL vs ALGLU. According to the ERG's preferred base case assumptions, AVAL changes from being [redacted] to having an ICER of £398,367 per QALY versus ALGLU.

Table 5 Cumulative change from the corrected company base case to the ERG preferred base case for the LOPD model

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Company base-case	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
+ no vial sharing	ALGLU	[redacted]	[redacted]	[redacted]	£237,040
	AVAL	[redacted]	[redacted]	[redacted]	
+ changes to utility values for patients and caregivers	ALGLU	[redacted]	[redacted]	[redacted]	£201,042
	AVAL	[redacted]	[redacted]	[redacted]	
+ Plateau duration for FVC% / 6MWT	ALGLU	[redacted]	[redacted]	[redacted]	£319,645
	AVAL	[redacted]	[redacted]	[redacted]	
+ 6MWT decline rate of [redacted]/year	ALGLU	[redacted]	[redacted]	[redacted]	£319,612
	AVAL	[redacted]	[redacted]	[redacted]	
+ OS survival: HR of 0.85 (AVAL vs. ALGLU)	ALGLU	[redacted]	[redacted]	[redacted]	£398,367
	AVAL	[redacted]	[redacted]	[redacted]	
ERG base case	ALGLU	[redacted]	[redacted]	[redacted]	£398,367
	AVAL	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER, incremental cost-effectiveness ratio; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALYs, quality-adjusted life years; OS, overall survival; HR, hazard ratio; FVC%, forced vital capacity; 6MWT, six-minute walk test

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Sanofi on the clinical effectiveness and cost effectiveness of AVAL for treating Pompe Disease. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 13th January 2022. A response from the company via NICE was received by the ERG on 1st February 2022 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on Pompe disease

The CS (section B1.3) provides a clear overview of Pompe disease, including its definition, cause, prevalence, effect on health-related quality of life (HRQoL) and the morbidity and mortality associated with it.

Pompe disease is a rare, inherited, multisystemic, progressive metabolic disease resulting in severe disability and a reduced life expectancy.[2 3] There are around 200 people in the UK diagnosed with the condition.[4] The cause of Pompe disease is mutations in the gene that encodes the enzyme acid alpha-glucosidase (GAA). GAA is needed to break down glycogen into glucose.[5] In Pompe disease there is reduced or absent activity of GAA, which causes accumulation of glycogen in muscle resulting in irreversible muscle damage. Disease severity is influenced by the level of residual GAA activity.[3] Currently Pompe disease is managed with enzyme replacement therapy (ERT) comprising the drug ALGLU. In addition, patients also require tailored supportive care from multi-disciplinary teams of health professionals.

There are a range of phenotypes of Pompe disease, which differ in age of onset, extent of organ involvement and rate of progression.[2] The CS classifies Pompe disease into two broad subtypes, established by the American College of Medical Genetics and Genomics Work Group on Management of Pompe disease: Infantile-onset Pompe disease (IOPD) and Late-onset Pompe disease (LOPD).[2]

2.2.1.1 Infantile-onset Pompe disease (IOPD)

- Patients with IOPD present with symptoms during the first 12 months of life.[2]
- The most common symptoms, typically seen in the first few weeks of life, in untreated patients are: enlarged heart (cardiomegaly), thickening of the wall of the heart (hypertrophic cardiomyopathy), respiratory distress, progressive muscle weakness and diminishing muscle tone (hypotonia).[6]
- Untreated infants do not obtain expected motor development for their age; will need assisted ventilation by 6 months and typically do not survive beyond 12 months of age.[3]
- All people with IOPD have GAA activity of less than 1% of normal range, and are distinguished according to their **cross-reactive immunological material (CRIM) status**:
    - **CRIM-positive** people make a form of GAA with severely impaired activity.
    - **CRIM-negative** people are unable to make any form of GAA. CRIM-negativity is associated with poorer health outcomes, and necessitates immunomodulatory therapy (e.g. with methotrexate) when ERT is initiated. [3 7] In the UK, approximately 45% of IOPD patients are CRIM-negative.[7]

2.2.1.2 Late-onset Pompe disease (LOPD)

- LOPD is defined by symptom onset after 12 months of age.[8] It consists of childhood/ juvenile-onset Pompe disease (JOPD) and adult-onset Pompe disease. JOPD presents during childhood but later than infancy, while adult-onset Pompe disease can present any time during adulthood. Mean symptom onset is between 30 to 50 years, with our clinical expert on LOPD advising that patients diagnosed at a younger age experience faster disease progression.
- LOPD affects multiple systems and is characterised by progressive myopathy and respiratory involvement.[8] Unlike IOPD, there is minimal and less severe cardiac involvement and all LOPD patients are CRIM-positive.[9] As the disease progresses, patients with LOPD become wheelchair-bound and require non-invasive or invasive ventilation with respiratory failure the leading cause of death.[10]

2.2.1.3 Enzyme replacement therapy with ALGLU

CS section B.1.3.7 provides information on current service provision in the NHS in England for patients with Pompe disease. NHS England commissions services for adults and children with Pompe disease from Highly Specialised Lysosomal Storage Disorder (LSD) Centres.[11]

The CS accurately outlines that the only currently available pharmacological treatment for Pompe disease is ERT with ALGLU. ALGLU (brand name Myozyme®) was launched in 2006 and is a human GAA, produced by recombinant DNA technology, which aims to replace the absent or malfunctioning enzyme.[12] As highlighted by one of our clinical experts, the purpose of ERT is to slow the inevitable progression of Pompe disease, thus it is not a curative treatment. The licensed dose is 20 mg/kg as intravenous (IV) infusion every other week.[12] Although ALGLU is reimbursed for IOPD and LOPD in England, it has not undergone a NICE appraisal. Our clinical experts advised that ERT infusions are initially given in hospital (at least four infusions for patients with IOPD and up to three infusions for patients with LOPD). Patients receive subsequent transfusions at home, provided by a home care company contracted to NHS England. Initially the home care nurse inserts the cannula and is present throughout the infusion, removing the cannula at the end. Over time, as patients and their families become familiar with the process, some are able to manage the infusion themselves with the role of the home care company reduced to delivering the drug and supplies only. Patients with IOPD or LOPD can also experience infusion-related reactions, i.e. a hypersensitivity reaction, around the time of infusion with ERT. One of our clinical experts informed us these reactions are not related to CRIM status and can be treated inexpensively using medications such as chlorpheniramine, paracetamol and ibuprofen.

2.2.1.4 Treatment with ALGLU in the IOPD population

The CS B.1.3.7.1 states that "in patients with IOPD 40 mg/kg [of alglucosidase alfa] is used for the first three months in order to resolve cardiomyopathy. In addition, according to clinical advice, the dose may be escalated in IOPD patients experiencing decline on ERT". Expert clinical advice to the ERG suggests that doubling the licensed dose of ALGLU for only the first three months to 40mg/kg is not currently done anywhere in the world. It was initially done when ERT was introduced, as there was perceived increased mortality which, it became evident, was due to late diagnosis. Our IOPD clinical expert informed the ERG that clinicians in England prefer to treat IOPD patients with a dose of 40mg/kg, off-label, subject to approved funding request, as better outcomes are shown to be related to higher doses. They also highlighted that patients in other countries, e.g. the Netherlands, receive a dose of ALGLU four times greater than the licensed dose of 20mg/kg every other week.

For IOPD, the NHS LSD service document recommends rapid initiation of treatment except for those requiring mechanical ventilation prior to diagnosis. The CRIM status of patients with IOPD should also be confirmed as soon as possible.[13] This is to allow

immunomodulatory treatments, such as methotrexate and rituximab, to be given to CRIM-negative patients, who will otherwise develop a high level of antibodies against ALGLU, and consequently have a poor response to ERT.[13] Our clinical expert in IOPD advises they currently give CRIM-negative patients three doses of methotrexate and up to four doses, but usually one or two doses, of rituximab.

Patients usually continue ERT until clinical decline means they are no longer benefitting from treatment. The NHS LSD service document recommends that IOPD patients should stop ERT "unless there is evidence that the treatment is improving the patient's condition or preventing decline" (p. 9).[14] Our clinical expert in IOPD highlighted that stopping treatment with ERT is putting the patient on a palliative pathway. In line with the NHS LSD service document recommendation, our expert considered that worsening cardiac disease, despite adequate dosing, would also be a reason to withdraw ERT.

Benefits of ERT have been seen in terms of survival (e.g. 24-month survival rate of 94.4%), and improvement in muscle, motor and functional skills.[7 15] However, after a few years of treatment, even patients responding initially well to ERT show increasing muscle weakness and eventually require walking devices and wheelchairs.[3]

2.2.1.5 Treatment with ALGLU in the LOPD population

Criteria for starting treating with ERT in LOPD patients are in accordance with the European Pompe Consortium (EPOC) 2017 guidelines.[16] Patients should be symptomatic with a confirmed diagnosis of Pompe disease, have clinically and self-perceived important residual skeletal and respiratory muscle function and not be in the advanced stages of another life-threatening illness. In addition, both the patient and their clinician should commit to regular treatment and monitoring.

Our LOPD clinical expert informed the ERG that patients usually continue treatment in the long term until clinical decline means they are no longer benefitting from treatment - they may be near or totally immobile and require full time care (as assessed by the six-minute walk test (6MWT) and spirometry.

The EPOC guidelines recommend that treatment be stopped if the patient:

- suffers from unmanageable severe infusion-associated reactions.
- has high antibody titres are detected that significantly counteracts ERT.
- wishes to stop ERT.

- does not comply with regular infusions or yearly clinical assessments
- has another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate.
- has no stabilisation or improvement in skeletal muscle function and/or respiratory function in the first 2 years after start of treatment.

It should be noted that the guidelines state that the decision to continue or discontinue ERT during pregnancy and lactation is at the discretion of the treating clinician and patient.[16] Our LOPD clinical expert advised the ERG that adverse events do not usually cause treatment withdrawal. Furthermore, even if a patient is wheelchair bound there are still benefits to be had from continuing treatment with ERT and clinicians will be reluctant to stop treatment unless this is the patient's wish. Our expert also highlighted that stopping treatment with ERT is putting the patient on a palliative pathway.

Evidence from clinical studies shows that ALGLU slows the progression of disease in LOPD.[17] [18] A large Dutch cohort study of LOPD patients, including 88 patients receiving ALGLU 20mg/kg every week, found improvements in respiratory function, muscle strength, and daily function for the first two to three years of treatment with ALGLU, followed by a plateau or decline. A systematic review of survival and long-term outcomes following treatment with ALGLU, found beneficial effects on survival (five times lower mortality in treated versus untreated patients), 6MWT (improvement over first 20 months of treatment followed by a plateau) and respiratory function (improvement in forced vital capacity during first two months of treatment, followed by a decline to baseline over the subsequent 36 months and then further decline). In our LOPD clinical expert's experience, there is usually a marked improvement in symptoms in the first 6 to 12 months of starting ERT followed by a plateau where the improvement levels off. All LOPD patients will eventually require use of a wheelchair and a ventilator, but treatment with ALGLU will delay this by several years. This is broadly in agreement with the view of the company's advisory board of three metabolic consultants and two clinical nurse specialists (CS Appendix M).

2.2.1.6 Best supportive care

Due to the heterogenous symptomology of Pompe disease, patients require support and care from a multidisciplinary team of health and care professionals, including metabolic specialists, cardiologists, physiotherapists, and others. Severe IOPD patients are likely to require respiratory support either by invasive or non-invasive ventilation, which may be long term and involve admission to a paediatric intensive care unit or a high dependency unit.[14]

2.2.2 Background information on AVAL

The company describe the key characteristics of AVAL (Nexviadyme®) in CS sections B.1.2 and B.1.3.9. In common with ALGLU, AVAL is manufactured by Sanofi, thus, the intervention and comparator treatments in this NICE appraisal are owned by the same company (see section 2.3). AVAL, like ALGLU, is a human GAA, produced by recombinant DNA technology, which aims to replace the absent or malfunctioning enzyme. However, unlike ALGLU, AVAL has a higher binding affinity to cell surface mannose 6-phosphate (M6P) receptors.[19] It is therefore able to enter cells more easily, leading to reduced glycogen levels at doses five times smaller than that of ALGLU.[20 21] Both our clinical experts agree that the mode of action of AVAL and ALGLU are the same, but a key difference is muscle uptake. ALGLU enters any cells, notably the liver and spleen but has a low muscle-cell uptake. In contrast, AVAL is more efficient in muscle uptake, which is the point-of-action

The draft Summary of product characteristics (SmPC) (CS Appendix C) states the indication for use is

"[redacted]" (p1)

"[redacted]" (p2) and

"[redacted]" (p2)

In September 2020, AVAL received promising innovative medicine designation from the Medicines and Healthcare products Regulatory Agency (MHRA), and in March 2021 it received an Early Access to Medicines Scheme (EAMS) positive scientific opinion. However, both were for more limited populations compared to the anticipated licensed indication and the population addressed in the CS:

- Treatment of LOPD in symptomatic patients who have received Pompe disease ERT with ALGLU for ≥2 years.
- Treatment of IOPD in symptomatic patients ≥1 year old who have received Pompe disease ERT with ALGLU for ≥6 months.

CS Table 2 states that MHRA and European Medicines Agency marketing authorisation is anticipated in [redacted]. However, in a clarification question meeting between the company,

NICE and the ERG on 20th January 2022, the company stated that marketing authorisation is now expected in [redacted].

2.2.3 The position of AVAL in the treatment pathway

The company regard AVAL as "an additional, improved treatment option for new patients and existing patients already receiving ALGLU" (CS section B.1.2.3.9).

CS B.1.3.8 and CS Appendix M outline the current unmet need for Pompe disease.

- For IOPD there is an unmet need for effective treatments for patients with rapidly progressing IOPD, particularly those that are CRIM-negative who experience poorer outcomes.
- For LOPD, there is an unmet treatment need for an alternative treatment given the plateauing and decline experienced with ALGLU.

Our LOPD clinical expert stated that many clinicians and patients desire a better treatment, so many will want to initiate new patients with it or switch to it from ALGLU. Our IOPD expert believes clinicians will be inclined to treat IOPD patients with the higher 40mg/kg dose if available.

ERG comment on the proposed use of AVAL

The CS defines the anticipated use of AVAL in the treatment of Pompe disease as an alternative to the existing standard of care, ALGLU. Particular unmet need is suggested for subgroups of IOPD patients with rapidly progressing disease and those who are CRIM-negative. For the LOPD population the company highlights the overall need to increase the period over which ERT benefits accumulate before levelling off and inevitable onset of clinical decline. Expert clinical advice to the ERG agrees there is significant unmet need, particularly for therapies to be given at doses sufficient to reduce the rate of disease progression beyond the that achieved by ALGLU at its current licensed indication.

2.3 Critique of the company's definition of the decision problem

Table 1 compares the company's decision problem to the final scope for this appraisal issued by NICE. The ERG consider that the decision problem adheres to the NICE scope with the following exceptions.

2.3.1 Outcomes

IOPD

- Change in respiratory function is not reported in the CS. The CSR report for Mini-COMET states "[redacted]". The ERG considers this reasonable.
- Immunogenicity response (development of antibodies during treatment) is not reported in the CS but provided in by the company in response to clarification question A4.

LOPD

- Cardiac outcomes are not reported in the CS. The company's response to clarification question A5 justifies this, stating "As cardiovascular involvement is not a usual feature of LOPD, cardiac data were not collected as part of either COMET, or NEO1/ NEO-EXT. The only exception is that electrocardiograms were used to monitor safety in both trials." The ERG considers this reasonable.
- As with the IOPD population, immunogenicity response is given in response to clarification question A4.

2.3.2 Economic analysis

In the CS the company present a cost-comparison analysis as the main form of economic evaluation, and provide a cost-utility analysis "for reference" in Appendix L.

The company's justification for conducting a cost-comparison analysis for LOPD is based on the interim results of the pivotal phase 3 COMET trial, in which AVAL demonstrated non-inferiority vs ALGLU in the primary endpoint of FVC% predicted at Week 49 (we discuss the company's approach to assessing non-inferiority in section 3.2.4) The company suggests the greater health benefits seen in people receiving AVAL compared to ALGLU and the fact that [redacted], justifies the use of cost-comparison analysis as the primary economic analysis.

For the IOPD population the company also favours cost-comparison analysis. The phase 2 Mini-COMET trial showed trends for improvement or stabilisation of symptoms with AVAL across several clinical outcomes. However, the company argue that the data are insufficient to model long-term events. (NB. we discuss the limitations of this study in section 3.2.2, and 3.2.4 and throughout the rest of the report where necessary).

The ERG, however, considers that the company's cost-comparison analysis does not meet the NICE reference case as it omits valuation of health effects. We therefore focus our critique on the company's cost-utility analysis.

Table 6 Summary of the decision problem

	Final scope issued by NICE	Company's Decision problem	Differences between scope and decision problem
Population	Children and adults with Pompe disease	As per final scope	None - Decision problem matches scope
Intervention	Avalglucosidase alfa	As per final scope	None - Decision problem matches scope
Comparator(s)	Alglucosidase alfa	As per final scope	None - Decision problem matches scope
Outcomes	The outcome measures to be considered include: change in respiratory function change in cardiac function change in motor function change in muscular function mortality	As per final scope	**IOPD** • The ERG notes that change in respiratory function is not reported in the CS. However, the CSR for the Mini-COMET trial states "[redacted]" • Immunogenicity response is not reported in the CS but provided in company clarification response A4. **LOPD** • Company clarification A5 provides a rationale for this omission of cardiac outcomes stating "As cardiovascular involvement is not a usual feature of LOPD, cardiac data were not collected as part of either COMET, or NEO1/

	Final scope issued by NICE	Company's Decision problem	Differences between scope and decision problem
	immunogenicity response adverse effects of treatment health-related quality of life (for patients and carers)		NEO-EXT. The only exception is that electrocardiograms were used to monitor safety in both trials." • Immunogenicity response is not reported in the CS but provided in company clarification A4.
Economic analysis	The reference case[22] stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	A conservative cost-comparison approach is presented as the base-case.	**Company** • LOPD: In the pivotal phase 3 COMET trial, AVAL demonstrated non-inferiority compared to ALGLU in the primary endpoint of FVC% predicted at Week 49. There was a trend for improvement across secondary clinical outcomes. • IOPD: Despite trends for improvement or stabilisation with AVAL across several clinical outcomes in the phase 2 Mini-COMET trial, extrapolation of outcomes in a cost-effectiveness analysis would incur significant uncertainty. • AVAL offers greater health benefits than ALGLU [redacted]. • A cost-utility analysis is provided "for reference" in CS Appendix L, estimating AVAL to be a cost-effective and cost-saving option.

	Final scope issued by NICE	Company's Decision problem	Differences between scope and decision problem
	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		**ERG** • The limited clinical effectiveness evidence for AVAL in IOPD does not confirm equivalence or otherwise of AVAL with ALGLU in efficacy and safety. This is insufficient as a rationale for cost-comparison analyses. • The cost-comparison analysis is not within the NICE reference case. And • The ERG's assessment therefore focuses on the company's cost-utility analysis.
	If the evidence allows the following subgroups will be considered: • People with infantile onset Pompe disease		None - decision problem matches scope

	Final scope issued by NICE	Company's Decision problem	Differences between scope and decision problem
	• People with late onset Pompe disease		

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company identified clinical effectiveness evidence for AVAL from a single, broad systematic review (CS section B.2.1.1). The purpose of this wide review was to find the following evidence:

- clinical efficacy and safety data for both AVAL and ALGLU
- HRQoL studies conducted with patients with Pompe disease and their carers
- economic outcomes of treatment for Pompe disease
- costs and resource use in Pompe disease

The methods of the review are briefly summarised in CS section B.2.1.1 and full details are reported in CS Appendix D. The ERG provides a critique of the methods and processes of the review in Table 7. A full version of Table 7, including our comments justifying our judgements, is available in Appendix 2. We critique the review in relation to its fitness-for-purpose in identifying clinical effectiveness evidence. The ERG's critique of the review in relation to the cost-effectiveness evidence is available in section 4.1.

Our critique of the review identified the following issue about the selection of studies to include in the CS:

- Due to broad study eligibility criteria, the review identified 147 studies that met the eligibility criteria for the review, including 103 clinical trials and observational studies (CS Appendix D, Figure 1). Of these, four studies were included in the CS. It is unclear if any of the remaining 99 studies were potentially relevant to the decision problem, because the company does not provide the reasons for why these studies were not included in the CS.
- The company lists the studies identified for inclusion in the review in CS Appendix D, section D.1.1. However, this is not a full list; only 92 of the 147 studies identified for inclusion are listed. Furthermore, the company has only provided references for 63 of the 103 clinical trials and observational studies that met the inclusion criteria.
- The ERG checked the titles (and, where necessary, abstracts or full texts) of the 63 clinical trials and observational studies listed to assess their potential relevance to the company's decision problem and the NICE scope. We did not identify any relevant studies not already included in the CS. As details were not provided for the other 40 studies identified for data extraction in the company's review, we are unable to check the potential relevance of these. The ERG re-ran the database searches in

December 2021 and did not identify any relevant studies among the 92 references we found. As details of the 40 studies were not provided, it is unclear whether all relevant studies have been included in the CS.

In addition, we noted the following issue also about study selection:

- CS Appendix D, section D.1.1. states that "LOPD studies with a sample <100, conducted outside the UK and the Netherlands, and without humanistic outcomes" (which the ERG discerns to mean HRQoL outcomes) were not data extracted. The PRISMA flowchart (Appendix D, Figure 1) shows that 17 of the 147 studies eligible for inclusion in the review were not data extracted for this reason. It is unclear from the CS which studies these were. The company also does not explain their reason for this approach. It is therefore unclear if these exclusions were appropriate and if any of the studies may have potentially been relevant to the company's decision problem and the NICE scope.
- Given that Pompe disease is a rare condition and there are already limited data included in the CS (particularly for the IOPD population; see section 3.2.1), the ERG's initial impression, without explanation from the company, is that it is not reasonable to exclude studies with a sample size <100 people.
- Without explanation from the company, we are unclear why studies conducted outside the UK and the Netherlands would be considered less relevant to the decision problem.

Our critique of the review (as shown in Table 7) also identified this issue:

- The company did not include a quality assessment for two studies, including one used in the cost-effectiveness economic model. The ERG carried out a quality assessment of this study (see section 3.2.2).

Table 7 ERG appraisal of systematic review methods

Systematic review components and processes	ERG response (Yes, No, Unclear)
Was the review question clearly defined using the PICOD framework or an alternative?	Yes
Were appropriate sources of literature searched?	Yes
What time period did the searches span and was this appropriate?	Yes
Were appropriate search terms used and combined correctly?	Yes

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	No – the eligibility criteria were specified, but these were not appropriate to the decision problem
Were study selection criteria applied by two or more reviewers independently?	Yes
Was data extraction performed by two or more reviewers independently?	Unclear
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes – but only for two of the four included studies
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No
Is sufficient detail on the individual studies presented?	Yes
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	No. Post hoc pooled regression analysis of FVC% predicted has limitations.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company included one study of AVAL treatment for people with IOPD:

- **Mini-COMET** (NCT03019406)[23] – a phase 2, ascending dose, cohort study.

The company also included the following three studies of AVAL for treating people with LOPD:

- **COMET** (NCT02782741)[24 25 26] – a phase 3 randomised controlled trial (RCT), comparing treatment with AVAL against ALGLU
- **NEO1** (NCT01898364) – a phase 1, ascending dose, study, and
- **NEO-EXT** (NCT02032524)[27] – a phase 2 extension study to NEO1, examining the long-term safety and pharmacokinetics of AVAL.

All four studies were sponsored by the company. Data from the COMET and NEO-EXT studies were used to inform clinical effectiveness estimates in the cost-effectiveness

economic model (CS Appendix L, section L.3.2.2 and CS Appendix L, Table 27). The Mini-COMET and NEO1 studies did not inform the model. The company also used results from the COMET trial to support the cost-comparison model assumption that AVAL was non-inferior to ALGLU (CS section B.4.5.2).

In their submission, the company provided NICE and the ERG with interim clinical study reports (CSRs) of the COMET,[26] NEO-EXT[27] and Mini-COMET studies.[23] The CSR for the NEO1 study[28] was provided on request (clarification response A9).

Published journal articles were provided reporting the results of the COMET[25 26] and NEO1 studies.[29]

3.2.1.1 Study characteristics

The CS details the characteristics and methodology of the Mini-COMET, COMET, NEO1 and NEO-EXT studies in CS sections B.2.2 and B.2.3 and CS Tables 7 and 11.

Mini-COMET (IOPD, ERT-treatment experienced population)

The Mini-COMET study examined the efficacy and safety of AVAL in treating children (aged <18 years) with IOPD. Although it was not used to inform the company's economic evaluation, we provide an overview of the study here, as it is the only clinical effectiveness evidence included in the CS for this population.

Mini-COMET was a phase 2, open-label, ascending dose, cohort study, with an RCT element conducted in stage 2 of the study. All the included participants had previously been treated with ALGLU and had experienced either clinical decline or a sub-optimal response to the treatment. Table 8 shows the two stages of the study, the number of participants included, and the drugs and doses given in each stage. The stage 2, RCT part of the study meets the NICE scope and the company's decision problem, as a comparison of treatment with AVAL is made against ALGLU. A total of 22 participants entered the Mini-COMET study. Of these, 11 were randomised to either AVAL or ALGLU in the RCT element (i.e. stage 2) (see CS Figure 24). Of the remaining participants, six were in cohort 1 and five in cohort 2.

CS section B.2.3.2 states that all Mini-COMET study participants have completed the six month (25 weeks) primary analysis phase. Participants then entered an extended treatment period (ETP), which is currently ongoing.

[redacted][23] (details of the doses administered are provided in Table 8). The end of study visit is planned for [redacted] (CS Figure 5). The CS states all participants in Cohort 3 have completed Week 97. Findings in the CS are presented from the 28th May 2021 data cut (clarification response A2); interim results from the extended treatment phase are presented.

Table 8 Overview of the Mini-COMET study

Study stage / cohort	**Intervention**	**Comparator**
Stage 1/ Cohort 1 (participants with clinical decline on ALGLU)	AVAL IV 20 mg/kg qow (N=6) for 25 weeks [redacted][23] [a]	No comparator
Stage 1 / Cohort 2 (participants with	AVAL IV 40 mg/kg qow (N=5) for 25 weeks [redacted][23]	No comparator

clinical decline on ALGLU)		
Stage 2/ Cohort 3 (participants with suboptimal response to ALGLU) – participants were randomised using a 1:1 ratio to AVAL or	AVAL IV 40 mg/kg qow [redacted] for 25 weeks [redacted] [redacted] [23] b	ALGLU at current stable dose [redacted] [redacted] [redacted] for 25 weeks [redacted] [redacted] [23]

ALGLU		

Source: this table is a reproduction of selected information provided in CS Table 7, incorporating additional information from CS section B.2.3.1 and the Mini-COMET CSR.[23]
[a] [redacted].[23]
[b] It was unclear from the CS if people in cohort 3 who were randomised to AVAL could be treated with 20 mg/kg qow or 40 mg/kg qow (for example, see text in CS section B.2.3.2). The Mini-COMET CSR suggests that [redacted].[23]
ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IV, intravenous; kg, kilogram; mg, milligram; qow, every other week; qw, every week.

A major limitation of the Mini-COMET study, as acknowledged in CS section B.2.13.1, is its small sample size (n=11 patients). This increases uncertainty in the results and limits the conclusions that can be drawn about the efficacy and safety of ALGLU versus AVAL in the IOPD population. We acknowledge, however, the challenges of recruiting sufficient participant numbers in a rare disease setting.

We note that [redacted]. A clinical expert advising the ERG suggested that, in practice, clinicians will likely opt to use the [redacted] with their IOPD patients, if it is licensed. The use of this higher dose in the study therefore reflects how AVAL might be used in practice, if approved.

We also note that in the Mini-COMET study [redacted].[12] [redacted]. The use of higher doses than licensed in this study is acknowledged in CS section B.2.13.3, where it is stated that this reflects global variation in the use of the drug. We understand from one of our clinical experts that only the licensed dose of ALGLU – 20 mg/kg qow – can be used in practice in England, unless clinicians apply for off-label use. The expert noted that the dose used in England is lower compared to other countries. The expert advised that the maximum doses used in UK practice for IOPD are 40 mg/kg qow or 20 mg/kg qw. The expert stated that data suggests a higher dose of ALGLU is related to better survival outcomes.[30] The variation in dosing in the ALGLU arm in Cohort 3 of the Mini-COMET study does not fully reflect how ALGLU is used in the UK; [redacted] of

the [redacted] participants randomised to this arm were receiving doses that exceed the maximum used in the UK. However, if this had any impact on the results of the study, this would potentially bias the results in favour of ALGLU, rather than AVAL.

A clinical expert consulted by the ERG believes that the participant inclusion and exclusion criteria in the Mini-COMET study are not fully representative of the patients seen in practice, as the study includes treatment-experienced participants whose disease has likely not been adequately managed using a 20 mg/kg qow dose of alglucosidase. The expert also believed that it is likely that patients who take part in trials will come from the most motivated families whose children will have likely experienced poor clinical progress.

No evidence was included in the CS for the IOPD, treatment-naïve population

Given that the Mini-COMET study was the only evidence included in the CS for the IOPD population and that this study was conducted in people who were treatment-experienced, there is no evidence available in the CS on the efficacy and safety of AVAL in treating people with IOPD who were treatment-naïve. This is a limitation of the presented evidence-base.

COMET (LOPD, ERT treatment-naïve population)

The COMET trial meets the company's decision problem and the NICE scope. As shown in Table 9, COMET was a phase 3, multicentre, RCT that compared AVAL to ALGLU in people with LOPD who were ERT-treatment-naïve. The trial used the licensed dose of ALGLU[12] and [redacted] (see CS Table 2 and CS Appendix C).

[redacted] Participants were treated for a 49-week period – this was called the 'primary analysis phase' (PAP). This was then followed by an extended treatment period, during which participants receiving AVAL remained on their treatment and those receiving ALGLU switched to AVAL. This means that the two drugs are only directly compared within the PAP. The treatment switching means that in the ETP, the ALGLU arm shows outcomes over time for participants who were initially treated with ALGLU for 49 weeks and then moved to treatment with AVAL.

Table 9 The design and characteristics of the COMET trial

Study characteristic	Description
Study design	Phase 3, multicentre, RCT

Locations	[redacted], including the UK[26] (UK participant n = 5)
Population	People aged >3 years old with LOPD who were ERT-treatment-naïve
Intervention (N)	AVAL 20 mg/kg qow (N=51)
Comparator (N)	Alglucosidase alfa 20 mg/kg qow (N=49)
Treatment period and follow-up	49-week blinded treatment period in both trial arms (PAP), for a total of 25 doses. Then an open-label ETP, with the end of study visit planned for week 293. Participants who were randomised to ALGLU were switched to AVAL during the ETP. The trial CSR[26] states that, of the 49 participants randomised to ALGLU, [redacted] began the ETP and switched to avalglucosidase.

Source: This table is an adapted version of CS Table 8, with information also incorporated from CS Table 7, CS section B.2.3, CS Figure 4, CS Appendix L, sections L.3.2.2 and L.3.3.1, CS Appendix L, Table 27, and the COMET trial interim CSR.[26]
ETP, extended treatment period; FVC, forced vital capacity; kg, kilogram; LOPD, late-onset Pompe disease; mg, milligram; PAP, primary analysis phase; qow, every other week; RCT, randomised controlled trial; UK, United Kingdom; 6MWT, six-minute walk test

CS section B.2.3.1 states that all participants have completed the PAP, but that the ETP is ongoing (the final study visit is planned for [redacted]; see CS Figure 4). The company's clarification response A1 stated that complete data from the PAP are reported in the CS from a data cut dated 19th March 2020. Interim data are presented from the ETP to Week 97, from a data cut dated 8th June 2021. Interim results from later timepoints in the ETP are provided in CS Appendix O.

As the COMET trial is ongoing, a limitation of the evidence presented in the CS is that outcome results beyond Week 49 are only reported for a proportion of the participants (see CS section B.2.6.1 and CS Appendix O). For example, data are available for [redacted] of the randomised participants at Week 97 (around two years of treatment) and [redacted] at Week 193 (around four years of treatment) for the outcome of FVC% predicted (percentages calculated by the ERG from data in CS Appendix O, Figure 1). This means there is limited long-term outcome data available from the trial for the effects of avalglucosidase on FVC% predicted and 6MWT for participants treated with it throughout the trial. Clinical expert advice to the ERG is that follow-up data over a period of five or six years would be needed to assess the impact of treatment for LOPD. As shown in Table 9, the end of study visit is planned for Week 293, equating to around five and a half years of treatment. Therefore, when the study is complete, sufficient long-term data may become available.

NEO1 and NEO-EXT (LOPD, ERT-experienced and -naïve population)

The NEO1 study was a phase 1 ascending dose study of AVAL in 24 adults aged ≥18 years with LOPD, who were either ERT-naïve or had previously been treated with ALGLU. It examined three doses of AVAL: 5 mg/kg, 10 mg/kg and 20 mg/kg, all given every other week (qow). Participants received AVAL for 24 weeks. NEO-EXT is an on-going extension study to the completed NEO1 study. NEO-EXT includes people with LOPD completing NEO1. During this study, [redacted]. The NEO-EXT study is ongoing.

Of the 24 participants enrolled in NEO1, 19 participants entered NEO-EXT of which 17 are currently receiving AVAL long-term (CS Figure 34). Results in the CS are from the 27th February 2020 data cut-off. Measured outcomes included change from baseline in FVC % predicted and 6MWT. Results for change in FVC % predicted and 6MWT are provided in the CS up to Week 312 (equating to six years of treatment). [redacted] participants had data available at this timepoint, while [redacted] to [redacted] participants (depending on outcome) had data available at Week 208 (equating to four years of treatment) (CS Tables 25 and 27).

There was no comparison to ALGLU in the NEO1/NEO-EXT study; therefore, strictly speaking it does not meet the NICE scope or the company's decision problem. Results from NEO-EXT inform the company's economic model: it informed how long the treatment effects with AVAL were assumed to be maintained after one year of treatment (see below for more detail). [redacted] (CS Appendix L, section L.3.2.2). A limitation of the study, and thus this assumption in the model, is its small sample size, and particularly the low number of participants who currently have data available at six years of treatment. This means the duration of the treatment effect assumed in the model is subject to uncertainty. One of the experts advising the ERG noted that it will be important to understand if AVAL can affect the longer-term decline seen in patients in clinical practice treated with ALGLU (i.e. those who are treatment-experienced). We note, however, that there is not sufficient evidence available in the CS to answer this question.

The COMET and NEO1/NEO-EXT studies excluded people more severely affected by LOPD

The participant eligibility criteria for the COMET and NEO1/NEO-EXT studies in people with LOPD are provided in CS Table 11. One of the ERG's clinical experts noted that the studies excluded more severely affected patients; patients who would be treated in practice. For

example, people who were unable to walk 40 metres without stopping and without an assistive device were excluded from the COMET trial. Those who were wheelchair dependent were excluded from both the COMET and NEO1/NEO-EXT studies. People who were receiving invasive ventilation were also excluded from both studies. Clinical expert advice to the ERG is that, in practice, treatment might not be started for people needing invasive ventilation, but clinicians would not stop ERT treatment if patients were already receiving it and showing disease progression. The findings of the LOPD studies therefore may not be generalisable to people more severely affected by LOPD.

How the COMET and NEO-EXT studies informed the cost-effectiveness model

Clinical efficacy results from the COMET trial and NEO-EXT study informed the LOPD cost-utility model in the following ways:

- The FVC% predicted and 6MWT values observed in the **COMET** trial for people treated with each of AVAL and ALGLU at Week 49 were assumed to be those gained at one year for each of these treatments in the model (CS Appendix L, section L.3.2.2). (The model assumed there was no difference between the effectiveness of the treatments before the one year timepoint.)
- The **COMET** relative FVC% predicted and 6MWT changes from baseline at one year were then predicted to be maintained for specified periods of time in the model for each treatment (the 'plateau periods'). The durations of the plateau periods for ALGLU were informed by data from the Pompe Registry[7] and clinical expert advice. As stated above, the plateau durations for AVAL were informed by data from **NEO-EXT** (see CS Appendix L, section L.3.2.2, and CS Appendix L, Table 26).
- HRQoL data from **COMET,** measured using the EQ-5D-5L and mapped to EQ-5D-3L values, were used to inform the baseline utility value and the utility gains during the plateau periods for both AVAL and ALGLU (CS Appendix L, Table 27).

Section 4.2.6 of this report discusses clinical effectiveness evidence in the economic model in more detail.

3.2.1.2 Patients' baseline characteristics

The company summarised some participant baseline and demographic characteristics in CS Tables 12 and 13 for the COMET, NEO1/NEO-EXT and Mini-COMET studies.

Mini-COMET (IOPD, ERT-treatment experienced population)

As noted in CS section B.2.3.6.2, there were multiple imbalances in baseline characteristics between the two arms in Mini-COMET. This might be expected due to the small sample size (AVAL arm: randomised n = [redacted]; and, ALGLU arm: randomised n = [redacted]). Participants were generally healthier at baseline in the AVAL arm than in the ALGLU arm (see CS Table 13). CS section B.2.13.3 points out that participants allocated to ALGLU were younger than those allocated to AVAL, and they therefore were likely to have a lower disease burden. We note the groups also differed slightly in age at first Pompe disease symptoms onset ([redacted]). Participants allocated to AVAL were additionally aged younger at diagnosis than those in the ALGLU arm ([redacted]) and were [redacted] when they received their first treatment for Pompe disease ([redacted]). Clinical expert advice to the ERG is that earlier initiation of ERT, by a few weeks, seems to achieve better outcomes, and therefore may have introduced bias in favour of the avalglucosidase arm.

We understand from our clinical experts that CRIM status is a prognostic factor in IOPD. People with CRIM negative disease generally have worse clinical outcomes than those with CRIM positive disease. Immunomodulation has tempered the historical disparities between patients with CRIM-negative and -positive disease to some extent, but despite immunomodulation, people with CRIM-negative disease still tend to have worse outcomes. CRIM status at baseline in the Mini-COMET study was not reported in the CS. We note from the Mini-COMET CSR[23] that the study included [redacted] Additionally, [redacted] with CRIM-negative disease was assigned to Cohort 2 (one of the single-arm parts of the study) in Mini-COMET and was treated with AVAL. The proportion of participants with CRIM negative status is lower in the Mini-COMET study than seen in practice in the UK; the CS states that around 45% of patients in the UK have CRIM negative disease (CS section B.1.3.8.1.1). The ERG's IOPD clinical expert commented that the baseline characteristics of the Mini-COMET participants are reasonably representative of the IOPD patient cohort seen in clinical practice, with the exception of their CRIM status.

COMET (LOPD, ERT treatment-naïve population)

In CS section B.2.3.6.1, the company concludes that the baseline characteristics of the two treatment arms in the COMET trial were overall well-balanced. We generally agree, but note

some exceptions, which are shown in Table 10. As the table shows, participants allocated to AVAL had a shorter mean period of time between being diagnosed and starting ERT treatment than those allocated to ALGLU. The participants assigned to AVAL also had better median predicted FVC % predicted and 6MWT scores at baseline than those assigned to ALGLU. Clinical expert advice to the ERG is that, taken together, this suggests that the AVAL group might have started treatment earlier in the course of their disease and that this might mean that they had a greater chance of showing benefit.

Table 10 Differences in baseline characteristics between the treatment arms in the COMET trial

Characteristic	AVAL (n = 51)	ALGLU (n = 49)
Age at first symptoms, years		
Mean (SD)	32.94 (16.58)	37.73 (15.74)
Median	32.35	39.42
Min, Max	3.8, 66.3	6.1, 73.2
Time from Pompe disease diagnosis to first infusion of study drug, months		
Mean (SD)	15.60 (32.06)	26.52 (59.86)
Predicted FVC (%), upright		
Mean (SD)	62.5 (14.4)	61.6 (12.4)
Median	65.5	60.8
Min, Max	32, 85	39, 85
Distance walked from 6MWT (m)		
Mean (SD)	399.3 (110.9)	378.1 (116.2)
Median	415.7	387.0
Min, Max	118, 630	138, 592

Source: selected data presented from CS Table 12 and CS section B.2.3.6.1.
ALGLU, alglucosidase alfa; AVAL, AVAL; FVC, forced vital capacity; n, number; SD, standard deviation, 6MWT, six-minute walk test.

Clinical expert advice to the ERG is that the baseline characteristics of the participants in the COMET trial were similar to those of newly diagnosed patients seen in practice.

NEO1 and NEO-EXT (LOPD, ERT-experienced and -naïve population)

Baseline characteristics for the NEO1/NEO-EXT study are presented in CS Table 12. In the NEO1/NEO-EXT study, participants received AVAL, and there was no comparison with ALGLU treatment. In CS section B.2.3.6.3, the company summarises differences between

the participants within the study who were treatment-naïve and -experienced and note some differences. In discussing the baseline characteristics of this study here, we focus on the similarity and differences between the participants in this study and those included in the COMET trial, as data from NEO-EXT was used to estimate how long the treatment effect found in COMET for AVAL was assumed to persist over time in the cost-effectiveness economic model. Participants in the NEO1/NEO-EXT study had had a similar age of first Pompe disease symptoms onset, but were, on average, younger than those in the COMET trial at study entry and were younger when they were diagnosed. They also had higher average predicted FVC% and 6MWT scores at baseline. The participants in this study therefore had a better outlook and were healthier at baseline than those in the COMET trial, which may mean that the duration of treatment effect found in these participants may not be applicable to those in the COMET trial.

One of the clinical experts advising the ERG believed the baseline characteristics of the participants in the NEO1/NEO-EXT study were similar to those of newly diagnosed patients seen in practice. The characteristics may not reflect, though, those who have already been on treatment for several years.

3.2.1.3 Ongoing studies

The CS notes the ETP phases of the COMET, NEO-EXT and Mini-COMET trials are ongoing. In addition to these studies, the CS (section B.2.11) notes one other ongoing study of AVAL: Baby-COMET (NCT04910776).[31] This is a single group (i.e. no comparator) study evaluating AVAL treatment in babies with IOPD who are aged ≤6 months of age at study entry. It excludes babies who have previously received ERT therapy with a recombinant human acid a glucosidase (rhGAA). The Baby-COMET study is therefore being conducted in a treatment-naïve, IOPD population (there is no data included in the CS for this population). We note the study began in September 2021 and is due to fully complete in December 2026.

ERG comment on included clinical effectiveness studies

The evidence for the clinical efficacy and safety of AVAL in the IPOD population is from a single study of treatment-experienced (the Mini-COMET study). The RCT part of Mini-COMET, comparing AVAL to ALGLU, included 11 participants. There were multiple baseline characteristic imbalances between the treatment arms that could potentially bias the results (some in favour of AVAL and another in favour of ALGLU). These imbalances were likely due to chance. Additionally, a range of drug doses were used in ALGLU treatment arm, with only [redacted] receiving the standard

licensed dose. [redacted] of the [redacted] participants receiving ALGLU were taking doses higher than the maximum used off-label in the UK. Thus, the dosing does not fully reflect how ALGLU is used in England. Overall, conclusions about the clinical efficacy of AVAL in the IOPD population are highly uncertain.

The absence of treatment-naïve IOPD patients in Mini-COMET means there is a significant evidence gap at the current time on the safety and efficacy of AVAL in IOPD patients not yet exposed to ERT.

A further limitation of the Mini-COMET study is that it only included [redacted] with CRIM-negative disease; [redacted] who happened to be randomised to the ALGLU arm in the RCT part of the study, and [redacted] treated with AVAL in one of the single-arm parts of the study. Consequently, there are little data currently available on the efficacy and safety of AVAL in CRIM-negative IOPD – a subgroup who tend to have worse outcomes and who represent an estimated 45% of IOPD patients in the UK.

Regarding the evidence provided in the CS for the LOPD population, the COMET trial was conducted in a reasonable sample size, given the rarity of Pompe disease. There are, however, also limited data available in the CS from the COMET and NEO1/NEO-EXT studies on the longer-term clinical efficacy of AVAL, as the ETP parts of these studies are ongoing and only a proportion of the enrolled participants have results available at four to six years of receiving treatment. This means that the results presented in the CS for the longer-term efficacy of AVAL are uncertain. This includes the results used from the NEO-EXT study in the cost effectiveness economic model to determine how long the treatment benefit seen with AVAL at one year in the COMET trial lasted. A further limitation of using NEO-EXT to inform the treatment effect plateau in the model is that participants appeared to be healthier at baseline than those in the COMET trial.

Additionally, we note, based on clinical advice, that both the LOPD studies (COMET and NEO1/NEO-EXT) excluded people more severely affected by their LOPD, so the studies do not fully reflect the characteristics of the people treated in practice and the findings may not be generalisable to more severely affected patients. We also noted baseline imbalances between the two treatment arms in the COMET trial, which clinical expert advice to the ERG indicates could have biased findings in favour of AVAL.

3.2.2 Risk of bias assessment

The company only assessed the risk of bias for the randomised open-label Mini-COMET (Cohort 3 only) trial and the randomised double blinded COMET trial. The company's risk of bias assessments are presented in CS Appendix D.1.3. They use Version 2 of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2).[32] Each of RoB 2's five risk of bias domains and its overall judgement of a trial's risk of bias can be rated as low risk, some concerns, or high risk.

The ERG independently assessed the risk of bias in the Mini-COMET (Cohort 3 only) and COMET trials also using Version 2 of the Cochrane risk of bias tool; an overview of our judgements are presented in Table 11 below (please see Appendix 1 for our justification for these judgements). Users of the tool are directed to apply a separate set of risk of bias ratings for individual outcome measures, or groups of similar outcome measures, in a trial. The ERG selected the primary outcome of each trial as the outcome of interest for its risk of bias assessment i.e. safety and tolerability up to week 25 for the Mini-COMET (Cohort 3 only) trial and FVC% predicted at week 49 for the COMET trial.

Table 11 Overview of company and ERG risk of bias judgements

	Mini-COMET (cohort 3 only) Outcome: safety and tolerability		**COMET trial Outcome: FVC % predicted**	
	Company	**ERG**	**Company**	**ERG**
Domain 1: Risk of bias arising from the randomization process	Low risk of bias	Low risk of bias	Low risk of bias	**Some concerns**
Domain 2: Risk of bias due to deviations from the intended interventions	Low risk of bias	**Some concerns**	Low risk of bias	Low risk of bias
Domain 3: Risk of bias due to missing outcome data	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Domain 4: Risk of bias in measurement of the outcome	Low risk of bias	**Some concerns**	Low risk of bias	Low risk of bias

Domain 5: Risk of bias in selection of the reported result	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Overall risk of bias judgement	Low risk of bias	**Some concerns**	Low risk of bias	**Some concerns**
Source: partly reproduced from CS Appendix D Tables 25 and 26 Note. Bold text shows where the ERG's judgement differed to the company's.				

3.2.2.1 Mini-COMET (lOPD)

The company assessed that the Mini-COMET is at low risk of bias for each of the five domains and consequently the study is at overall low risk of bias. The ERG agrees with the company's judgements for three domains. However, we note some concerns for:

- **Domain 2 (risk of bias due to deviations from the intended interventions).** This was due to insufficient available details to determine if there were protocol deviations from the intended intervention arising from the experimental context. Such deviations potentially could bias the outcomes in this open-label trial.
- **Domain 4 (risk of bias in measurement of the outcome**). There is a possibility that the assessment of outcomes could be influenced by investigator knowledge of the intervention or comparator group status trial participants given that Mini-COMET was an open label trial.

Given the concerns for domains 2 and 4, **the ERG's overall risk of bias judgment for this trial is** '**some concerns'.** For context, we reiterate our other concerns (not all of which are strictly related to bias), outlined earlier in this report, that is: a very small sample of patients (n=11); baseline chance imbalances between trial arms in participant demographics and key efficacy parameters and heterogenous doses of the comparator treatment ALGLU, not fully reflective clinical practice in England.

3.2.2.2 COMET (LOPD)

For the COMET trial the ERG agrees with the company's risk of bias judgement for four of the five domains of RoB 2, with disagreement on the remaining domain. We therefore disagree with the company's overall assessment that COMET is at low risk of bias; we judged that there were 'some concerns' about the risk of bias in this study.

In summary, we identified some concerns about the risk of bias in the Mini-COMET and COMET trials. The findings of these studies should therefore all be interpreted with caution.

3.2.3 Outcomes assessment

3.2.3.1 IOPD

The trial outcomes for Mini-COMET are defined in CS Table 11 and CS B.2.6.2.3, and are also listed below in Table 12. The primary outcome was the safety and tolerability of AVAL versus ALGLU at week 25.

[redacted] (CSR section 8.5.2.1). A range of secondary efficacy measures were included, covering aspects of motor function, cardiac function, and health related quality of life. The ERG is not aware of any clinically relevant outcomes not included in this study.

Table 12 List of outcomes in Mini-COMET

	Outcome measures
Primary	• Safety and tolerability of AVAL vs ALGLU at week 25
Secondary - efficacy	• GMFM-88 total score • GMFCS-E&R by study visit • QMFT • Pompe-PEDI functional skills scale • Echo-LVM Z-score M-model and LVMI M-MODE scores[2] • Eyelid position measurements
Secondary – health related quality of life	• PedsQL Generic Core Scale, PedsQL Pediatric Pain Questionnaire, and Observational Visual Analogue Score
Other[1]	• Pulmonary function testing (not required for patients unable to reliably undergo testing or for patients who were invasively ventilated) • 6MWT (only for those who were ambulatory, defined as the ability to ambulate 40 metres without stopping and without an assistive device) • Creatine kinase

[1] Reported in CSR only. [2] LVMI M scores reported in company clarification response A5 only.
6MWT: six minute walk test; GMFM-88: Gross Motor Function Measure-88; GMFCS-E&R: Gross Motor Function Classification System - Expanded & Revised; LVM: left ventricular mass; LVMI: left ventricular mass index; PedsQL: Pediatric Quality of Life Inventory Pompe-PEDI: Pompe Pediatric Evaluation of Disability Inventory; QMFT: Quick Motor Function Test
Source: CS Table 11, CS.B.2.6.2.3, CS B.2.10.2, CSR 8.5.1, Company clarification response A5

3.2.3.2 LOPD

The outcomes measured in the COMET and NEO1/NEO-EXT studies are defined in CS Table 11, CS B.2.6.1 and CS B.2.6.3, and listed below in Table 13. These include measures of lung function, motor function, mobility, and health related quality of life and are clinically

appropriate to assess changes in LOPD symptoms. We note that FVC% predicted in the upright position (the primary outcome in COMET) has been used as a measure of efficiency in previous ERT (ALGLU) evaluation studies.

FVC% predicted and the 6MWT are well established clinical measures used across a range of health conditions (including other LSDs) in which respiratory function and muscle function are impaired (respectively). ERG clinical experts confirmed that these measures are used in practice to assess in Pompe disease symptoms and disease progression. Their inclusion in clinical evaluations of ERT is therefore clinically relevant. [34]

The CS cites evidence showing a positive association between FVC% predicted and other LOPD outcomes, including 6MWT, SF-36, and the Patient Global Impression of Change (PGIC). This evidence can be used to assess the clinical significance of given changes in FVC% predicted, to understand how such changes impact patients' symptoms and health related quality of life. The ERG has not critically appraised this evidence to judge the validity of the associations, but we are not aware of any evidence to the contrary.

Table 13 List of outcomes in COMET and NEO1/NEO-EXT

Endpoint	COMET	NEO1/NEO-EXT
Primary	• change from baseline in % predicted FVC in upright position to week 49	• Safety and tolerability
Secondary - efficacy and safety	• 6MWT • MIP and MEP (% predicted) • Lower extremity muscle strength by HHD • QMFT • Adverse events	• FVC% predicted in upright position • 6MWT • GSGC[1] • GMFM-88[1] • QMFT[1] • HHD[1]
Secondary – health related quality of life	• SF-12 • EQ-5D-5L • PDSS and PDIS • R-Pact	• PedsQL – adult report[1,2]

[1]Listed as outcomes in CS Table 11. Outcomes were only assessed for NEO1 and outcome data were only reported in company clarification response A6.[2]Company clarification A6 reported this outcome as 'PedsQL multidimensional fatigue scale'

6MWT: 6 minute walk test FVC: Forced vital capacity; GMFM-88-DE: Gross Motor Function Measure-88 (Dimensions D and E); GSGC: Gait, Stairs, Gowers, Chair ability; HHD: Hand-held dynamometry; MEP: Maximum expiratory pressure; MIP: Maximum inspiratory pressure; PDIS: Pompe disease impact scale; PDSS: Pompe disease symptom scale; PedsQL: Pediatric Quality of Life Inventory; QMFT: Quick motor function test; R-Pact: Rasch-built Pompe-specific Activity scale; SF-12: Short form health survey – 12 questions

Sources: CS Table 11, NEO1 Statistical Analysis Plan sections 1.21 and 2.4, NEO-EXT CSR section 7.1, company clarification response A6

3.2.4 Statistical methods of the included studies

In this section we focus on the statistical methods of the COMET trial, as this is the pivotal phase 3 trial informing the assessment of clinical effectiveness and cost-effectiveness of AVAL in LOPD. The mini-COMET and NEO1 studies did not evaluate study outcomes using formal statistical testing. Rather, outcomes were summarised descriptively and sample sizes were based upon "empirical considerations" rather than formal statistical power calculations.

The key statistical methods used in the COMET trial and the ERG's appraisal of them are summarised in Table 14. The trial was designed to test the hypothesis that AVAL is non-inferior to ALGLU in terms of improvements in lung function, as measured by the primary outcome of change from baseline to week 49 in FVC% predicted in the upright position. If non-inferiority was concluded the trial would then assess whether AVAL is superior (i.e. more effective) than ALGLU in terms of improvement in secondary outcomes, such as the 6MWT.

The assumptions informing the sample size calculation with respect to demonstrating non-inferiority in the primary outcome were:

- A normal distribution for FVC% predicted with a common standard deviation of 5.1% predicted, estimated from the results from a phase 3 randomised placebo-controlled trial of ALGLU in the treatment of LOPD (the Late-Onset Treatment Study - LOTS).[35]
- A mean treatment difference of 2.0% predicted, based on results of the LOTS and NEO1 studies.
- A two-sided 5% significance level
- Expected percent of missing data of 10%
- A non-inferiority margin of 1.1%, representing approximately 50% of the lower bound of the 80% CI for the ALGLU vs. placebo treatment effect in the LOTS study. An 80% CI rather than the traditional 95% CI was used on the advice of regulatory bodies given the rarity of Pompe disease.

The ERG considers the sample size calculation to be clearly reported and appropriate to assess non-inferiority in the primary outcome. Expert clinical advice to the ERG is that it is reasonable to use the results of the LOTS study to estimate the sample size for COMET, because estimates of efficacy and safety in the trial were similar to those seen in clinical

practice (with the caveat that LOTS does not capture the clinical decline seen in practice at later time points).

The modified intention-to-treat (mITT) population was defined as all randomised patients who received at least one partial or total infusion and was identical in number to the randomised population (the 'true' ITT). Patients were analysed in the trial arm to which they were randomly allocated. The ERG considers the use of the mITT population to be appropriate in this study.

Table 14 Statistical methods used in the COMET trial

	Summary details	ERG comment
Analysis populations	• Randomised n=100/100 (100%) • Modified intention to treat (mITT) n=100/100 (100%) • Per protocol n=85/100 (85%) (sensitivity analysis of primary outcome) • Safety n=100/100 (100%)	No concerns
Sample size calculations	Statistical power calculation to assess non-inferiority of AVAL vs AGLU for primary outcome of FVC% predicted at week 49, informed by previous phase 3 ALGLU outcome data.	No concerns
Methods to account for multiplicty	Hierarchical fixed sequential testing strategy used for the primary and key secondary outcomes. Testing was stopped after a non-significant difference in the key secondary outcome was found (as per the trial protocol)	No concerns
Analysis of outcomes	A mixed model for repeated measures was used, including randomisation strata, age, gender, treatment, visit and treatment-by-visit interaction as fixed effects.	No concerns
Handling of missing data	Missing data was not imputed and was assumed to be missing at random during the primary analysis period.	No concerns

Sensitivity & post-hoc analyses	The per-protocol population was used for a sensitivity analysis of the primary endpoint during the primary analysis period. Company regards the AVAL effect for FVC% predicted is underestimated by an extreme outlier patient. A post-hoc sensitivity analysis explored removal of the outlier.	No concerns

ERG comment on study statistical methods

Overall, the ERG considers the statistical design and execution of the COMET trial is appropriate, and had no concerns to note. The sample size calculation for assessing the non-inferiority of AVAL to ALGLU appears adequate and is informed by a previous phase 3 placebo-controlled trial of ALGLU, considered representative of clinical practice by expert clinical advice to the ERG. As discussed in Section 4, the non-inferiority of AVAL to ALGLU supports the company's choice of cost-comparison as their primary approach to economic evaluation (NB. When discussing the economic evaluation the CS tends to use the term 'equivalence' rather than non-inferiority, which is permissible in a general sense but not in statistical terms because of a difference in how they are defined and measured).

3.2.5 Efficacy results of the intervention studies

In this section, we focus on summarising the clinical effectiveness results for the outcomes from the studies that informed the cost-effectiveness economic model. These were:

- FVC (% predicted) change from baseline to Week 49 from the COMET trial
- Total distance (metres) walked during the 6MWT change from baseline to Week 49 from the COMET trial
- Health related quality of life, measured using the EQ-5D-5L and mapped to the EQ-5D-3L (Appendix L, section L.3.3.1), from the COMET trial

For comparison, we also present FVC (% predicted) and 6MWT results from the NEO-EXT study at Week 52.

As described in section 3.2.1, data from the NEO-EXT study informed the plateau durations for AVAL in the cost-effectiveness economic model (see CS Appendix L, section L.3.2.2, and CS Appendix L, Table 26). The plateau durations estimate how long treatment effects found at Week 49 in the COMET study on FVC (% predicted) and the 6MWT persist over time. Results for the FVC (% predicted) and the 6MWT measures during the extended treatment

periods of the COMET and NEO-EXT studies were reported in the CS and we summarise them here.

The results of the Mini-COMET study did not inform the cost-effectiveness model, but we have briefly summarised them here, as this was the only comparative study in the IOPD population.

3.2.5.1 Results for the IOPD population (Mini-COMET study)

The primary aim of the Mini-COMET study was to assess the safety of AVAL in treating people with IOPD. The secondary aim of the study was to assess the efficacy of AVAL in comparison to ALGLU on a range of outcomes (see CS Table 11). The CS presented the following results from stages 1 and 2 of the Mini-COMET study (i.e. from participants in cohorts 1, 2 and 3). AVAL was compared to ALGLU in the RCT, stage 2 part of the study (see section 3.2.1.1 for an overview of the design of the study):

- **GMFM-88 total percent scores**: There were generally modest increases over time in mean GMFM-88 total percent scores during the PAP, but there was variability between participants (CS section B.2.6.2.3.1 and CS Figure 25).
- **GMFCS-E&R**: [redacted] (CS section B.2.6.2.3.2 and CS Table 22).
- **QMFT**: [redacted] (CS section B.2.6.2.3.3 and CS Figure 26). [redacted] (CS section B.2.6.2.3.3).
- **Pompe-PEDI functional skills scale**: Some participants experienced improvements over time in the caregiver-assessed Pompe-PEDI functional skills scale (CS section B.2.6.2.3.4). At Week 25, of the participants treated with the 20 mg/kg qow dose of AVAL in Cohort 1 (n = 6), the scaled score increased in four participants and decreased in two. Of those treated with the 40 mg/kg qow dose in Cohort 2 (n = 5), two experienced an increase, while three remained stable. In the stage 2, RCT

element of the study, three of the five participants randomised to AVAL 40 mg/kg qow, had increased scaled scores and data were not available for two participants. In the ALGLU arm (mixed doses), all six participants experienced an increased scaled score. The CS suggests that the younger age of the participants at the study visit in the ALGLU arm may have favoured the results for this group (as demonstrated in spaghetti plots [redacted]; see CS Figure 27).

- **Echo-LVM Z-score**: In terms of the Echo-LVM Z-score measure, the CS notes all participants experienced improvements or remained stable at Week 25 (CS B.2.6.2.3.5). Only [redacted], who had CRIM-negative disease, had an abnormal baseline score on this measure; all other participants with available assessments were within the normal range at baseline. [redacted] moved into the normal range by Week 25.
- **Eyelid position measurements**: Improvement in eyelid position measurement occurred in all participants treated with AVAL 40 mg/kg qow at Week 25. Stabilisation or a decline was observed in those treated with the 20 mg/kg qow dose or ALGLU (CS section B.2.6.2.3.6).

HRQoL: Across the HRQoL measures used in the study, [redacted] (CS section B.2.6.2.4).

Due to the limitations of the Mini-COMET study noted in section 3.2.1 (small sample size in the Cohort 3, RCT element [n = 11], participant baseline characteristic differences between treatment arms in the RCT, and [redacted]), we consider the results from it to be subject to uncertainty.

3.2.5.2 FVC% predicted in upright position (LOPD population)

FVC % predicted in the upright position was the primary outcome of the COMET trial. FVC % predicted results are reported in CS section B.2.6.1.2. The main objective of the trial was to test non-inferiority of AVAL compared to ALGLU on this outcome (CS section B.2.6.1.2). Table 15 shows the FVC % predicted results from the trial at Week 49 of the PAP and at Week 97 of the ETP. Interim results up to Week 193 are reported from the ETP in CS Appendix O.

In the COMET trial, at Week 49 (the end of the PAP), AVAL was found to be non-inferior to ALGLU, with the lower boundary of the 95% confidence intervals above the planned non-inferiority margin of -1.1 (see Table 10). There was no statistically significant difference between the treatment arms on this outcome; AVAL was not found to be superior to ALGLU (the CS reports the p-value for the superiority test as 0.0626).

At Week 97, during the ETP, participants assigned to AVAL showed greater improvements from baseline in FVC % predicted than those who were assigned to ALGLU and who switched to AVAL (Table 15). The statistical significance of this difference is not reported. Clinical expert advice to the ERG is that the lower change from baseline in FVC % predicted in participants who switched from ALGLU to AVAL may reflect that they were further along in their disease course than the participants who remained on AVAL throughout the trial (for a discussion of baseline differences in participants' characteristics in this trial, please see section 3.2.1.2). This means they may have had less potential for improvement. Results reported in CS Appendix O, Figure 1, show that

[redacted]

A pre-specified responder analysis of FVC % predicted was also conducted. We have not summarised the results here. The results are presented in CS section B.2.6.1.2.

Table 15 Observed FVC% predicted results from the COMET study of people with LOPD who were ERT-naïve

Timepoint	AVAL	ALGLU [a]	Difference
Primary Analysis Period (PAP)			
N (mITT population) [b]	51	49	
Baseline, mean (SD)	62.55 (14.39)	61.56 (12.40)	–
Week 49, mean (SD)	65.49 (17.42)	61.16 (13.49)	–
CFB to Week 49, least squares mean (SE),[c] 95% CI	2.89 (0.88), 1.13, 4.65	0.46 (0.93), –1.39, 2.31	2.43 (1.29), –0.13, 4.99
Extended Treatment Period (ETP)			
N (at Week 97)	[redacted]	[redacted] [d]	
CFB to Week 97, least squares mean (SE)	[redacted]	[redacted]	Not reported

Source: the first rows of this table reporting the COMET trial PAP results are a reproduction of CA Table 17, with minor modifications. The following rows of the table contain information sourced from CS section B.2.6.1.2 and CS Figure 10.

[a] At the end of the PAP, participants assigned to ALGLU could switch to AVAL
[b] mITT population is identical to the ITT population.
[c] Based on an MMRM model so does not equal difference between observed values; the model includes baseline FVC% predicted as continuous, sex, age (in years at baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects.
[d] These participants switched from ALGLU to AVAL.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; CI, confidence interval; FVC, forced vital capacity; MMRM, mixed-effects model with repeated measures; SD, standard deviations; SE, standard error.

Table 16 summarises selected FVC% predicted results from the NEO1/NEO-EXT study of people with LOPD who were either ERT-naïve or -experienced, and who were treated with AVAL. Full results over the study at timepoints between baseline and Week 312 are provided in CS Table 25. The CS states that "FVC % predicted generally remained stable on treatment over time, although there was some variation between patients due to age and co-morbidities".

[redacted] (although it is difficult to draw conclusions given the low number of participants included in the analyses). One of the ERG's clinical experts commented that this might indicate that the treatment benefit in people with LOPD may depend on whether people are treatment-naïve or -experienced, rather than being a function of which ERT they received. In the NEO1/NEO-EXT study, change from baseline in FVC % predicted in the ERT-naïve group at Week 52 was similar to the results found in ERT-naïve participants in the COMET trial at Week 49. All the FVC % predicted results need to be interpreted with caution due to the low numbers of participants included in the analyses (data were available for between [redacted] participants in each group).

Table 16 FVC% predicted results from the NEO1/NEO-EXT study of people with LOPD who were either ERT-naïve or -experienced and treated with AVAL

Week and N	ERT-naïve All AVAL doses	ERT-experienced All AVAL doses
N (at baseline)	10	14
Baseline	69.213 (19.265)	77.304 (16.450)
N (at Week 52)	8	11
Week 52, mean (SD)	[redacted]	[redacted]
CFB to Week 52, mean (SD)	2.640 (8.199)	–2.510 (6.011)
N (at Week 208)	7	10
Week 208, mean (SD)	[redacted]	[redacted]
CFB to Week 208, mean (SD)	1.258 (7.012)	–1.705 (5.293)
N (at Week 312)	[redacted]	[redacted]
Week 312, mean (SD)	[redacted]	[redacted]
CFB to Week 312, mean (SD)	[redacted]	[redacted]

Source: this is a modified version of CS Table 25.
Abbreviations: AVAL, avalglucosidase alfa; CFB, change from baseline; SD, standard deviations.

3.2.5.3 6MWT (LOPD population)

In the COMET trial, participants assigned to AVAL showed greater mean improvements in 6MWT at Week 49 compared to baseline than those assigned to ALGLU (Table 17). Non-inferiority was not statistically assessed for this outcome. A clinical expert advising the ERG questioned whether the absolute difference between the trial arms on this outcome at Week 49 is clinically significant. Participants also showed greater improvements at Week 97 during the ETP, but the statistical significance of this difference was not reported in the CS. Mean change from baseline in this outcome is reported over time up to Week 169 in CS Appendix O. It is unclear why data are only reported up to this timepoint for this outcome, while FVC% predicted results were reported in the Appendix up to Week 193. The results for timepoints beyond Week 97 are not reported in the COMET trial interim CSR provided to the ERG,[26] so the ERG could not access any other source to check if data were available for later than Week 169. (The company stated in their clarification response A10 that CSRs for more recent data cuts are not available yet.) The data show that treatment benefits gained with AVAL on this outcome were maintained over time in the AVAL group. Clinical expert advice to the ERG indicates there was no clear benefit over time on this outcome, though, for the ALGLU group who switched to AVAL. As with the FVC% predicted data provided from the ongoing COMET ETP, the

[redacted].

Table 17 Observed 6MWT results from the COMET study of people with LOPD who were ERT-naïve

Timepoint	AVAL	ALGLU [a]	Difference
Primary Analysis Period (PAP)			
N (mITT population) [b]	51	49	-
Baseline, mean (SD)	399.3 (110.9)	378.1 (116.2)	-
Week 49, mean (SD)	[redacted]	[redacted]	-
CFB to Week 49, least squares mean (SE),[c] 95% CI	32.21 (9.93), 12.47, 51.94	2.19 (10.40), –18.48, 22.86	30.01 (14.43) 1.33, 58.69
Extended Treatment Period (ETP)			
N (at Week 97)	[redacted]	[redacted] [d]	-
CFB to Week 97, least squares mean (SE)	[redacted]	[redacted]	Not reported

Source: the first rows of this table reporting the COMET trial PAP results is a reproduction of CA Table 18, with minor modifications. The following rows of the table contain information sourced from CS section B.2.6.1.3.1.
[a] At the end of the PAP, participants assigned to ALGLU could switch to AVAL
[b] mITT population is identical to the ITT population.
[c] Based on an MMRM model so does not equal difference between observed values; the MMRM model for 6MWT distance adjusts for 6MWT distance at baseline, baseline FVC% and baseline 6MWT (distance walked in metres), age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.
[d] These participants switched from ALGLU to AVAL.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; CI, confidence interval; FVC, forced vital capacity; MMRM, mixed-effects model with repeated measures; SD, standard deviations; SE, standard error.

6MWT results from the NEO1/NEO-EXT study were reported in CS section B.2.6.3.3.2 as mean 6MWT % predicted. Selected results for this outcome are presented in Table 18. CS section B.2.6.3.3.2 reports results for more study timepoints. As noted in section 3.2.1, the NEO-EXT study is ongoing, and, as such, only incomplete participant data are available. The CS states that the results show that participants [redacted] (CS section B.2.6.3.3.2).

Table 18 6MWT results from the NEO1/NEO-EXT study of people with LOPD who were either ERT-naïve or -experienced

Week and N	ERT-naive	ERT-experienced
N (at baseline)	10	14
Baseline mean (SD) 6MWT % predicted	65.483 (15.540)	62.243 (17.632)
N (at Week 52)	[redacted]	[redacted]
Week 52, mean (SD) 6MWT % predicted	[redacted]	[redacted]
CFB to Week 52, mean (SD)	[redacted]	[redacted]
N (at Week 208)	[redacted]	[redacted]
Week 208, mean (SD) 6MWT % predicted	[redacted]	[redacted]
CFB to Week 208, mean (SD)	[redacted]	[redacted]
N (at Week 312)	[redacted]	[redacted]
Week 312, mean (SD) 6MWT % predicted	[redacted]	[redacted]
CFB to Week 312, mean (SD)	[redacted]	[redacted]

Source: this is a modified version of CS Table 27.
Abbreviations: CFB, change from baseline; SD, standard deviations.

3.2.5.4 HRQoL outcomes (LOPD population)

Five patient reported outcome measures were used in the COMET study to assess: 1) HRQoL (SF-12 and EQ-5D-5L), 2) range and severity of disease symptoms (PDSS), 3) mood and difficulties undertaking physical activity (PDIS), and, 4) the impact of living with Pompe disease on daily and social activities (R-Pact) (CS section B.2.3.7). Results for all these outcome measures are reported in CS section B.2.6.1.4. The EQ-5D-5L results informed the cost-effectiveness economic model, so we only report results for this outcome here. EQ-5D-5L values, mapped to EQ-5D-3L values, were used to inform utility benefits for patients during the plateau periods for both those receiving AVAL and those receiving ALGLU (CS Appendix L, Table 27). HRQoL does not appear to have been measured in the NEO1/NEO-EXT study.[27]

EQ-5D-5L results from the COMET trial for the domains assessed are provided in CS section B.2.6.1.4.2 for the PAP and for the ETP up to Week 97. At the request of NICE and the ERG, the company also provided mean EQ-5D-5L index score utility values for both trial arms at baseline and other measured timepoints (clarification response A8). The company also provided data on the changes in these scores from baseline at each timepoint in their clarification response. Data were provided up to Week 217. At this timepoint data were only available for [redacted] participants.

We provide a summary of the COMET trial EQ-5D-5L results included in the CS and the company's clarification response here. All participants had completed the PAP. The EQ-5D-5L results during the PAP were:

- The AVAL arm experienced greater mean improvement in the usual activities and mobility domain scores than the ALGLU arm between baseline and Week 49 (the end of the PAP). Score changes were similar between the arms on the anxiety/depression, pain/discomfort and self-care domains (CS Figure 19). The number of participants included in these analyses is unclear from the CS.
- [redacted] (CS Figure 20).
- Data in clarification response A8, Table 5, shows that during the PAP, EQ-5D-5L index score utility values were [redacted]. [redacted] (clarification response A8, Table 6). [redacted] (see clarification response A8, Tables 5 and 6).

The ETP is ongoing and the company provided available EQ-5D-5L results for this period in the CS and clarification response. The EQ-5D-5L results during the ETP were:

- [redacted] Results are not reported in the CS for the self-care and pain/discomfort domains for any of the ETP timepoints (CS section B.2.6.1.4.2). The number of participants included in these analyses is unclear from the CS.
- During the ETP, [redacted] (clarification response A8, Table 5). As is noted in CS Appendix O, [redacted]

3.2.5.5 Subgroup analyses

The only subgroups of people stated to be of interest in the NICE scope were people with IOPD and LOPD. Results for both these populations are reported in CS section B.2.6, where results for the relevant trials in these populations are provided. The company additionally provided other subgroup analyses in CS Appendix E from the COMET trial. As none of the subgroups analysed were specified to be of interest in the NICE scope, we have not summarised the results here.

3.2.5.6 Safety outcomes

IOPD

Data comparing adverse events between AVAL and ALGLU in the IOPD population comes from Cohort 3 of the Mini-COMET trial. There is uncertainty in this evidence given the small patient numbers (n=11), imbalances in baseline characteristics, and the heterogeneity of the doses of treatment received in the ALGLU arm. During the primary analysis period (PAP) the rate of experiencing at least one treatment emergent adverse event (TEAE) was similar in the AVAL versus ALGLU arms (100% versus 83.3%) (Table 19). Serious adverse events were less frequent in the AVAL arm than the ALGLU arm (0.0% versus 33.3%), although none were considered potentially treatment-related. [redacted] (CS section B.2.10.2.1.3) ([redacted] versus [redacted]; CSR Table 19). No patients met the criteria for anaphylaxis (CSR section 11.3.5.1).

There were no permanent discontinuations of treatment or deaths in either the AVAL or ALGLU arms.

During the PAP, the five most frequent adverse events (see table 2) were vomiting (40.0% versus 50.0%), upper respiratory tract infection (40.0% versus 16.7%), rhinorrhoea (40.0% versus 16.7%), rash (40.0% versus 16.7%) and pyrexia (40.0% versus 16.7%) in the AVAL versus ALGLU arms respectively.

[redacted] (Company clarification A4).

Results for the ETP can be found in CS section B.2.10.2.2.

Table 19 Summary of adverse events in cohort 3 of the Mini-COMET trial

Parameter, n (%)	AVAL 40 mg/kg N=5	ALGLU current dose N=6
TEAEs	5 (100)	5 (83.3)
TEAEs potentially related to study treatment	1 (20.0)	1 (16.7)
Serious TEAEs	0	2 (33.3)
Serious TEAEs potentially related to study treatment	0	0
Severe TEAEs	0	1 (16.7)
Severe TEAEs potentially related to study treatment	0	0
TEAEs leading to permanent treatment discontinuation	0	0
TEAEs leading to death	0	0
TEAEs leading to death potentially related to study treatment	0	0
Protocol-defined IARs	1 (20.0)	1 (16.7)
Algorithm-defined IARs	1 (20.0)	1 (16.7)
Treatment-emergent anaphylaxis	[redacted]	[redacted]
Proportion of patients experiencing most common TEAEs, n (%)		
Vomiting	[redacted]	[redacted]
Upper RTI	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Device occlusion	[redacted]	[redacted]
Middle ear effusion	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]
UTI	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Excessive cerumem production	[redacted]	[redacted]

IAR: infusion-associated reactions; RTI: respiratory tract infection; TEAE: treatment emergent adverse event, UTI: urinary tract infection

Source: Partly reproduced from CS Table 33 and Table 34, and includes information sourced from CS section B.2.10.2.1.3 and the Mini-COMET CSR

LOPD

In the primary analysis period (PAP) (to Week 49), the majority of the participants (>85%) in both the AVAL and the ALGLU arms of the COMET trial experienced adverse events. The rate of experiencing at least one treatment-emergent adverse event (TEAE) was less frequent in the AVAL arm than in the ALGLU arm (86.3% versus 91.8%), as was the rate of serious adverse events (15.7% versus 24.5%), severe TEAEs (11.8% versus 14.3%) and protocol defined infusion associated reactions (IARs) (25.5% versus 32.7%) (CS Table 28). The rate of treatment-emergent anaphylactic reaction was similar between the AVAL and the ALGLU arms ([redacted] versus [redacted]) (CS Table 31).

Adverse events led to permanent discontinuation of treatment in none of patients receiving AVAL and 8.2% receiving ALGLU (CS Table 28).

[redacted].

A treatment-emergent adverse event led to one death, in the ALGLU arm, during the PAP (CS Table 28).

[redacted].

The CS reports the most frequent adverse events occurring in ≥3% of patients by severity (CS Table 29). Focussing on adverse events that occurred in ≥10% of patients, the rate of nasopharyngitis and pain in extremity did not differ between trial arms, whereas back pain, influenza and fatigue were more frequent in the AVAL arm, and headache, falls, diarrhoea, nausea, arthralgia, myalgia and muscle spasms were more frequent in the ALGLU arm (see Table 20).

The rate of adverse events considered potentially related to treatment was similar between both the AVAL and ALGLU arms (45.1% and 49.0%). The CS reports the most frequent potentially related i.e. those occurring in ≥ 2% of patients during the PAP. Treatment-related headache, nausea and rash less frequent in the AVAL arm than the ALGLU arm, while rates of diarrhoea, vomiting and urticaria were more frequent. Similar rates of pruritus and fatigue were found.

[redacted] (Company clarification response A4).

Table 20 Summary of adverse events in the COMET trial

Parameter, n (%)	AVAL N=51	ALGLU N=49
TEAEs	44 (86.3)	45 (91.8)
TEAEs potentially related to study treatment	23 (45.1)	24 (49.0)
Serious TEAEs	8 (15.7)	12 (24.5)
Serious TEAEs potentially related to study treatment	1 (2.0)	3 (6.1)
Severe TEAEs	6 (11.8)	7 (14.3)
TEAEs leading to permanent treatment discontinuation	0	4 (8.2)
TEAEs leading to death	0	1 (2.0)
TEAEs leading to dose reduction	[redacted]	[redacted]
Protocol-defined IARs	13 (25.5)	16 (32.7)
Algorithm-defined IARs	[redacted]	[redacted]
Treatment emergent anaphylactic reaction	[redacted]	[redacted]
AEs reported in ≥10% of participants in either trial arm, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	********
[redacted]	[redacted]	[redacted]
Potentially treatment-related TEAEs occurring in ≥2% patients during PAP, n (%)		
Any class	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]

Parameter, n (%)	AVAL N=51	ALGLU N=49
Rash	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
IAR: infusion-associated reaction; TEAE: treatment emergent adverse event Source: Partly reproduced from CS Tables 28, 30 and 31, and CSR Tables 24 and 31		

The ETP for this is study is ongoing. Interim results are presented in CS section B.2.10.1.2. These show that during the PAP and ETP combined, [redacted] of participants who received AVAL during the PAP and ETP experienced a TEAE potentially related to the study treatment. In this group, [redacted] had TESAEs potentially related to the study treatment. TEAEs leading to permanent treatment discontinuation occurred in [redacted] of the participants in this group. There were [redacted] TEAEs leading to death in this group.

There was no comparison to ALGLU in NEO1/NEO-EXT study; therefore, it does not meet the NICE scope or the company's decision problem. Adverse events in the NEO1/NEO-EXT study are reported in CS section B.2.10.3.

Overall, for IOPD, adverse effects were comparable between AVAL and AGLU, with some indication there is less immunogenicity response with AVAL than ALGLU. However, this is subject to uncertainty given the small trial size, imbalances in baseline characteristics, and the heterogeneity of the doses of treatment received in the ALGLU arm of Mini-COMET. For LOPD, the less frequent TEAEs, severe TAES, SAEs, adverse events leading to discontinuation, and protocol defined infusion associated reactions (IARs) in patients receiving AVAL versus ALGLU suggest AVAL is better tolerated.

3.2.6 Pooled analysis of FVC% predicted at one year (LOPD)

[redacted]

[redacted]

3.3 Additional work on clinical effectiveness undertaken by the ERG

The ERG has not undertaken any additional analyses of clinical effectiveness data, but we have identified where further evidence and analyses could be informative at technical engagement – please see Section 1 for details of key issues identified.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review (SLR) to identify relevant economic evaluation studies. The databases and conference proceedings searched are listed in CS Appendix D Table 1 and the search strategy is shown in CS Appendix Table 2. The original search was run on 24th August 2020 and updated on 13th August 2021. The search was designed to find clinical effectiveness studies, economic studies and HRQoL studies. The selection criteria are shown in CS Appendix D Table 22.

Seven economic studies of Pompe disease were included, of which four were cost-effectiveness studies. The studies compared ERT with ALGLU versus no ERT. These studies are summarised by the company in CS Appendix L Table 1. The ERG notes that none of the studies include AVAL. The studies are conducted in the Netherlands, Iran, Columbia and England. The ICERs in the studies range from £96,809 US$ per QALY to $1,000,000 EUR per QALY for IOPD. The ICER for the study assessing LOPD was £3,167,914 per QALY. The CS does not comment on how the structure of these models compare to their economic models.

ERG comment

The ERG considers the company's review of cost-effectiveness evidence comprehensive and appropriate. The sources searched (including all recommended databases) is adequate, the search structure and syntax are accurate, the search strategies reflect the patient population, the searches are reasonably up to date and the reporting is clear. The ERG is not aware of any other relevant cost effectiveness studies.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

The CS presents cost-comparison models for AVAL versus ALGLU for the IOPD and LOPD patient populations as their base case economic evaluation. The cost comparison approach was chosen by the company on the assumption that AVAL and ALGLU are equivalent in efficacy and safety, [redacted]. In addition, cost utility models for the two populations were presented by the company in Appendix L.

4.2.1 NICE reference case checklist

The NICE reference case checklist for the company's economic evaluation is shown in Table 21. The ERG considers that the company's cost comparison model does not meet the criteria of the NICE reference case as it does not include health effects or utilities. However, the company's cost utility model meets almost all the reference case criteria. For this reason, we focus our critique of the economic evaluation on the cost-utility analyses. We provide a brief description of the cost comparison analysis in Appendix 3.

Table 21 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's cost-comparison analysis	ERG comment on company's cost-utility analysis
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	No	Yes
Perspective on costs	NHS and PSS	Yes	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, 50 years for IOPD, 60 years for LOPD	Yes, 50 years for IOPD, 60 years for LOPD
Synthesis of evidence on health effects	Based on systematic review	Health effects not included.	Yes, although no evidence on long-term outcomes.
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.	Not included	Yes

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Not included	Yes, for LOPD, no for IOPD.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Not included	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Not included	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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes	Yes

4.2.2 Model structure

4.2.2.1 IOPD model

4.2.2.1.1 Overview of the model structure

The company's cost-effectiveness model is described in CS Appendix section L.4.1.1 and illustrated in CS Appendix L Figure 10 and the model structure is reproduced in Figure 1 below.

The IOPD model is a partitioned survival model with the following health states: ventilation-free, non-invasive ventilation dependent, invasive ventilation-dependent, and death. The model has monthly cycles.

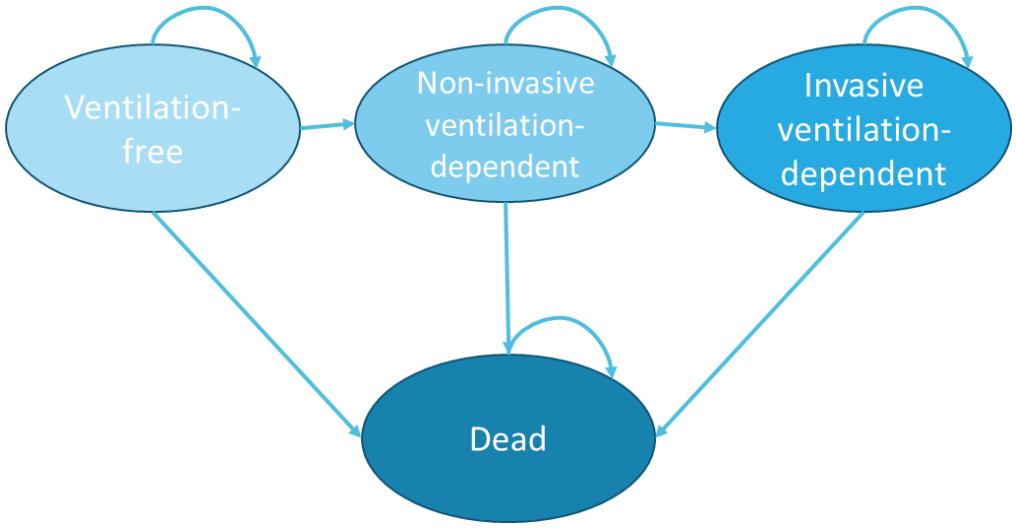

Figure 1 IOPD Model Structure

Source: reproduced from CS Appendix L Figure 10.

All patients start in the ventilation-free health state and begin ERT with either ALGLU or AVAL. As Pompe disease has a progressive nature, patients can only remain in their current health state or move to more severe health states over time; there is no option to transfer back to a previous health state. As stated in the CS, each consecutive health state reflects the patient's increasing loss of lung and motor functions, incurring higher costs and lower quality of life.

Disease progression is modelled with survival curves for OS, ventilation-free survival (VFS) and invasive ventilation-free survival (IVFS). These survival curves inform the number of patients who die or move into the non-invasive ventilation dependent and invasive ventilation

dependent health states, respectively. The company assumed that the number of patients with IVFS never exceeds those with VFS and that those with either IVFS or VFS never exceeds OS. The survival curves were estimated from a retrospective case-note review of 33 UK IOPD patients treated with ALGLU, by Broomfield et al.[7] The survival curves are discussed in more detail in section 4.2.6.1 below.

4.2.2.1.2 ERG critique of model assumptions

Table 22 shows the ERG's comments on the company's model assumptions for the IOPD population.

Table 22 IOPD company's model assumptions

Assumption	Company's justification	ERG comments
Patients only progress to worse health states.	Patients move to worse health states given the progressive nature of IOPD over an individual's lifetime. As such, improvements in health were not considered (see CS Appendix L, section L.4.1.1)	We agree
The number of patients with IVFS is lower than VFS, and both IVFS and VFS are lower than OS (IVFS < VFS < OS)	To avoid crossing of survival curves (see CS Appendix L, section L.4.2)	We agree
Ventilator status, as well as the use of a wheelchair, did not impact OS, only costs and QALYs	The model was structured as a partitioned survival analysis with four health sates: 'ventilation-free', 'non-invasive ventilation-dependent', 'invasive ventilation-dependent' and 'dead'. The health states were defined by OS and ventilation survival curves from Broomfield 2015. It was assumed that the OS curve captures the additional risk of death that a patient will experience in the ventilation-dependent disease states (see CS Appendix L, section L.4.2)	The ERG considers that the Broomfield study [7] includes a small population and therefore the OS curve could not capture the additional risk of death experienced by a ventilated patient. (see section 4.2.6.1)
Treatment effect for AVAL was assumed to be equal to that used for ALGLU	The company assumed equivalent benefits due to lack of long-term data for AVAL. Despite the Mini-COMET trial showed a benefit of AVAL versus ALGLU in the IOPD population, the data is not adequate to model long-term events. (CS Appendix L, section L.4.2)	We agree that the Mini-COMET trial is inadequate to inform the long-term outcomes and costs of the economic model particularly due to the very small sample size (see section 4.2.6.1). We also assumed equivalent benefits between arms in the ERG base case, but varied it in scenario analysis

Ambulatory infants were assumed to become ambulatory at 18 months of age	A study by Broomfield 2016 followed 33 patients, of whom 28 had motor ability recorded. Of 25 patients on either no ventilation or a non-invasive ventilation, 12 (48%) gained the ability to walk, at a mean age of 18 months (see CS Appendix L, section L.4.2.2)	We agree
Source: adapted from CS Appendix L Table 56. ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CS, company's submission; ERG, Evidence Review Group; IOPD, infantile-onset Pompe disease; OS, overall survival.		

ERG comment on model structure (IOPD)

A partitioned survival analysis model is a common approach in economic evaluations of progressive diseases and has been applied in many NICE appraisals. The ERG considers the chosen approach appropriate but we note there has been no previous NICE appraisal of treatments for Pompe disease and therefore no precedent to drawn on. The company's model has four health states and we consider they adequately reflect IOPD disease progression. We note that wheelchair use could have also been modelled as a separate health state, although the company has incorporated these costs and utilities by assuming that a proportion of patients in each of the model health states was dependent on a wheelchair (see more details in section 4.2.6.1 below).

4.2.2.2 LOPD model

4.2.2.2.1 Overview of the model structure

The company's model is described in CS Appendix L section L.3.1.1; the model structure is illustrated in CS Appendix L Figure 2 and is reproduced in Figure 2 below.

The company chose a patient-level simulation, namely a Discretely Integrated Condition Event (DICE) approach, to model the cost effectiveness of AVAL versus ALGLU in LOPD. The model is implemented in Microsoft Excel and uses EviDICE, an Excel visual basic application (VBA) DICE simulation platform, which allows modellers to use pre-defined functions necessary for a simulation. The company claims that an individual patient simulation model is appropriate for LOPD because it can capture the variation in patient characteristics of this patient population, including disease severity, age at onset or the point at which patients require ventilation or wheelchair use. Moreover, the company considers that the DICE model would accurately reproduce the course of the disease as a combination of evolving conditions (such as age, disease status, costs and utilities) and key events (such as treatment initiation or discontinuation, time to requiring ventilation or wheelchair use and

death) that consequently affect the conditions. The DICE model includes several tables containing ‘conditions’, ‘events’ and ‘outputs’, linked through formulas executed by a macro (Visual Basic for Applications; Microsoft).[36] As a guide:

- **Conditions** represent all information in the model, such as demographics or disease status;
- **Events** are moments in time that change the values of some conditions, such as disease progression or death; and
- **Outputs** are special conditions that store the results.

Patient characteristics were combined into eight ‘profiles’ that represent the LOPD population enrolled in the COMET trial. Each profile represents a set of patients with similar baseline characteristics, such as age, sex, weight, time since diagnosis, FVC% predicted, 6MWT and utilities (further details in section 4.2.3 below). Each set of patients are simulated over a lifetime horizon for both AVAL and ALGLU. The model outcomes are then averaged over all simulated patients for each treatment, based on the weight attributed to each profile (proportions of simulated patients in each profile).

The LOPD model includes six health states, listed below:

- Non-dependent on ventilation or wheelchair,
- Non-invasive ventilation-dependent,
- Wheelchair-dependent,
- Ventilation and wheelchair-dependent,
- Invasive ventilation-dependent, and
- Death

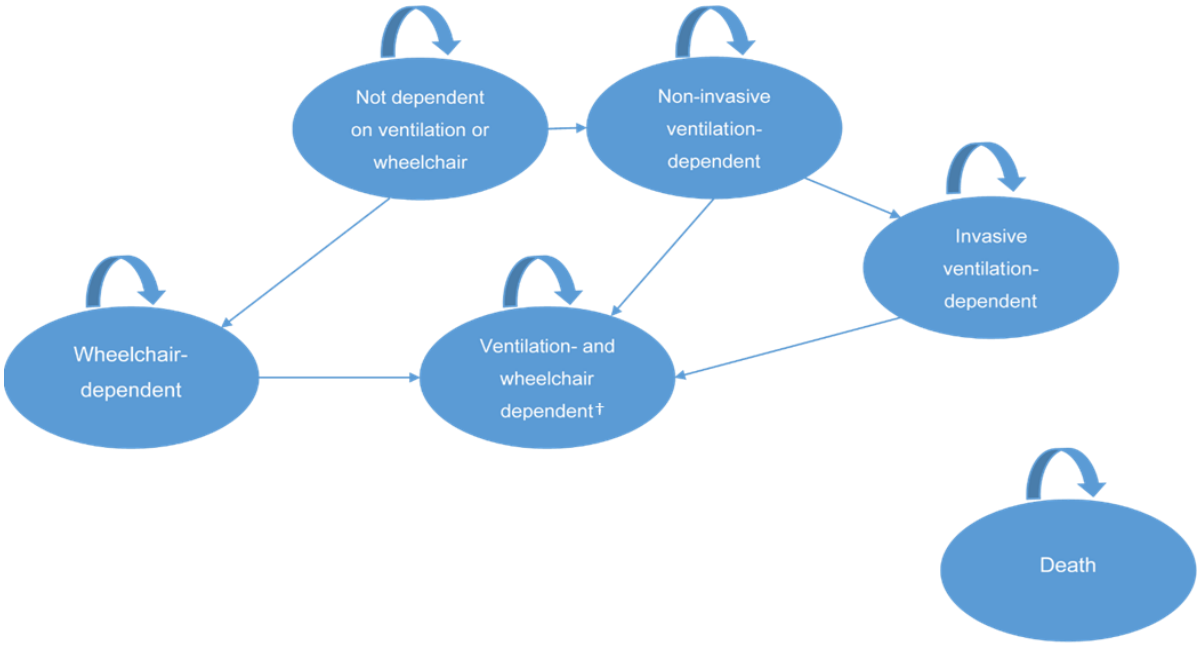

Figure 2 LOPD economic model schematic

Source: CS Appendix L, Figure 2
Note: death is an absorbing health state whereby patients from each health state can move into.

All patients start in the model without ventilation or wheelchair use and begin ERT with either AVAL or ALGLU. Patients can stay in the current health state or move to a worse health state depending on whether their FVC% predicted and/or 6MWT decline below a particular disease milestone (based on the Pompe registry [37] and explained further in section 4.2.6.2 below). If FVC% predicted falls below a given threshold, patients are assumed to start ventilation (first non-invasive and then invasive) while patients start using a wheelchair after a specified decline in 6MWT. Costs, quality of life and mortality are captured and updated for each health state.

4.2.2.2.2 ERG critique of model assumptions

Table 23 shows the ERG's comments on the company's model assumptions for the LOPD population. We generally agree with most of the company's assumptions, except for the decline rate of 6MWT in patients with no treatment and the survival benefit of AVAL over ALGLU.

Table 23 ERG critique of company's LOPD model assumptions

Assumption	Company's justification	ERG comments
The model assumed that mortality is independently impacted by treatment and disability status. The impacts of both are modelled as a hazard ratio (HR) applied to the baseline hazard of death (hazard of death for no treatment) under an assumption of proportional hazards.	Data on mortality for patients requiring a wheelchair or a ventilator was sparse, requiring some structural assumptions to meaningfully interpret the data. An assumption of proportional hazards was considered clinically plausible. (see CS Appendix L, section L.3.2.4)	We agree
Patients only progressed to worse health states.	Patients moved to worse health states given the progressive nature of LOPD over an individual's lifetime. As such, improvements in health were not considered. (see CS Appendix L, section L.3.1.1)	We agree
Patients were assumed to experience a linear decline in FVC% predicted and 6MWT.	This is a simplifying assumption, applied based on data from the literature. Analysis of disease progression by Van der Beek 2012 [38] suggested adults experience a steady linear decline in FVC% predicted. (see CS Appendix L, section L.3.2.2)	We agree
Treatment effects of AVAL and ALGLU were applied 1 year after treatment initiation.	This corresponds to the timing of the COMET trial primary endpoint. (see CS Appendix L, section L.3.2.2)	We agree
Long-term FVC% predicted and 6MWT decline rates were equal between ALGLU and AVAL.	There is no data available on a long-term treatment effect available, therefore the treatment effect was assumed to stop at [redacted] (both FVC and 6MWT) for AVAL and [redacted] (FVC) and [redacted] (6MWT) for ALGLU. This was based on registry analysis [37] and clinical feedback (CS Appendix M). (see CS Appendix L, section L.3.2.2)	We agree
Upon discontinuation from ERT, patients immediately experienced decline rates associated with no treatment.	This is a conservative assumption and was applied as there are no long-term data of treatment effects after discontinuation. (see CS Appendix L, section L.3.2.2)	We agree
The decline in 6MWT for patients on no treatment was assumed [redacted] to those on ERT.	There is little data available on the progression of 6MWT on no treatment. This represents the most conservative assumption. (CS Appendix L, section L.3.2.2)	The ERG assumes that the decline in 6MWT should be [redacted] for patients on no treatment than on patients treated with ERT therapies.
Mortality HR for AVAL was assumed to be equal to that used for ALGLU.	This was expected to be a conservative assumption as patients treated with AVAL experience greater changes in FVC% predicted and 6MWT. This assumption was necessary due to the lack of long-term data on the effect of AVAL on patient mortality. However, treatment with AVAL influenced treatment progression which in turn affected mortality risks in more severe health states.	The ERG assumes that AVAL will increase OS (and treatment costs) compared to ALGLU and assumes a HR < 1 of AVAL vs. ALGLU

	(CS Appendix L, section L.3.2.4)	

Source: reproduced from CS Appendix L Table 27.
6MWT, six-minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CS, company's submission; ERG, Evidence Review Group; ERT, enzyme replacement therapy; FVC, forced vital capacity; HR, hazard ratio; LOPD, late-onset Pompe disease; OS, overall survival.

ERG comment on model structure (LOPD)

The ERG considers that the health states included in the LOPD model adequately reflect the progressive nature of the disease. In the ERG's view, the model integrates the key aspects of the disease (ventilation and wheelchair use) that particularly affect costs, quality of life and survival.

The company chose a patient-level simulation to capture the heterogeneity of the patient population. Although we acknowledge that a patient-level approach can account for patient history, we consider that the DICE model is overly complex, and is difficult to interpret and therefore validate. The ERG does not have sufficient access to the model to observe how the different inputs link with each other and, likewise, to the intermediate parameters (e.g., survival curves; utilities) that are calculated during each simulation. In addition, making changes to model parameters, such as using alternative parametric survival curves, is complex and time-consuming. Further critique of the DICE model is presented in the ERG validation section (5.3.2.2) below.

4.2.3 Population

The starting characteristics of the patient populations modelled are shown in Table 24 below (Appendix L Table 26 and Table 38).

Table 24 Patient characteristics used in the cost-utility models

Patient characteristic	Value, IOPD	Value, LOPD
Age at baseline (years)	0.41	48.1
% Male	64%	53%
% CRIM+	55%	NA
Baseline FVC% predicted (%)	NA	61.53
Baseline 6MWT (m)	NA	378.47

NA, not applicable
Source: CS Table 48 and 61

4.2.3.1 IOPD model

The IOPD patient characteristics in the original company's model are based on Kishnani et al. 2007, a 52-week trial that compared ALGLU to a historical control group (no ERT treatment) in IOPD patients[39], while the characteristics reported in the CS (document B Table 61) are based on Broomfield et al.[7] The company clarified that this was an error and submitted an updated model in which the baseline characteristics were from the Broomfield study (clarification question B4). The ERG notes that the Broomfield study is based on UK patient data and is therefore expected to be more representative of the UK IOPD population.

4.2.3.2 LOPD model

The LOPD patient characteristics were based on the COMET trial. Clinical advice to the ERG suggested that these patient characteristics were generally similar to those in UK practice for newly presenting patients but the trial considered patients that are less severe than the general UK patient population with LOPD.

Individual patient data from the COMET trial were used to parameterise a multivariate normal (MVN) distribution into baseline variables, including gender. It is unclear how the characteristics were selected or whether they include all prognostic factors. Then 2,000 simulated patients were generated by draws from the MVN distribution. No justification of the choice of number of draws was provided. A truncated MVN distribution was used to ensure the sampled patients were similar to COMET albeit no details of the truncation were provided. Graphical inspection of mean FVC% predicted appears to show some differences in time since diagnosis and 6MWT (Economic model, technical report, Figures 11-13).[40]

The 2,000 simulated patients were grouped into eight patient profiles stratified by gender, age, and weight. No details are provided on how this grouping takes place. Patient characteristics were then averaged across simulated patients to generate averages for each profile (CS Table 3). There was no coding provided to the ERG to enable us to confirm whether these steps had been applied correctly. The eight profiles are run through the economic model individually and pooled together using weights (proportions of simulated patients in each profile) to calculate an overall ICER for the population. The ERG conducted a scenario applying equal weights to the profiles, but this had a minimal impact on results (see section 6.2.2 below). We consider that it is unclear whether these eight profiles are representative of the COMET population or a real-world UK population. It is also unclear why fewer profiles were not appropriate.

ERG comment on model population

The population used in the LOPD model includes patients with less severe disease than the general UK patient population with LOPD. The profile selection methods appear reasonable but there is a lack of data provided to validate the analysis.

4.2.4 Interventions and comparators

AVAL and ALGLU are both are administered as IV treatments at a standard licensed dose of 20mg/kg qow. Details on the dosage and dosing frequency used is discussed in section 4.2.8.1 of this report. Clinical advice to the ERG is that vast majority of people diagnosed with Pompe disease receive ERT with ALGLU, with supportive care as necessary to their stage of disease progression. Best supportive care without ERT is not standard practice and is therefore not a relevant comparator.

4.2.5 Perspective, time horizon and discounting

The company includes all direct health effects of treatments. Costs are estimated from the NHS and Personal Social Services (PSS) perspective. Costs and QALYs are discounted at 3.5% in the base case and at 0% and 1.5% as scenario analyses (updated results in the document containing the company's clarification responses, Tables 17 and 23). The ERG notes that changing the discount rates makes AVAL more expensive than ALGLU in the LOPD model and the ICER increases to £41,638 per QALY (discount rate of 0%) and £3,260 per QALY (discount rate of 1.5%).

For LOPD, the model outcomes and costs are estimated over a 60-year lifetime horizon in the base case and alternative time horizons of 15 and 30 years were explored in scenario analysis. For IOPD, a 50-year time horizon was applied in the base case to capture the potential long-term costs and outcomes of an extremely severe and life-limiting condition. However, as there is considerable uncertainty around the long-term effects of therapies in this condition, a shorter time horizon of 25 years was considered as a scenario analysis. Changing the time horizon does not have a significant impact on the model results for either LOPD or IOPD (updated results in the company's clarification response, Tables 17 and 23).

ERG comment on perspective, time horizon and discounting

The company adopted the recommended perspective and discounting rates and an appropriate time horizon, which are consistent with the NICE reference case.[41] Although there are some uncertainties with applying a 50-year time horizon to the

IOPD model, the model results do not appear to be very sensitive to using shorter time horizons.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 IOPD model

Given the limited data on treatment effectiveness available for AVAL in the IOPD setting, the ERG considers the results of this cost-utility model should be treated with caution and regarded as illustrative.

The company stated that the Mini-COMET trial showed a benefit for AVAL versus ALGLU in the IOPD population, but there is no long-term data from this study to inform long-term model assumptions.[23] So, the company assumes that AVAL and ALGLU have the same treatment effectiveness. The ERG also considers the data from the Mini-COMET trial to be too limited to draw definitive conclusions in terms of non-inferiority or superiority of AVAL compared to ALGLU (see section 3.2.5.1). This trial included a small sample size of 11 randomized patients and its primary endpoint is safety and tolerability. The baseline characteristics were imbalanced between arms and there is heterogeneity in the dose of ALGLU administered. Moreover, the Mini-COMET trial was restricted to patients previously treated with ALGLU, therefore it is unclear whether the results would apply to ERT naïve patients. Clinical advice to the ERG also suggests that, based on the currently available data, it is not realistic to assume a benefit for AVAL over ALGLU. Therefore, for pragmatic reasons, we assumed that the benefits of AVAL are equivalent to ALGLU for the ERG base case, but we tested this assumption in scenario analysis.

The treatment effectiveness of both AVAL and ALGLU was based on the study by Broomfield et al.[7] which, as mentioned earlier, is a retrospective case-note review of 33 UK IOPD patients treated with ALGLU. The model also has the option to choose to use the Kishnani et al. 2009[15] study, for the treatment effectiveness parameters of the IOPD population. Kishnani et al. 2009[15] report the results of a long-term extension study to the early mentioned 52-week trial of ALGLU reported by Kishnani et al. 2007.[42] The ERG notes that the Broomfield study is UK-based, more recent, includes a bigger sample size (33 vs. 16 patients) and has a longer follow-up (around 4 years versus 2 years) than the extension study. Although it is unclear whether the company conducted a systematic review to identify these two studies, we consider that the Broomfield study is an adequate source to inform

treatment effectiveness of IOPD patients. Clinical advice also suggests that the Broomfield study is appropriate since it refers to UK clinical practice.

The company extrapolated the Kaplan Meier (KM) data for VFS, IVFS and OS from the Broomfield study to estimate long-term disease progression. The company assumed that ventilator status only impacts costs and QALYs and not survival since no deaths were observed in ventilated patients in the study by Broomfield et al.[7] The ERG note that from the 13 patients (39%) that died in the Broomfield study, six required oxygen at baseline and two required long-term invasive ventilation. However, the study did not report ventilation as the cause of death for any of these patients. In the ERG's view, the study sample size is too small to capture the additional risk of death that ventilated patients experience. We do not expect that the assumption that ventilation does not impact survival is likely to affect the model results, given that the company assumed that treatment effectiveness is the same for both AVAL and ALGLU.

The company used separate extrapolation curves for CRIM-positive and CRIM-negative patients to capture the differences in outcomes observed in each patient group. To obtain the model outcomes, the company then calculated the weighted average by multiplying the survival for CRIM-positive and the survival for CRIM-negative patients by the proportion of patients in each status. It is unclear to the ERG why it is necessary to model according to CRIM status, rather than using the total population survival, reported in the study.

The proportional hazards assumption was tested to decide whether a hazard ratio could be applied to the KM curve of the combined population according to the CRIM-status or whether a separate KM curve is needed for each of the CRIM subgroups. The Schoenfeld global test indicated no violation of the proportional hazards assumption for VFS and IVFS, but indicated that it may not hold for OS. Only one test was used for proportional hazards, the ERG would have preferred multiple tests (such as log-log plots or Schoenfeld residuals), and the p-value for the Schoenfeld global test for OS was not reported.

4.2.6.1.1 Ventilation free survival

The company fitted parametric survival distribution curves to the individual patient data from Broomfield et al.[7] The generalised gamma distribution gives the best fit based on Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) for both the VFS and IVFS survival data (CS Appendix L Table 39 and 41). However, the CS notes that this parametric curve lacks face validity since it predicts that many patients will be surviving without

ventilation after the age of 50 years, i.e., around 15% without any ventilation and 25% without invasive ventilation (CS Appendix L Figure 13 and 15). The Weibull distribution was considered by the company to be the most conservative and was applied in their base case. The ERG considers that using a curve that reflects a less optimistic scenario is reasonable, given the lack of long-term evidence and the severity associated with the disease in question. We note that the exponential, log-normal, log-logistic and Gompertz survival distributions also predict low survival at 50 years (around 1% or less). However, these curves predict slightly higher survival at 10 years (around 13% for VFS and 7% for IVFS) than the Weibull (see Table 25 and Table 26 below). Clinical advice to the ERG suggested that the Weibull seems to predict the most reasonable estimates. Therefore, we used the Weibull in the ERG base case and tested the exponential, log-normal, log-logistic and Gompertz in scenario analyses. It is also worth noting that although uncertain, the choice of curve for VFS and IVFS is not critical since it does not change the model results significantly.

The hazard ratio (HR) estimates of starting ventilation or invasive ventilation (vs. no ventilation or non-invasive ventilation, respectively) due to CRIM-positive or CRIM-negative status were as follows: (CS Appendix L Tables 40 and 42):

- VFS HR for CRIM-positive: 0.55
- VFS HR for CRIM-negative: 1.52
- IVFS HR for CRIM-positive: 0.51
- IVFS HR for CRIM-negative: 1.56

Table 25 IOPD model: ventilation free survival (KM data and extrapolations) for the combined population

VFS	2 years	4 years	6 years	10 years	50 years
Broomfield et al. [7] KM	50%	36%	29%	29%	-
Kishnani et al. 2009[15] KM	66.7%	-	-	-	-
Weibull (company base case)	68.9%	39.9%	21%	4.8%	<1%
Exponential	66.7%	44.4%	29.6%	13.2%	<1%
Log-normal	66.7%	40%	25.6%	12.3%	<1%
Log-logistic	66.3%	39.1%	25%	12.8%	1.1%
Generalised gamma	59.4%	43.2%	35.8%	28.3%	13.5%
Gompertz	66.8%	44.3%	29.2%	12.4%	<1%
IOPD, infantile-onset Pompe disease; KM, Kaplan Meier; VFS, ventilation-free survival.					

Table 26 IOPD model: invasive ventilation free survival (KM data and extrapolations) for the combined population

IVFS	2 years	4 years	6 years	10 years	50 years
Broomfield et al.[7] KM	55%	55%	49%	49%	-
Kishnani et al.[15] KM	66.7%	-	-	-	-
Weibull (company base case)	70.9%	34.1%	12.2%	<1%	<1%
Exponential	68.8%	36%	19.6%	6.9%	<1%
Log-normal	68.8%	36%	19.6%	6.9%	<1%
Log-logistic	68.6%	34.5%	18.6%	7.4%	<1%
Generalised gamma	61.6%	44%	36.2%	28.3%	13%
Gompertz	69.8%	36.3%	11%	<1%	0%
IOPD, infantile-onset Pompe disease; KM, Kaplan Meier; IVFS, invasive ventilation free survival.					

4.2.6.1.2 Overall survival

The company considered that the Weibull, log-normal and generalised gamma distributions provided good fits to the observed KM data, and they chose the Weibull to extrapolate OS for CRIM-positive and CRIM-negative patients as it is the most conservative, i.e., least optimistic option.

For the CRIM-positive subgroup, the ERG notes that all curves are good fits of the observed KM data (CS Appendix L Figure 17), but the exponential gives the best fit by AIC and BIC (CS Appendix L Table 43) and in terms of face validity (see Table 27 below). We consider that the Weibull shows an implausibly high number of patients surviving to age 100 years (22.2%). Moreover, the Weibull suggests that the probability of death for IOPD patients declines with age and is lower than the probability of death for the general population after the age 40 years, which we consider unrealistic. Clinical experts to the ERG also indicated that using the Weibull would not be appropriate due to the reasons previously mentioned.

For the CRIM-negative subgroup, the log-normal gives the best fit by AIC and BIC (CS Appendix L Table 69). The Gompertz is the most conservative option, i.e., less optimistic in terms of surviving, but all the distributions predict similar estimates with the exception of the generalised gamma, which predicts better survival than the others (see CS Appendix L Figure 18 and Table 28 below). Based on the above, we used the exponential to extrapolate OS data for both CRIM-positive and CRIM-negative subgroups in the ERG base case.

Table 27 IOPD model: overall survival (KM data and extrapolations) for the CRIM-positive subgroup

OS	2 years	4 years	6 years	10 years	50 years
Broomfield et al.[7] KM	86.2%	86.2%	75.4%	75.4%	-
Exponential (ERG base case)	93.2%	86.9%	78.6%	70.3%	17.2%
Weibull (company base case)	90.1%	84.6%	78.6%	73.2%	39.1%
CRIM, cross-reactive immunological material; ERG, Evidence Review Group; IOPD, infantile-onset Pompe disease; KM, Kaplan Meier; OS, overall survival.					

Table 28 IOPD model: overall survival (KM data and extrapolations) for the CRIM-negative subgroup

OS	2 years	4 years	6 years	10 years	50 years
Broomfield et al.[7] KM	41.6%	41.6%	0%	0%	-
Exponential (ERG base case)	50.8%	25.8%	9.9%	3%	<1%
Weibull (company base case)	53.1%	19.4%	3%	3%	<1%
Log-normal	48.3%	18.9%	6%	2%	<1%
Log-logistic	46.1%	17.8%	7%	3%	<1%
Generalised gamma	44.8%	24.7%	15.4%	11%	2.6%
Gompertz	53.1%	22.5%	3.8%	<1%	0%
CRIM, cross-reactive immunological material; ERG, Evidence Review Group; IOPD, infantile-onset Pompe disease; KM, Kaplan Meier; OS, overall survival.					

4.2.6.1.3 Wheelchair use

Wheelchair use was modelled as the percentage of patients not ambulatory in the study by Broomfield et al.[7] The model assumes that 30% of non-ventilated or non-invasive ventilated infants (0-2 years) can walk as well as 27% of non-ventilated or non-invasive ventilated children and adults (2+ years).

ERG comment on treatment effectiveness and extrapolation (IOPD)

It is uncertain to what extent AVAL is superior or inferior compared to ALGLU as the Mini-COMET trial is limited by its small sample size. The company's assumption is that the two drugs are similar in effects, although this is not informed by empirical data. The ERG kept the company's assumption of equivalent clinical benefits between AVAL and ALGLU in our base case but explored this uncertainty in scenario analysis by assuming that AVAL is more effective than ALGLU. Based on the limited data available, we consider that the Weibull is an adequate choice to extrapolate

VFS and IVFS as the company did, but that the exponential is the most plausible parametric curve to extrapolate OS long-term data.

4.2.6.2 LOPD model

The disease course of LOPD was captured through changes in FVC% predicted and 6MWT. The company assumed that there is no improvement in these parameter values during the first year of treatment. After this, the COMET trial results at week 49 informed the change from baseline in FVC% predicted and 6MWT.[43] The improvement in FVC% predicted was 2.89% for AVAL and 0.46% for ALGLU while the improvement in 6MWT was 32.21m for AVAL and 2.19m for ALGLU (CS Appendix L Table 4).

[redacted][27][redacted]. After this period, FVC% predicted and 6MWT were assumed to decline linearly with time at the same rate for AVAL and AGLU. The mean values of FVC% predicted from the Pompe registry[37] at two and nine years, and of 6MWT at four and nine years, after ERT initiation were used to calculate the annual decline rate for AVAL and ALGLU [redacted]). Figure 3 and Figure 4 below show the trajectory over time for FVC% predicted and 6MWT used in the company's model.

Figure 3 FVC% predicted trajectory over time

FVC, forced vital capacity
Source: CS Appendix L Figure 3.

Figure 4 6MWT trajectory over time
6MWT, 6-minute walk test
Source: CS Appendix L Figure 4.

The Pompe Registry is a worldwide program created in 2001 to collect information about the treatment of Pompe disease. It is the largest patient registry of Pompe disease and is sponsored and administered by Sanofi Genzyme.[37] The ERG notes that we do not have access to the Pompe registry report (see clarification question B18) but [redacted]. The NEO-EXT is a phase 2 ongoing single-arm study, with a small sample size of 19 patients and a primary endpoint of safety and tolerability of AVAL. It reports FVC% predicted and 6MWT results at week 312 (CS Tables 25 and 27). We note that data for only seven patients are available for week 104 and for only two for week 312.

The ERG considers that no conclusions can be drawn on the stability of the treatment effect for AVAL based on this data. For the ERG base case, we assumed the [redacted] duration of treatment effect between arms: [redacted] for FVC% predicted and [redacted] for 6MWT. We varied these numbers in scenario analysis.

For patients who discontinue treatment with ERT therapies and therefore receive no further treatment, the annual decline rate in FVC% predicted was based on the study by van der Beek et al.[38] This is an observational study which assessed the natural progression of Pompe disease in 94 Dutch patients who had not previously received treatment with ERT therapies (average follow up of 1.6 years). The decline rate used in the company's base case (-1.04% per year) is based on the annual change observed in FVC measured in a sitting position. The company conducted a scenario in which they applied a faster decline

rate of -1.248% per year (CS Appendix L Table 35). Due to lack of data, the decline rate in the 6MWT (-7.940m) was assumed to be the same for patients on no treatment as for patients treated with AVAL and ALGLU. We agree that there is little evidence to inform the decline rate for no treatment but consider that using the same rate across therapies and no treatment lacks face validity. Therefore, a faster decline rate in 6MWT for no treatment was assumed in the ERG base case (-9.528m per year). We note that this same faster rate was already explored by the company in a scenario analysis (CS Appendix L Table 35).

The model uses threshold values of FVC% predicted and 6MWT over which patients move to the ventilation and wheelchair use health states. The threshold to start ventilation and wheelchair use was based on the Pompe registry.[37] A log-normal distribution was fitted to the FVC% and 6MWT data corresponding to the initiation of non-invasive ventilation and wheelchair use. For the threshold for invasive ventilation, a uniform distribution was fitted to the upper three quarters of FVC% predicted values and a lognormal distribution was fitted to the remaining lower quarter. The CS states that two distributions were fitted because the values of FVC% predicted at which patients start invasive ventilation were concentrated over a very narrow range of values (between 32% and 38%) with a tail of lower values (between 16% and 32%). For each simulation, values were sampled from the respective distribution to generate these thresholds. The mean values of the thresholds that has been set for patients to enter the most serious health states were the following: [redacted] and [redacted] in FVC% predicted for non-invasive ventilation and invasive ventilation, respectively, and [redacted] in 6MWT for wheelchair use. The ERG has been unable to verify the company's approach due to lack of access to the Pompe registry dataset. However, clinical advice to the ERG suggested that the threshold to start using wheelchair is higher than what is expected in clinical practice. Therefore, we conducted some analyses in the company's base case to explore the impact of different wheelchair thresholds in the model results (see section 6.1 below).

4.2.6.2.1 Overall survival

Overall survival was assumed to be equivalent between patients taking AVAL and ALGLU, but different versus no treatment. The minimum value between disease-specific mortality and general population mortality was used to model patient mortality.

The general population mortality, based on the UK lifetables 2016-2018,[44] was modelled using the Gompertz parametric curve. This is adequate since the Gompertz is commonly used to model the general population mortality. The OS data for patients receiving no treatment was based on the study of Gungor et al. 2011[45]. The Gungor study is an

international observational study that enrolled 268 LOPD patients prior to treatment with ERT therapies (median follow up of 2.3 years).

The company provided more details on the fit of the different parametric curves to the KM data of Gungor et al. 2011 as part of their response to the clarification questions (clarification question B7). The exponential, log-normal and log-logistic distributions were considered inappropriate by the company for two reasons: they do not allow for an increasing hazard over time, and they predicted curves deemed too optimistic compared to the expected survival of Pompe disease patients with no treatment. The generalised gamma has the lowest AIC and BIC. The Gompertz was selected for the company's base case on the basis that it is the distribution with the most plausible fit. The ERG notes that the generalised gamma predicts similar survival estimates, and also fits the observed KM data reasonably well (see Table 29 below). In the absence of long-term data and considering the severity of the disease, we agree that selecting the curves that give the least optimistic survival is a reasonable approach. We agree with the company's base case and use the Gompertz distribution to model OS. It is unlikely that the generalised gamma leads to significantly different results and the model is also not set-up to use this distribution.

Table 29 LOPD model: overall survival (KM data and extrapolations) for no treatment

OS	1 year	5 years	10 years	30 years	60 years
Gungor et al. 2011[45]	100%	98%	82%	40%	-
Gompertz (company's base case)	99%	96%	89%	39%	<1%
Generalised gamma	99.6%	96%	88%	38%	0%
Exponential	98%	90%	81%	54%	29%
Weibull	99.9%	97%	90%	42%	4.2%
Log-logistic	99.9%	97%	89%	45%	16%
Log-normal	100%	97%	88%	47%	20%
LOPD, late-onset Pompe disease; KM, Kaplan Meier; OS, overall survival.					

Treatment with ERT therapies was assumed to benefit survival independently of slowing disease progression. As insufficient data is available for AVAL, the company assumed that OS was the same for both arms. The study by Gungor et al. 2013[46] was an international observational study that followed 283 LOPD patients (72% treated with ERT therapies and 28% non-treated), demonstrated a positive effect of ERT on survival and reported a HR for ALGLU vs. no treatment of 0.41.[46] The company used this HR to model the OS for both ERT therapies vs. no treatment.

The model assumed that progression to ventilation and wheelchair impact survival and adjusted the baseline OS by applying additional HRs (see below) according to treatment and disease progression. These were based on the Pompe registry data.[37]

- Additional HR of survival for non-invasive ventilation: [redacted]
- Additional HR of survival for invasive ventilation: [redacted]
- Additional HR of survival for wheelchair dependency: [redacted]

The ERG consider that AVAL is likely to provide a survival advantage compared to ALGLU for LOPD patients, given that it showed improvement in short-term clinical parameters (FVC% predicted and 6MWT). This is not the case for IOPD patients, in which the data is too uncertain to predict a benefit of AVAL over ALGLU (see section 4.2.6.1 for further details).

The impact of treatment in extending survival by slowing disease progression is already being captured in the model to some extent by adjusting the OS for the impact of ventilation and wheelchair use (see the HRs that were used above). The model results show an incremental lifetime survival of around one month for AVAL over ALGLU. It is uncertain whether an additional survival benefit, independent of that accrued by slowing disease progression, should be considered. The long-term data is limited, but we expect a correlation between any improvements in FVC% predicted and 6MWT and the corresponding benefit in long-term survival. Table 30 and Table 31 show that the improvement in FVC% predicted and 6MWT of AVAL versus ALGLU at week 49 (based on the COMET trial[25]) is quite similar to that of ALGLU versus placebo at week 78 (based on the randomized, double-blind, placebo-controlled trial by van der Ploeg et al. 2010[47] that assessed the efficacy of ALGLU in 90 patients with LOPD. We note that it is not possible to predict an accurate survival benefit based on the changes in FVC% predicted and 6MWT observed. But as there is a similar relative effect between AVAL versus ALGLU as observed for ALGLU versus placebo, this leads us to suspect that the increase in survival in both cases would follow a similar pattern. We therefore consider the OS of AVAL to be more than one month greater than for ALGLU. We assume that AVAL would have an incremental lifetime survival of three months compared to ALGU in our base case and apply a HR of AVAL versus ALGLU of 0.85. We changed this assumption in scenario analysis and explored both a smaller and bigger treatment benefit of AVAL over ALGLU in terms of overall survival. Clinical advice to the ERG highlights the uncertainty of predicting the additional benefit of AVAL versus ALGLU without head-to-head long-term evidence.

Table 30 Change from baseline in FVC% predicted and 6MWT for ALGLU vs. no treatment

Change from baseline at week 78	ALGLU	Placebo	Relative effect
FVC% predicted	1.25 ± 5.55	-2.3 ± 4.33	+3.55
6MWT	26.08 ± 64.41	-4.87 ± 45.24	+30.95
Source: van der Ploeg et al. 2010 [47] 6MWT, 6-minute walk test; ALGLU, alglucosidase alfa; FVC, forced vital capacity.			

Table 31 Change from baseline in FVC% predicted and 6MWT for AVAL vs. ALGLU

Change from baseline at week 49	AVAL	ALGLU	Relative effect
FVC% predicted	2.89	0.46	+2.43
6MWT	32.21	2.19	+30.01
Source: COMET trial[25] 6MWT, 6-minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC, forced vital capacity.			

4.2.6.2.2 Treatment discontinuation

The all-cause discontinuation rate applied in the model was based on a study that analysed data on treatment discontinuation from patients that participated in a previous prospective cohort study including all patients with Pompe disease in the Netherlands that started treatment with ERT therapies in 2004 and discontinue treatment until January 2017 (n= 24 patients).[48] The all-cause discontinuation rate applied in the model, regardless of treatment, was 0.76% per year.

A rate of 0.052 per year was also applied to capture the adverse events that led to discontinuation. In addition, it is stated in the CS that a patient can also discontinue treatment if the patient starts invasive ventilation.

ERG comment on treatment effectiveness and extrapolation (LOPD)

The difference in treatment effectiveness (FVC%, 6MWT) between AVAL and ALGLU in the first year was based on the COMET trial, which is adequate in the ERG's view. However, more long-term data is required to determine whether the initial gains achieved by the patients treated with AVAL will persist for longer than the effect observed for patients treated with ALGLU. It is also uncertain how the initial gains of AVAL reported in the COMET trial affect the long-term survival of LOPD patients. The ERG expects a greater survival benefit than assumed in the company's base case and therefore applied a HR of 0.85 for the OS of AVAL vs. ALGLU and varied this assumption in scenario analysis.

4.2.6.3 Adverse events

The company did not model the occurrence of adverse events in either IOPD and LOPD models. The ERG notes that no significant differences in serious adverse events were observed between AVAL and ALGLU in the Mini-COMET and COMET trial (see section 3.2.5.6). The clinicians advising the ERG suggested that the safety profile of AVAL is expected to be similar to ALGLU and that there is some indication of less immune reactions with AVAL than ALGLU in the IOPD population, but there is no strong evidence to support this assumption.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review to identify HRQoL studies for patients with Pompe disease and their caregivers. The review is described in Appendix D, including the search strategy, databases searched and inclusion and exclusion criteria. The selection criteria used for the HRQoL studies is shown in Appendix D Table 22. Inclusion criteria included HRQoL / PROs measured using both generic and disease-specific instruments (EQ-5D, EQ-5D, SF-36, SF-12, SF-6D etc.), utility / disutility values and mapping algorithms. The Appendix does not report the number of HRQoL studies identified. Studies reporting the key outcomes of interest (EQ-5D, SF-36 or PDSS/PDIS) are summarised in CS Table 13 and include 14 studies. Of these studies, the study by Simon et al[1] is used for the utilities for the IOPD model and is described in more detail below. The ERG considers the company's review of HRQoL is adequate and has identified all relevant studies.

4.2.7.2 Study-based health related quality of life

The COMET trial collected EQ-5D 5L values for patients at baseline and 49 weeks. The CS .does not provide any further information about data collection. The company provided mean EQ-5D-5L index values of the COMET at all time points in their response to clarification question A8.

Data from the Pompe Registry was used for the disease health states in the economic model as these data cover a broader spectrum of disease severity than those from the COMET trial. The registry collected SF-36 data for patients, and these were mapped to EQ-5D using the mapping algorithm from Rowen et al.[49] The baseline characteristics of those patients

included in the utility analysis are shown in Appendix L Table 10. The utility values from the Pompe Registry analysis are shown in Table 32 (CS Appendix L Table 15).

The CS comments that previous analyses have found that neither the EQ-5D nor the SF-6D[50] (Appendix L p25) are sensitive enough to capture the symptoms of Pompe disease and therefore the analysis on the Pompe Registry data may not capture all important aspects of HRQoL in this population. The ERG further notes that there will be uncertainties in the utility data due to the mapping process from SF-36 to EQ-5D.

4.2.7.3 HRQoL utility estimates used in the cost-effectiveness analyses

IOPD model

The IOPD model uses health state utility values taken from Simon et al[1] for patients and caregivers. Simon et al is a US study that used the time-trade off method in the general population (without Pompe disease) (n=862) to estimate utility values for infants (6 months old), children (8 years old) and adults (≥18 years old). Pompe disease was defined as mild, moderate or severe and the company assumes that these categories are synonymous with the health states for not ventilation dependent, non-invasive ventilation dependent and invasive ventilation dependent respectively.

No data were available for infants with mild or moderate symptoms. Further the value for children with moderate symptoms was considered counterintuitive and was not used. The assumptions used to derive these values are described in Appendix L 4.3.4 and the utility values used in the IOPD model are shown in Appendix L Table 46.

The ERG does not agree with utilities values used for IOPD.

- Firstly, the values used for adults are inconsistent between the IOPD and LOPD models. We suggest the utility values for adults in the IOPD analysis should be those from the Pompe registry (as used in the LOPD model).
- Secondly, the Simon et al. study[1] does not meet the NICE reference case, as the utilities are not estimated from patients with Pompe disease, but from members of the general population
- Thirdly, the disutilities are estimated using several assumptions due to missing or counterintuitive values.

The ERG's preferred approach is to use the same disutilities for infants and children as for adults. The calculated utility values using the same disutilities applied to the general population utility for each age group is shown in Table 33.

Caregiver disutilities were included for children assuming all patients had 1.72 caregivers. No caregiver disutility was assumed for adults. There were no data reported for the infant age group for mild and moderate symptoms and these disutilities were derived using the same relative impact as was seen in children. The moderate symptoms disutility for children appeared to be counterintuitive and so was excluded. The caregiver disutilities are shown in Appendix L Table 47.

The ERG considers that it is inconsistent to use caregivers' disutility in the LOPD model for adults, but not in the IOPD model, therefore we suggest that caregivers disutility should also be included for adults in the IOPD model. The ERG's preferred estimates for caregiver disutilities are shown in Table 34.

LOPD model

The baseline utility for each patient profile is assigned based on the mean baseline EQ-5D 5L values observed for that profile in the COMET trial (Appendix L Table 3). The profile's utility value is adjusted according to a utility gain for treatment and disutility for the health states. The utility gain due to treatment is based on the COMET trial at the end of 49 weeks and is applied after one year. A utility gain was applied of [redacted]. Disutilities for the health states are taken from the Pompe Registry analysis and are shown in Table 32. The utility value for the ventilator and wheelchair health state in the Pompe Registry analysis appeared counterintuitive and this may be due to small sample size. For this health state, it was assumed that the disutility for patients using both a ventilator and a wheelchair was equivalent to the sum of the disutilities applied for each disability.

The ERG notes that the preferred method to estimate utilities in composite health states is using the multiplicative method(NICE DSU TSD 12, Ara et al[51]), rather than the additive method. However, due to the aforementioned model programming issues (see Section 4.2.2) the ERG is unclear how this should be coded into the company model. We therefore we have not included this change in the ERG base case.

Table 32 Utilities based on the Pompe Registry analysis and calculated disutilities by disease state

Health state	Mean Registry utility	Calculated disutility
Not dependent on ventilator or wheelchair	[redacted]	–
Non-invasive ventilator	[redacted]	[redacted]
Wheelchair-dependent	[redacted]	[redacted]
Invasive ventilator-dependent	[redacted]	[redacted]
Ventilator & wheelchair	–	*

*For patients on both a ventilator and wheelchair, the individual disutilities for the ventilator and wheelchair states are additively applied.
Source: CS Appendix L Table 15

Caregiver disutilities were also included in the model and these values were obtained from Simon et al.[1] The caregiver disutilities reported for the mild and moderate states was averaged (0.117) for use for patients not dependent on ventilator or wheelchair. All other states were assumed to have the disutility of the severe health state of 0.131 (Appendix L Table 17). Patients are assumed to have a single caregiver in each state.

The ERG is unclear why the disutility for patients not dependent on ventilator or wheelchair has been calculated by averaging the mild and moderate states as the mild state is assumed to be equivalent to this health state. Therefore, we suggest that the values from the mild state should be used for the not dependent on ventilator or wheelchair state and the moderate state should be used for the non-invasive ventilation dependent health state.

Table 33 Summary of LOPD and IOPD utility values, ERG preferred values

Health state	Infant, age 1 year	Child, age 8 years	Adult, age 45 years	Disutility vs general population
General population utility	1	0.9875	0.8639	-
Not dependent on ventilator / wheelchair	0.7881	0.7756	0.652	-0.212
Non-invasive ventilator	0.7501	0.7376	0.614	-0.250
Invasive ventilator dependent	0.6811	0.6686	0.545	-0.319
Wheelchair use	-	-	0.504	-0.360

Wheelchair + ventilator	-	-	0.397	-0.467

Table 34 Summary of LOPD and IOPD caregiver disutility values, ERG preferred values

Health state	Infant	Child	Adult
Not dependent on ventilator / wheelchair	-0.099	-0.072	-0.072
Non-invasive ventilator	-0.139	-0.102	-0.102
Invasive ventilator dependent	-0.180	-0.131	-0.131
Wheelchair use	-	-	-0.131
Wheelchair + ventilator	-	-	-0.131

Source: Appendix L Table 15 and Table 47

Age-related disutility

Age-related disutility is included in the IOPD model (although it does not appear to be described in the CS). At each timepoint the utility values are multiplied by the general population utility value. The ERG considers there is an incorrect implementation of the age-adjusted utility and this will result in an underestimation of the utility value, for example for the not dependent on ventilator and wheelchair state at age 45, the utility value used is 0.8639 x 0.652 = 0.563. The correct implementation of age-adjusted utilities would use the general population utilities adjusted by disutilities for the health states at each timepoint. The ERG considers it is better to exclude the age-adjusted utility in this case, given the large uncertainty around the utility estimates.

ERG comment on HRQoL

The ERG has several concerns with the utility values used in the company's cost utility models. The main source of utilities used in the IOPD model uses values from a study[1] that did not include patients with Pompe disease. There are inconsistencies between the utility values for adult patients and caregivers in the IOPD and LOPD models. Furthermore, the adjustment made in the IOPD model to incorporate age-adjusted utility has not been implemented correctly. The ERG addresses these concerns by using the disutilities from Pompe registry for IOPD and making alternative assumptions for the disutilities for the caregivers for LOPD in the ERG base case analyses (section 6.2.1).

4.2.8 Resources and costs

The cost-comparison models do not include health-state costs. The health state costs reported below are included in the cost-utility models only.

4.2.8.1 Drug acquisition

AVAL is administered IV at a dose of 20 mg/kg of body weight once every two weeks for patients with LOPD and IOPD. AVAL is available in single-use vials containing 100mg AVAL. The list price of AVAL is [redacted]. The treatment is available at a simple price discount to the NHS (Patient Access Scheme). The PAS price for AVAL is [redacted] (Table 35, CS Table 45).
[redacted].

ALGLU is administered at a dose of 20/mg/kg of body weight once every two weeks for patients with LOPD and IOPD. ALGLU is available in single-use vials containing 50mg ALGLU. The list price per vial of ALGLU is £356.06 (Table 35, CS Table 45).

The company state that doses are generally rounded to the whole vial to obtain the correct dose as an average of two infusions. However, the ERG notes that the model calculations include vial sharing, i.e. no rounding to the whole vial. We view this as incorrect, and based on clinical advice, suggest that the cost calculation should be based on no vial sharing and number of vials should be round up to the whole vial. The ERG corrects this in the model, see section 5.3.3.

Table 35 Acquisition cost of AVAL and ALGLU for Pompe disease

Treatment	Unit Cost	Unit Strength	Package Size	Dose	Frequency per 4 weeks	Compliance
AVAL	[redacted]	100 mg	1 vial	20 mg/kg	2	100%
ALGLU	£356.06	50 mg	1 vial	20 mg/kg	2	100%

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; Source: CS Table 45

For IOPD, there is an increased dosing for AGLU in the first 12 weeks, where ALGU is administered weekly, rather than every other week. The company states that this is based on clinical advice received. The ERG notes that the licenced dose for AGLU is 20 mg/kg every two weeks, however clinical experts advised that the higher dose would be preferred. We consider that the dosage of AVAL should be consistent with the dosage of AGLU, as our experts did not consider that a lower dosage of AVAL than AGLU would be used in clinical practice (see ERG analyses in section 6.2).

4.2.8.2 Drug administration

For both AGLU and AVAL, treatment administration was assumed to occur in an outpatient hospital setting for the first three infusions and then at home thereafter. The cost of home administration included the cost of a community nurse who reconstitutes the drug and

administers it. Some patients ([redacted]) are considered independent or semi-independent and have a lower cost for the duration of the reconstitution of the treatments only. An overview of the cost and distribution of administrations are presented in CS Table 46 and Table 47. The reconstitution duration is assumed to be [redacted]. As the vial size of AVAL is twice that of ALGLU, there will be half the number of vials for reconstitution with AVAL. The infusion time is 3.7 hours.

The ERG notes that there are mistakes in the calculation of the administration costs in the IOPD model in the first 3 cycles. We correct these calculations, as discussed in section 5.3.3. In response to clarification question B14, the company updated the hourly cost of a nurse to £44/hour, based on the most recent cost of a Band 5 community nurse (PSSRU 2021).

4.2.8.3 Health state costs

Health state costs were calculated as one-off state costs and annual costs. In addition, there were disease monitoring costs and treatment-related monitoring costs associated with antibody testing.

4.2.8.3.1 Ventilation-related costs

The one-off costs associated with invasive ventilation represents a 4 month inpatient stay in a high-dependency unit (at a cost of £800 per day).[52] The cost was inflated from 2006 to 2020 prices using the PSSRU pay and prices index.[53] The annual costs for non-invasive and invasive ventilation for adults and children were taken from Noyes et al[52] and Dretzke et al[54] respectively. The invasive ventilation costs were assumed to be the same for adults and children. Noyes et al estimated the costs associated with 35 ventilator-dependent children and young people (age < 19 years) in UK. Dretzke et al[54] estimated the cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease. The ventilation health care costs are shown in Table 36 (CS Appendix L Table 22 and 51).

In response to clarification question B12, B15 and B16, the company updated the costs for the outpatient assessment, hoist, and the health state costs for non-invasive and invasive ventilation. The updated costs are shown in Table 36. The updated values were calculated with the updated PSSRU[53] published in December 2021.

Table 36 Health state costs for ventilation and wheelchair states

Description	One-off cost	Annual cost	Source
Ventilation			
Non-invasive ventilation: home, paediatric	–	£24,460.56[a]	Noyes 2006[52]
Non-invasive ventilation: home, adults	£4,878.20 [a]	£1,908.19 [a]	Dretzke 2015[54]
Invasive ventilation: home	£133,277 [a]	£142,790 [a]	Noyes 2006[52]
Ventilation-related costs			
Outpatient assessment, paediatric	£217[a]	–	Dretzke 2015[54]
Outpatient assessment, adults	£181[a]	–	NHS reference costs (2019/20) [11]
Wheelchair (powered)			
Paediatric	£ 1,375.63	£ 645.89	NHS reference costs WC08 and WC10 (2019/20) [11]
Adult	£ 1,306.48	£ 425.29	
Wheelchair-related cost			
Home adjustments	£30,000.00	–	Maximum disability facilities grant in England (2020) [55]
Hoist	£826.48	–	NRS Healthcare, sunlift mini mobile hoist [56]

Abbreviations: IOPD, infantile-onset Pompe disease; NHS, National Health Service.
[a] Value updated in company clarification response document (B15,,B16)
Source: CS Appendix L Table 51 and 52.

Wheelchair costs

Annual wheelchair maintenance costs were estimated, assuming a replacement wheelchair every three years for children and every five years for adults. A one-off cost for home adjustments, equal to the maximum disability facilities grant in England, and a hoist were included. Health state costs for patients in the wheelchair dependent state are shown in Table 36 (CS Appendix L Table 52).

Disease related monitoring and management

Disease related monitoring included pulmonary function, respiratory muscle strength, muscle strength and sleep study. Management costs included those for outpatient visits (day case GP visits), other provider visits (nurse and other therapists). Disease related costs were taken from an analysis of the Clinical Practice Research Datalink (CPRD)[57] and are presented in Table 37 (CS Appendix L Table 53). The CPRD is an observational study that linked primary care records to Hospital Episode Statistics (HES) for a subset of UK patients wtth Pompe disease from 2000-2019. For Pompe disease, a total of 108 patients, including

12 IOPD; and 96 LOPD patients were included in the analyses. Costs were not assumed to differ by health state. In response to clarification question B13, the company updated the values used for LOPD patients. The ERG notes that the values used for IOPD do not match those reported in the CPRD analysis. We correct these values in section 5.3.3.

Table 37 Disease-related costs from the CPRD analysis

Cost category	Cost per patient year, IOPD	Cost per patient year, IOPD[b]	Cost per patient year, LOPD[a]
Elective and day-case	£798.42	£553	£338
Non-elective	£4,701.84	£3616	£386
ITU	£3,083.14	£2,585	£65
Outpatient	£223.58	£93	£217
A&E	£90.99	£51	£49
Primary care consultations	£511.49	£364	£270
GP prescribing	£3,678.75	£4618	£615
Total	**£13,088**	**£11,880**	**£2,186**

Abbreviations: A&E, accident and emergency; GP, general practitioner; ITU CPRD Clinical Practice Research Datalink;
[a] Values updated in company clarification response (B13).
[b] Values reported in the CPRD analysis
Source: CS Appendix L Table 53

Antibody testing was applied four times a year in the first two years of treatment and then twice a year thereafter.

ERG comment on resources and costs

In general, the company's approach to costing is reasonable. We have concerns with regard to the difference in dosing assumed between AGLU and AVAL in the first 12 weeks and the assumption of vial sharing included in the model. In addition, the ERG identified several discrepancies in the cost input parameters and the company corrected these values in their update submitted for clarification response.

5 COST EFFECTIVENESS RESULTS

The results presented in this section are for the company's cost utility models for IOPD and LOPD. The results of the cost minimisation models are presented in Appendix 3.

5.1 Company's cost effectiveness results

The company's cost-effectiveness results for IOPD are presented below in section 5.1.1 and for LOPD in section 5.1.2. They include a confidential PAS discount price for AVAL and the list price for ALGLU, as ALGLU does not have a PAS discount.

5.1.1 IOPD model

CS Appendix L, section L.4.6.1 reports the company's base case pairwise results for AVAL versus ALGLU for the IOPD population. As the company assumes equivalent clinical effectiveness for AVAL and ALGLU, the results show no difference in QALYs and LYs. The results show that AVAL is a [redacted] therapy compared to ALGLU due to the reduced number of doses in the initial phase and the [redacted] (CS Appendix L Table 57).

As part of the clarification responses, the company submitted an updated base case with changes in the following parameters:

- Baseline characteristics based on the study by Broomfield et al.[7] (clarification question B4),
- Cost of a nurse per hour (clarification question B14),
- Cost of the hoist (clarification question B15),
- Non-invasive and invasive ventilator costs (clarification question B16)

The updated results also show that AVAL is [redacted], yielding a [redacted] mean cost of [redacted] versus ALGLU (see Table 14 in the clarification responses document and Table 38 below).

Table 38 Company's updated base-case results for IOPD (discounted, PAS price for AVAL)

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental, AVAL vs. ALGLU			
				Costs (£)	LY	QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: reproduced from company clarification responses, Table 14.
ICER, incremental cost-effectiveness ratio; LY, life-years; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALYs, quality-adjusted life years.

5.1.2 LOPD model

CS Appendix L, section L.3.6.1 reports the company's base case pairwise results for AVAL versus ALGLU for the LOPD population.

As part of the clarification responses, the company submitted an updated base case with changes in the following parameters:

- Cost of outpatient administration (clarification question B12)
- Disease-related costs (clarification question B13)
- The cost of a nurse per hour (clarification question B14)
- Wheelchair related one-off cost (hoist, clarification question B15)
- Cost of non-invasive and invasive ventilation (clarification question B16)

The updated results show that AVAL yields [redacted] versus ALGLU (see Table 18 in the clarification responses document and Table 39 below).

Table 39 Company's base case results for the LOPD population (discounted, PAS price for AVAL)

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental, AVAL vs.			
				Costs (£)	LY	QALYs	ICER (£/QALY)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: reproduced from company clarification responses, Table 18.
ICER, incremental cost-effectiveness ratio; LY, life-years; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALYs, quality-adjusted life years.

5.2 Company's sensitivity analyses

5.2.1 Univariate sensitivity analyses

5.2.1.1 IOPD model

CS Appendix L, section L.4.7. reports the IOPD deterministic sensitivity analysis (DSA) results. The list of parameters considered in the DSA includes:

- Settings: discount rate costs, time horizon and patient weight.
- Treatment effect and disease progression: the parameters of the distribution curves and the hazard ratio for the overall survival, ventilator-free survival and invasive ventilator-free survival.
- Proportion of patients ambulatory and age of ambulation
- Acquisition and administration costs
- Other costs
- Utilities

The DSA varies the input parameters between -20% to +20%. The ERG consider that the main parameters were varied in the DSA, but we prefer that the parameters were varied

within their confidence intervals (CI) where possible; for example, the age of ambulation (see Broomfield et al. 2016[7]) and the parameters of the distribution functions fitted to the survival curves.

The DSA results for the IOPD population are presented as a tornado diagram in CS Appendix L, Figure 19. The figure shows that the unit cost of the interventions (AVAL and ALGLU) and the HR for OS and IVFS are the key drivers of the model results. The HR for VFS also impacts the model results, but to a lesser extent. The updated DSA, submitted as part of the company's clarification responses (company clarification response, Figure 6), shows the same key drivers of the model.

5.2.1.2 LOPD model

CS Appendix L Table 33 lists the parameters included in the LOPD univariate sensitivity analysis with the ranges used. The ranges were varied using the 95% CI, where available. Where ranges for short-term treatment effects were derived from the COMET trial (%FVC predicted and 6MWT), the lower bound of the CI was adjusted to zero to avoid clinically implausible values. In the absence of data to inform 95% CIs, parameters were varied by +/- 20%. The ERG considers this reasonable and standard practice for testing the sensitivity of individual parameters.

Some of the parameters listed in CS Appendix L Table 26 were not varied in the univariate sensitivity analysis. These are the following:

- Rate of annual decline rate of FVC% predicted and 6MWT,
- The thresholds at which patients start using ventilation and wheelchair,
- The intercept and shape parameters of the OS curve of no treatment,
- Number of caregivers.

Of the parameters above which were not varied in the univariate sensitivity analysis, the rate of annual decline rate of FVC% predicted and 6MWT, and the intercept and shape of the OS curve were varied in the PSA or in scenario analyses.

The LOPD model considers a simulated population represented by 8 profiles. As mentioned in section 4.2.3 above, although the profile selection methods appear reasonable, the company did not provide enough data to validate if the analysis has been correctly performed and applied in the model. In that regard, the ERG consider that the parameters associated with the profiles' generation should have been varied in sensitivity analysis in

order to test their influence on the model results. The ERG conducted a scenario analysis applying equal weights to all the profiles (see section 6.2.2 below).

The univariate sensitivity analysis results for the LOPD population are presented as a tornado diagram in CS Appendix L Figure 6. The figure shows that treatment discontinuation and adverse effects leading to discontinuation are the key drivers of the model results. The mortality adjusted HRs (due to wheelchair and non-invasive ventilation use), utility gain, 6MWT treatment effect for AVAL, and mortality HR for ALGLU versus no treatment also impact the model results, but to a lesser extent.

Although some of the costs changed in the updated company's model, the results of the univariate sensitivity analysis are similar to the original model (company clarification response Figure 7).

5.2.2 Scenario analyses

5.2.2.1 IOPD model

The company explores a range of scenarios to test structural and methodological uncertainty, which are reported in CS Appendix L, section L.4.7.

After the company provided some clarification (see clarification questions B8 and B9), the ERG was able to validate all the scenarios against those reported in the CS. We consider the scenarios explored by the company to be reasonable, but we would also like to have seen a scenario exploring alternate assumptions for OS for AVAL and ALGLU and therefore we tested this in the ERG analyses (see section 6.2.1). A set of scenarios exploring different parametric distributions for VFS and IVFS curves; and a scenario with no vial sharing were also tested as part of the ERG analyses.

CS Appendix L, Table 60 reports the results of the scenario analyses for the IOPD population. The updated results are in the company clarification response, Table 17.
All scenarios show that AVAL is [redacted] compared to ALGLU. The scenarios where the discount rate is set to 0% and the one that considers only the CRIM-positive population have the greatest impact in the model results. The remaining scenarios have less impact in the incremental costs.

5.2.2.2 LOPD model

The scenario analyses conducted by the company to test structural and methodological uncertainty are reported in CS Appendix L, section L.3.7.3.

We consider that the company could have explored more scenarios. As suggested above, we would like to have seen how the different profiles or profile weights affect the model results. In addition, we also consider that scenarios testing a wider range of parametric distributions would also be appropriate. Therefore, the ERG explored the impact of the profile weights in the model results. We have not conducted scenarios using different parametric distributions as the model settings currently implemented does not allow it. We have also extended the range of scenario analyses to other parameters as part of the ERG analyses (see section 6.2.2): different plateau durations of the treatment effect for AVAL and ALGLU; and different OS HRs between AVAL and ALGLU.

CS Appendix L, Table 35, reports the results of the scenario analyses for the LOPD population. The ERG was not able to replicate all the scenarios and therefore asked the company to provide some clarifications. As part of their clarification responses, the company submitted an updated model and clarified the changes to the model that were needed to replicate these scenarios. The ERG was then able to replicate and validate all the scenarios against the CS. The updated model showed some differences in the cost values, but the scenario analyses results were similar to the original model (company clarification response, Table 23).

AVAL was dominant in all the scenarios tested, i.e. more effective and cheaper, with the exception of the following scenarios:

- Discount rates of 0% and 1.5% and
- Only patients below the median age were included.

The ERG notes that the ICER is only above the £20,000-£30,000 per QALY threshold when the discount rate is set to 0%.

5.2.3 Probabilistic sensitivity analysis (PSA)

5.2.3.1 IOPD model

The company did not report probabilistic sensitivity analysis (PSA) results for the IOPD population, although there is the capability to run PSA in the IOPD cost-effectiveness model. The reason provided by the company to not report PSA results is the assumption of clinical

equivalence between AVAL and ALGLU. Based on this assumption, no ICERs were estimated, and therefore the company decided to run only the deterministic analysis to test the differences in incremental costs. However, the ERG notes that the CS does not fully meet the NICE reference case which requires PSA.

Although CS Appendix L did not report the results of the PSA, we have run the PSA in the IOPD model, and we obtained results that are similar to the deterministic findings. We also find that the scatterplot and the cost-effectiveness acceptability curve (CEAC) were correctly linked to the PSA results.

5.2.3.2 LOPD model

The CS Appendix L states that a 1,000 simulation run was conducted, with each simulation consisting of 10 replications of the eight profiles. However, the cost-effectiveness model and the Technical Report[40] submitted by the company assumes a PSA with 300 simulations, with each simulation consisting of 100 replications. In both situations, the PSA results are significantly different from the base case results. The ERG considers that this happens because the model is not stable at these number of replications (both 10 and 100). The ERG ran the PSA with 1,000 simulations and 10 replications to validate the company's submitted results but notes that the scatterplot and CEAC figures shown in the CS appendix L are more likely to represent the results of a run with 300 simulations.

All the variables included in the PSA are summarised in CS Appendix L Table 34 along with the corresponding distributions.
They assigned the following distributions:

- Normal distribution to FVC% predicted change, 6MWT change and utility gain;
- Log-normal distribution for FVC% predicted plateau period, 6MWT plateau period, mortality HR (, FVC decline (%/year) and 6MWT decline (m/year);
- Beta distribution for treatment discontinuation rate, adverse event rate and disutility; and
- Gamma distribution for cost-related parameters

A multivariate normal distribution was assigned for survival parameters. These parameters are based on normally distributed coefficients (for instance, shape and scale for the survival curves) that correlate between them. We consider that all relevant input parameters are included in the PSA. As for the univariate sensitivity analysis, only the parameters

corresponding to the selected survival curves are varied in the PSA. However, other survival curves are tested as scenario analyses.

CS Appendix L section L.3.7.4 and Table 36 summarise the probabilistic results for the LOPD population. CS Appendix L Figure 7 presents the scatterplot, and CS Appendix L Figure 8 illustrates the CEAC. The updated probabilistic results as well as the updated scatterplot and CEAC were provided as part of the company clarification responses (see Table 24 and Figures 8 and 9).

As explained above, the probabilistic results reported in the CS are quite different from the base case and the model results. This is the case for both the original and updated company submissions. In Table 40, we compare the base case result (1 simulation and 200 replications), the PSA result considering 1,000 simulations and 10 replications (as described in the CS Appendix L) and two PSA results with 300 simulations (as the model set up) and different number of replications. The results presented below correspond to the updated model. The PSA results indicate that AVAL is [redacted] than for the base case results, although the QALYs estimated by the PSA runs are greater than the QALYs estimated for the base case analysis.

Furthermore, we analysed the model stability of the company PSA. For more information about the stability of the PSA simulation, see section 5.3.2.2 below and Appendix 4.

Table 40 Comparison of the results for different numbers of PSA runs versus the base case results (AVAL vs. ALGLU)

Simulations	Replications	Incr. cost	Incr. LYs	Incr. QALYs	ICER (£/QALY)
1	200[a]	[redacted]	[redacted]	[redacted]	-10,823.77
300	200	[redacted]	[redacted]	[redacted]	-£913.73
1000	10	[redacted]	[redacted]	[redacted]	-£232.65
300	100	[redacted]	[redacted]	[redacted]	-£222.45

Source: Excel LOPD company's updated CE model.
QALYs, quality-adjusted life years; LY, life years; ICER, incremental cost-effectiveness ratio.
[a] Company base case results)

5.3 Model validation and face validity check

5.3.1 Company's model validation

The company briefly described their approach to model validation in CS Appendix L section L.5. The Technical Report of the model [40] has more information on the LOPD model in the Validation section (page 25). Clinical experts advising the company validated the assumptions, inputs and outputs of both the LOPD and IOPD models. The cost-effectiveness models for LOPD and IOPD were reviewed by researchers not involved in the model development to search for coding errors and inconsistencies and to do a logical check of the model outputs.

5.3.1.1 IOPD model

For the external validation, the company only identified a single study by Castro-Jaramillo et al [58] assessing the cost-effectiveness of ERT therapies (ALGLU) in the IOPD population conducted from a UK perspective. This study yielded more costs and QALYs compared to the model submitted by the company. In the company's view, this is due to differences in utilities and mortality data. The Castro-Jaramillo study considered a simplified and higher utility (0.7 applied to all patients alive treated with ERT) and mortality rate (25% per year).

5.3.1.2 LOPD model

The company has not provided a comparison considering a UK perspective for external validation, but they compared the LOPD model outcomes for ALGLU to the results observed in a Dutch study.[59] As the Kanters study considers the Dutch tariff for utilities and takes a Dutch perspective for costs, the company only validated the modelled discounted life years against it. The ERG notes that both the Kanters study and the company's LOPD model reported similar results in terms of discounted life-years for ALGLU (21.84 and [redacted], respectively). The baseline age is also similar between the models (49.1 years for the Kanters study and [redacted] for the company's LOPD model). Both models considered a lifetime time horizon.

ERG conclusion

The ERG agrees that, in the absence of studies taking a UK perspective and comparable assumptions regarding survival, utilities and costs, the external validation of the IOPD and LOPD models is limited. However, we conduct some additional comparisons for the purpose of both external and internal validation as part of the ERG's internal model validation (see section 5.3.2.3).

5.3.2 ERG model validation

The ERG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources;
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses;
- Checking the individual equations within the model;
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses;
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks);

5.3.2.1 IOPD model

The model is generally well-implemented, with a few discrepancies in parameter values between the CS and the company's model. The company provided updated tables with their clarification responses (clarification questions B4, B12, B13, B15, and B16), in which the original issues were corrected.

5.3.2.2 LOPD model

The LOPD model is based on an Excel-based discretely integrated condition event (DICE) simulation framework. This framework is relatively recent, with few studies applying this methodology in the health technology assessment process. The ERG notes that compared to the Markov model, the validation of a DICE simulation requires additional steps, for example, to check the generation of the profiles and the simulation stability. For this reason, the ERG suggests that the company provide more extensive documentation to allow the ERG to appropriately validate its content.

The original CS does not describe the model implementation, such as the conditions, events, equations, and outputs. The ERG received more technical information on the DICE model in reply to clarification question B2 and the late access to the documentation delayed the ERG validation process. Along with the documentation provided, we would like to have received the DICE model manual as well. Consequently, we only executed minor modifications to the LOPD model to define the ERG base case. The ERG considers that the model validation process would be improved if:

- All the most common parametric distributions were directly implemented in the model, not only the company's preferred ones.
- The documentation (Blueprint) provided by the company was more detailed. For example, the equations used in the model are only accompanied by a brief description of the function, that does not fully explain these parameters.
- Some key information could be exported in a friendly format after each simulation, such as overall survival curves.

Even though the steps above would help the ERG model validation, we consider that some modifications can only be done by the model developers. For instance, the ERG preferred to use a different method to estimate utilities in composite health states (see section 4.2.7.3 for further details). However, it is unclear how to change the additive method to the multiplicative method in the model.

During the validation, the ERG observed issues with the stability of the model results. The CS does not justify the chosen number of replications, 200, for the base case simulation. The ERG consider that 1,000 replications is the more appropriate number for the company's base case. We present our rationale to estimate at which number of replications the model would be stable in Appendix 4.

The same issue of stability of the model results was identified for the PSA. In this case, it is related to the combination of number of replications vs the number of simulations. The ERG analysed the behaviour of the company PSA by testing four different number of simulations (10, 50, 100, and 300) combined with the same number of replications (200). Due to time constraints, the ERG was not able to run a higher number of simulations. The results of the simulations tested by the ERG show that the ICER decreases from £314,100 per QALY for 10 simulations to £244,271 per QALY for 300 simulations (see Appendix 4 below). These ICERs refer to the results of the company's model after the ERG correction of the three errors in the company's PSA, as described in the next paragraph. Although we do not consider that this number of simulations is sufficient to be certain of model stability, pragmatically the time taken to run the simulations limit the number of simulations possible. However, the ERG considers that the configuration proposed by the company (300 simulations and 200 replications) provides results with an adequate confidence interval (5.2%) for the company base case PSA.

Moreover, the ERG found three errors in the company's PSA calculations: the formula for the total cost of AVAL (LOPD model, 'PSA results' sheet, cell G42) was incorrectly referring to the ALGLU costs instead of AVAL; the formula for the total QALYs of AVAL and ALGLU (LOPD model, 'PSA results' sheet, cells I41 and I42) did not consider the adverse effect and caregivers disutilities; and the confidence interval of the invasive ventilator purchase parameter (LOPD model, 'PSA inputs' sheet, cell F40) should be 10% of the invasive ventilator purchase parameter used in the base case.

An additional observation is that two PSA runs with the same number of simulations and replications have the same result. We assume that the initial number (seed) of the random number generator is fixed. As the PSA is meant to be random, the ERG considers that the PSA is not fully stochastic.

ERG comment

The ERG considers that the documentation and information provided in the original submission was insufficient for the ERG to conduct a proper validation of the model. The ERG estimated that the most appropriate number of replications to obtain stable results in the LOPD base case would be 1000, rather than 200 as the company used. Due to time restrictions, it was not possible for the ERG to determine the adequate balance between the number of replications and simulations in order to obtain stable PSA results. However, the company setting with 300 simulations and 200 replications provides results with an appropriate confidence interval for the company base case PSA.

5.3.2.3 Internal and external validity checks

5.3.2.3.1 IOPD model

The ERG compared the company's modelled estimates of the VFS, IVFS and OS with the patient data observed in the work of Broomfield et al.[7] and Kishnani et al.[15]). The analyses are presented in section 4.2.6.1. Table 25 compares the observed KM data and the parametric curves for the VFS and Table 26 compares the observed KM data and the parametric curves for the IVFS. Table 27 compares the observed KM data and the parametric curves for OS for the CRIM-positive population, while Table 28 presents the results for the CRIM-negative population.

For VFS, the Weibull curve (company's and ERG base case) shows comparable survival estimates to both Broomfield et al and Kishnani et al at two and four years. It predicts slightly lower estimates than Broomfield at six and ten years.

For IVFS, the Weibull curve (company's and ERG base case) shows comparable survival estimates to both Broomfield et al and Kishnani et al at two years. At four, six and ten years, the Weibull curve predicts much lower results than the Broomfield study. However, the ERG notes that the Broomfield study includes a small number of patients with invasive ventilation and therefore the results should be interpreted with caution.

For OS, both the Weibull curve (company's base case) and the Exponential curve (ERG base case) extrapolates survival comparable to the Broomfield study estimates at two, four, six and ten years for the CRIM-positive population. For the CRIM-negative population, the Broomfield study shows no patients alive at six and ten years. None of the parametric curves fitted to the KM data predict 100% of death at this point, but both the Weibull and the exponential show low numbers of patients alive after six years.

5.3.2.3.2 LOPD model

The ERG compared the modelled OS for ALGLU (extrapolated using the Gompertz and Weibull distributions) with the data from the CPRD dataset [57] and the Gungor et al. 2011 study.[45]

Table 41 shows that the modelled OS using the Gompertz and Weibull distributions is slightly higher than the survival observed in the CPRD dataset at 5 and 10 years. We observed that the modelled survival (with Gompertz) is within the confidence intervals of the CPRD dataset results.

We also note that the study by Gungor et al. 2011, which reported survival data for LOPD patients receiving no treatment, shows a similar or even higher survival than that reported in the CPRD dataset. It is therefore uncertain if there is a difference in disease severity between the patients enrolled in the Gungor study and the patients registered in the CPRD dataset or a higher proportion of patients receiving no treatment than ERT therapies in the CPRD dataset.

Anyway, we expect that treatment with ERT therapies has a survival advantage over no treatment (HR of 0.41, as reported by Gungor et al. 2013[46]). We note that the company's

modelled OS for ALGLU (with Gompertz) at 10 years show better survival than the no treatment estimates of Gungor et al. 2011.

Table 41 LOPD model: validation of modelled OS for ALGLU

	1 year	5 years	10 years	30 years
Modelled OS: Gompertz (company's base case)	99%	97%	91%	36%
Modelled OS: Weibull	99%	96%	91%	39%
CPRD dataset [57]	100%	88.8% (CI 80.0, 98.6)	82.4% (CI 71.2, 95.4)	-
Gungor 2011[45]	100%	98%	82%	40%
ALGLU, alglucosidase alfa; CI, confidence interval; CPRD, Clinical Practice Research Datalink; OS, overall survival				

5.3.3 ERG corrections to the company model

5.3.3.1 IOPD model

The company's original model had some inconsistencies, identified by the ERG (see section 5.1.1). These were amended by the company as part of the clarification responses (see section 5.3.2.1) and the company's updated model. The ERG identified a further error for the cost of administration in the IOPD model. The cost of weekly dosing for ALGLU for the administration costs had not been included in cycle 3. The ERG corrected this cost in cycle 3 and re-ran the analysis. The overall effect of this change is small, i.e., a change in incremental costs from [redacted] for AVAL vs ALGLU (Table 42).

Table 42 Cost effectiveness results for the IOPD model from the ERG correction of administration costs (discounted)

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Company base-case	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
ERG correction to the administration cost	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	

5.3.3.2 LOPD model

The ERG consider that the company did not use a high enough number of replications to provide stable model results (see Appendix 4). In our view, we preferred to use 1000

replications, rather than 200 (see Table 43 below) although it leads to minor differences in the incremental results.

Table 43 Cost effectiveness results for the LOPD model for the ERG's preferred of number of replications (discounted)

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Company base-case	ALGLU	[redacted]	[redacted]		Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
ERG correction to the number of replications	ALGLU	[redacted]	[redacted]		Dominant
	AVAL	[redacted]	[redacted]	[redacted]	

The PSA has minor errors, which were previously discussed in section 5.3.2.2. After correction, the results still diverge from the base case result (incremental cost [redacted] for base case vs. [redacted] for the PSA) where the base case is [redacted] and the PSA result is [redacted]. Table 44 shows the PSA results submitted by the company and after the ERG correction and both PSA runs have 300 simulations and 200 replications.

Table 44 PSA results for the LOPD model from the ERG corrections of the total cost for AVAL (discounted)

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Company PSA	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
ERG correction	ALGLU	[redacted]	[redacted]	[redacted]	£244,271
	AVAL	[redacted]	[redacted]	[redacted]	

5.3.4 ERG summary of key issues and additional analyses

A full summary of ERG observations on key aspects of the company's economic models is presented in Table 45.

Table 45 ERG observations of the key aspects of the company's economic model

Parameter	Company base case	ERG comment	ERG base case
Treatment effectiveness - IOPD			
OS (CRIM-positive and CRIM-negative)	Modelled with Weibull	Large proportion of patients alive at the end of time horizon and decreasing mortality rate likely to be unrealistic	Modelled with the exponential distribution
Treatment effectiveness - LOPD			
Duration of FVC% predicted (AVAL)	5 years		1 year as for ALGLU

Duration of 6MWT (AVAL)	5 years	No evidence of a greater plateau effect of AVAL over ALGLU	3 years as for ALGLU
6MWT: decline rate for no treatment	-7.940m	A slower decline rate is expected when patients are treated with ERT therapies	-9.528m as in company's scenario analysis
HR of OS for AVAL vs. ALGLU	1	A survival benefit greater than one month of AVAL over ALGLU is expected based on the benefits reported for FVC% predicted and 6MWT	0.85
Utilities			
Utility values for IOPD	Values taken from Simon et al.	Study by Simon et al[1] does not follow NICE refence case.	Values taken from the Pompe Registry,
Age-adjusted utility	Age adjusted utility only included in IOPD model.	Age-adjusted utility incorrectly implemented in IOPD model.	Age-adjusted utility not included in IOPD or LOPD model as utility included for three different age groups.
Utility value for ventilator and wheelchair state	Value calculated using addition of ventilator and wheelchair disutilities.	Value should be calculated using multiplicative method (TSD 12). [51]	Value calculated using additive method. (Unclear to the ERG how to change this in the company model).
Resource use and costs			
Dose frequency for IOPD	For first 12 weeks, weekly administration for ALGLU, every 2 weeks for AVAL.	No evidence that dose will be different between ALGLU and AVAL.	For first 12 weeks, weekly administration for ALGLU and AVAL.
Vial sharing	The company calculation of costs assumes vial sharing	Vial sharing should not be assumed.	The ERG assumes vial sharing is not possible.
ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; 6MWT, 6-minute walk test; ERG; Evidence Review Group; FVC, forced vital capacity; HR, hazard ratio; IOPD, infantile-onset Pompe disease; IVFS, invasive ventilation free survival; LOPD, late-onset Pompe disease; OS, overall survival; VFS, ventilation free survival			

6 ERG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

For the LOPD population, the mean value of the threshold for wheelchair use for 6MWT was [redacted] (see section 4.2.6.2). The clinical expert to the ERG considered that this threshold value was higher than expected. The ERG conducted two scenarios using the company's corrected model, with 1,000 replications, to evaluate two lower threshold values of [redacted] and

[redacted]. Reducing the threshold value for wheelchair use has a small effect on the model results and AVAL continues to be [redacted] (see Table 46).

Table 46 Exploratory analysis using alternate 6 MWT thresholds for wheelchair use

scenario	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Corrected company base-case	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
Mean 6MWT threshold of 100m	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
Mean 6MWT threshold of 200m	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	

6.2 ERG's preferred assumptions

6.2.1 IOPD results

Based on the ERG critique of the company's economic model discussed in section 4.2, we have identified seven key aspects of the company base case with which we disagree. Our preferred model assumptions are discussed below:

- **Double dosing for AVAL for the first 12 weeks:** we consider the dosing for AVAL should be the same as for ALGLU;
- **No vial sharing:** we consider that the calculated number of vials should be rounded up to the nearest whole number;
- **Extrapolation of OS**: the ERG notes the uncertainty in estimating OS and therefore prefers the exponential parametric curve for OS instead of the Weibull (company base case).
- **Health state utility values:** we prefer to use the values estimated from the Pompe registry instead of the values from Simon et al. 2019.[1]
- **Age-adjusted utilities:** This has been incorrectly implemented in the company model. The ERG prefers to remove age-adjusted utility as utility values have been specified for three age groups (infant, children and adult).
- **Disease-related costs from CPRD:** The company use incorrect values for disease related costs. The ERG corrects these values.

The cumulative effect of the ERG's preferred assumptions to the company's analyses are shown in Table 47. Applying the ERG preferred assumptions increases the company's base case ICER for AVAL versus ALGLU from [redacted]. The change that has the

largest impact on the cost results is the assumption that there is no vial sharing. The impact of this assumption is related to the different vial size of ALGLU and AVAL. ALGLU is commercialised in a vial of 50mg, while AVAL is in a vial of 100mg. Therefore, the wastage produced by not sharing a vial is larger for AVAL than for ALGLU (see section 6.2.2 below for further details).

Table 47 IOPD: Cumulative change from the corrected company base case to the ERG preferred base case

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Corrected company base-case	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
Double dosing for AVAL for first 12 weeks	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
No vial sharing	ALGLU	[redacted]	[redacted]	[redacted]	Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
OS, exponential	ALGLU	[redacted]	[redacted]	[redacted]	Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
Utility values from Pompe registry	ALGLU	[redacted]	[redacted]	[redacted]	Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
No age adjusted utilities	ALGLU	[redacted]	[redacted]	[redacted]	Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
Corrected disease related costs	ALGLU	[redacted]	[redacted]	[redacted]	Dominated
	AVAL	[redacted]	[redacted]	[redacted]	
ERG base case	ALGLU	[redacted]	[redacted]	[redacted]	Dominated
	AVAL	[redacted]	[redacted]	[redacted]	

We performed a range of scenario analyses on the ERG base case, as shown in Table 48. Briefly, we conducted these analyses to assess the impact of changing the following model assumptions on the overall cost effectiveness results. Most of these scenarios are replicated from the company's scenario analyses but in addition we vary the assumptions around the equivalence of OS between ALGLU and AVAL.

The cost effectiveness results for AVAL vs ALGLU vary from [redacted] to an ICER of £1,006,487 per QALY. The scenarios that have the greatest effect on the cost-effectiveness are varying the relative treatment effect for OS between AVAL and ALGLU (ICER of between £716,567 and £1,006,487 per QALY). This ICER increase is driven by the longer time on treatment and consequently the higher treatment costs.

Table 48 Scenarios with the ERG preferred base case

Assumption	ERG Base case	Incremental costs (£/QALY)
ERG base case		[redacted]
Discount rate set to 1.5%	3.5%	[redacted]
Discount rate set to 0%	3.5%	[redacted]
25-year time horizon	50 years	[redacted]
Generalised gamma curve used for VFS	Weibull	[redacted]
Exponential curve used for VFS	Weibull	[redacted]
Log-normal curve used for VFS	Weibull	[redacted]
Log-logistic curve used for VFS	Weibull	[redacted]
Gompertz curve used for VFS	Weibull	[redacted]
Generalised gamma curve used for IVFS	Weibull	[redacted]
Exponential curve used for IVFS	Weibull	[redacted]
Log-normal curve used for IVFS	Weibull	[redacted]
Log-logistic curve used for IVFS	Weibull	[redacted]
Gompertz curve used for IVFS	Weibull	[redacted]
Log-normal curve used for OS	Exponential	[redacted]
Weibull curve used for OS	Exponential	[redacted]
CRIM+ only	Combined population	[redacted]
CRIM- only	Combined population	[redacted]
No double dosing for AVAL	Double dosing for first three months for ALGLU and AVAL	[redacted]
4.5 initial outpatient visits for AVAL	3 outpatient visits	[redacted]

Table 49 Scenarios for increased OS for AVAL with the ERG preferred base case

Assumption	Treatments	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case	AVAL vs ALGLU	[redacted]	[redacted]	Dominated
OS HR = 0.98, 1.1 months increase for AVAL VS ALGLU	AVAL vs ALGLU	[redacted]	[redacted]	£1,006,487
OS HR = 0.95, 2.8 months increase for AVAL VS ALGLU	AVAL vs ALGLU	[redacted]	[redacted]	£744,901
OS HR = 0.90, 5.8 months increase for AVAL VS ALGLU	AVAL vs ALGLU	[redacted]	[redacted]	£716,567

6.2.2 LOPD results

Based on the ERG critique of the company's economic LOPD model discussed in section 4.2, we have identified six key aspects of the company base case with which we disagree. Our preferred assumptions for the LOPD model are discussed below:

- **No vial sharing:** we consider that the calculated number of vials should be rounded up to the nearest whole number.
- **Utility values for caregivers:** we suggest that the disutility values from the mild state should be used for the not dependent on ventilator or wheelchair state and the

moderate state should be used for the non-invasive ventilation dependent health state (see section 4.2.7.3).

- **Disutilities for patients using both a ventilator and wheelchair:** the ERG prefer to use a multiplicative method instead of adding the disutilities applied for each health state separately (see section 4.2.7.3). As we are unclear on how to implement this change in the model, we have not included it in the ERG base case.
- **Duration of treatment effect for FVC / 6MWT**: we assume the [redacted] of treatment effect for AVAL and ALGLU ([redacted] for FVC% predicted and [redacted] for 6MWT) while the company have assumed [redacted] for AVAL.
- **Decline rate for 6MWT for no treatment:** the ERG assumes a faster decline rate of 6MWT for those patients on no treatment ([redacted] per year) than for patients treated with ERT therapies, instead of the [redacted] decline rate as for ALGLU and AVAL.
- **OS survival:** we assume a HR for OS of 0.85 for AVAL vs. ALGLU, instead of a HR of 1.

For the LOPD, the cumulative effect of the ERG's preferred assumptions to the company's analyses are shown in Table 50. Applying the ERG preferred assumptions increases the company's base case ICER for AVAL versus ALGLU from [redacted] to an ICER of £398,367 per QALY. The changes that have the largest impact on the cost results are assuming that there is no vial sharing and assuming that AVAL has a greater benefit in survival than ALGLU. The change that has the largest impact on QALYs is the change in the plateau duration of FVC% predicted and 6MWT.

Table 50 LOPD: Cumulative change from the ERG corrected company base case to the ERG preferred base case

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
Company base-case	ALGLU	[redacted]	[redacted]	[redacted]	Dominant
	AVAL	[redacted]	[redacted]	[redacted]	
+ no vial sharing	ALGLU	[redacted]	[redacted]	[redacted]	£237,040
	AVAL	[redacted]	[redacted]	[redacted]	
+ changes to utility values for patients and caregivers	ALGLU	[redacted]	[redacted]	[redacted]	£201,042
	AVAL	[redacted]	[redacted]	[redacted]	
+ Plateau duration for FVC% / 6MWT	ALGLU	[redacted]	[redacted]	[redacted]	£319,645
	AVAL	[redacted]	[redacted]	[redacted]	
+ 6MWT decline rate of [redacted]	ALGLU	[redacted]	[redacted]	[redacted]	£319,612
	AVAL	[redacted]	[redacted]	[redacted]	
	ALGLU	[redacted]	[redacted]	[redacted]	£398,367

+ OS survival: HR of 0.85 (AVAL vs. ALGLU)	AVAL	[redacted]	[redacted]	[redacted]	
ERG base case	ALGLU	[redacted]	[redacted]	[redacted]	£398,367
	AVAL	[redacted]	[redacted]	[redacted]	
Abbreviations: ICER, incremental cost-effectiveness ratio; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALYs, quality-adjusted life years; OS, overall survival; HR, hazard ratio; FVC%, forced vital capacity; 6MWT, six-minute walk test					

Vial sharing has the greatest impact in the model results, yielding a change in the ICER of AVAL versus ALGLU of more than £240,000 per QALY. The impact of this assumption is related to the different vial size of ALGLU (50 mg) and AVAL (100mg) as discussed in section 6.2.1 above. Table 516 presents the number of vials required for the treatment of LOPD for each model profile and the corresponding wastage. For example, patients represented by profile four, with a baseline weight of 87.14kg, would need 35 vials of ALGLU (7mg wastage) or 18 vials of AVAL (57mg wastage).

Table 51 LOPD: number of vials and wastage for the patient profiles

Profile	Weight	Drug amount required (mg)	Number of vials required		Difference (round up) fraction of vials		Difference (round up) in amount (mg)	
			ALGLU	AVAL	ALGLU	AVAL	ALGLU	AVAL
1	61.40	1,228.0	24.56	12.28	0.44	0.72	22.0	72.0
2	86.45	1,729.0	34.58	17.29	0.42	0.71	21.0	71.0
3	61.81	1,236.2	24.72	12.36	0.28	0.64	14.0	64.0
4	87.14	1,742.8	34.86	17.43	0.14	0.57	7.0	57.0
5	66.32	1,326.4	26.53	13.26	0.47	0.74	23.5	74.0
6	95.95	1,919.0	38.38	19.19	0.62	0.81	31.0	81.0
7	65.68	1,313.6	26.27	13.14	0.73	0.86	36.5	86.0
8	94.83	1,896.6	37.93	18.97	0.07	0.03	3.5	3.0
Source: adapted from CS appendix L, Table 3. Both ALGLU and AVAL require a dose of 20mg/kg AVAL, avalglucosidase alfa; ALGLU, aglucosidase alfa								

We performed a range of scenario analyses on the LOPD ERG base case, as shown in Table 52 In addition to the scenarios replicated from the company's scenario analyses, the ERG also varied the following assumptions:

- Change the weight (share) of the profiles
    - Assume that all the profiles have [redacted] for the model results, i.e., [redacted].
- Assume different plateau durations for AVAL
    - [redacted] for %FVC and 6MWT (as in the company's base case)
- Change OS HR of AVAL versus ALGLU
    - HR of 1 as in the company's base case

    - HR of 0.70 (means assuming an incremental lifetime survival of 6 months)
- Round the number of vials to the nearest whole number

The ERG would also have liked to conduct a scenario using the generalised gamma fitted curve for OS (see further explanation in section 4.2.6.2). As explained in section 5.3.2.2, this was not possible because only the Gompertz and Weibull distributions are directly implemented in the LOPD model. However, the ERG suspects that the use of the generalised gamma is not likely to have a significant impact in the model results because the survival extrapolations do not differ much from the Gompertz distribution (see Table 29).

In all LOPD ERG scenarios, AVAL has an ICER of more than £100,000 per QALY (from £177,642 to £543,547) except for the scenario rounding the number of vials to the nearest whole number (-£28,029 per QALY). The scenarios that have the greatest effect on the cost-effectiveness are:

- Rounding the number of vials to the nearest whole number (decrease of £426,396 per QALY versus ERG base case)
- Using alternative disutilities from Duchenne muscular dystrophy (DMD) (decrease of £220,725 per QALY versus ERG base case)
- Effect persistence for FVC% of AVAL set to [redacted] (decrease of £131,417 and £163,156 per QALY versus ERG base case, respectively)
- Assuming a younger cohort, i.e., only patients below the median age (increase of £136,180 per QALY versus ERG base case)

Table 52 LOPD: Scenarios with the ERG preferred base case

Assumption	ERG Base case	ICER (£/QALY)
ERG preferred base case		£398,367
Effect persistence for AVAL set to [redacted]	FVC: 1 year, 6MWT: 3 years	£235,211
Effect persistence for AVAL set to [redacted]	FVC: 1 year, 6MWT: 3 years	£312,626
Discount rates set to 0%	3.5%	£422,390
Discount rates set to 1.5%	3.5%	£407,594
Time horizon set to 15 years	60 years	£435,733
Time horizon set to 30 years	60 years	£357,072
FVC decline no treatment [redacted]	[redacted]	£401,693
FVC decline no treatment [redacted]	[redacted]	£393,985
Weibull curve used for OS	Gompertz	£395,006
Patients below the median age only	All patients	£534,547
No caregiver disutility	Include caregiver disutility	£455,064
[redacted]	3 infusions	£398,758

Alternative disutilities from DMD	CS appendix L, Table 24	£177,642
ERG additional scenarios		
Profiles: same weights	CS appendix L, Table 3	£403,340
Effect persistence for AVAL set to [redacted] for FVC and 6MWT	(FVC: [redacted], 6MWT: [redacted])	£266,950
OS hazard ratio of 1	0.85	£319,612
OS hazard ratio of 0.70	0.85	£460,538
Round the vials to the nearest whole number	Round up vials to the nearest whole number	-£28,029
Abbreviations: ICER, incremental cost-effectiveness ratio; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALYs, quality-adjusted life years; FVC, forced vital capacity; 6MWT, six-minute walk test; DMD, Duchenne muscular dystrophy.		

Table 53 shows the ERG preferred base case results compared to the PSA results using the ERG preferred assumptions. The PSA was run for 300 simulations and 200 replications. Compared to the ERG base case, the PSA results show that the incremental QALYs [redacted], but the incremental cost [redacted].

Table 53 LOPD: PSA results for the ERG preferred assumptions (discounted, PAS price for AVAL)

Assumption	Treatments	Total costs	Total QALYs	Incremental costs	ICER (£/QALY)
ERG base case	ALGLU	[redacted]	[redacted]		£398,367
	AVAL	[redacted]	[redacted]	[redacted]	
ERG PSA result	ALGLU	[redacted]	[redacted]		£247,390
	AVAL	[redacted]	[redacted]	[redacted]	

Given the high variation in costs due to the assumptions of vial sharing, the ERG investigated this issue further. Figure 5 shows how the wastage of medication for AVAL and ALGLU varies for different patient weights, from 60kg to 100kg, with a dose of 20mg/kg, ALGLU vial of 50mg, and AVAL vial of 100mg. For example, for a patient of 60kg, there is no vial wastage for AVAL and ALGLU. However, if this patient is slightly heavier, 60.2kg, the vial wastage for ALGLU is 46mg, and for AVAL is 96mg.

Figure 5 Vial wastage per weight

The ERG conducted two illustrative scenarios with the ERG base case to investigate the impact changes to the patients' weight has on the ICER: one scenario where the profile's weight does not produce vial wastage and a second scenario with just a small increment on the first scenario's weight to produce maximum wastage. Table 54 shows the ICERs for these scenarios using the ERG base case assumptions. These two scenarios can be considered best- and worst-case scenarios. The ICER varies from £114,576 to £455,428 per QALY for the two scenarios. We note the considerable variability in the cost effectiveness results due to the starting weight of the profiles.

Table 54 Comparison between scenarios with different profile weights and the ERG base case

Profile	Base case Weight (kg)	Weight Best case (kg)	Weight Worst case (kg)
1	61.40	60.00	60.01
2	86.45	85.00	85.01
3	61.81	60.00	60.01
4	87.14	85.00	85.01
5	66.32	65.00	65.01
6	95.95	95.00	95.01
7	65.68	65.00	65.01
8	94.83	90.00	90.01
ICER (£/QALY)	£398,367	£114,576	£455,428

6.3 Conclusions on the cost effectiveness evidence

The company developed two sets of models for this appraisal for IOPD and LOPD: cost minimisation models and cost utility models. The company presented the cost minimisation models as their base case in the CS. The ERG preferred the cost utility models, as the cost minimisation models do not fully meet the NICE reference cost, as they have not included health benefits.

The treatment effectiveness data from the Mini-COMET trial were limited and the ERG judged that these data were insufficient to reliably inform long-term treatment effectiveness of AVAL vs ALGLU. For this reason, we consider the results presented for the IOPD model to be illustrative.

The LOPD model is a patient-level simulation, using DICE methodology. We consider that the company's DICE model is overly complex,[60] and that it is not easy to interpret and therefore validate. The ERG did not have access to how the different inputs link with each other within the DICE model and also to the intermediate parameters (like survival curves or utilities) that are calculated during each simulation. In addition, we consider that making changes to the model, such as implementing different parametric curves, is complex and time-consuming and requires experience with DICE models.

The company base case results for IOPD shown that AVAL is dominant compared to ALGLU ([redacted]). For LOPD, AVAL is also dominant against ALGLU (cheaper and more effective).

The ERG identified a number of issues with the company's models. These include:

- **Double dosing for AVAL for the first 12 weeks:** we consider the dosing for AVAL should be the same as for ALGLU (IOPD only);
- **No vial sharing:** we consider that the calculated number of vials should be rounded up to the nearest whole number;
- **OS survival:** The company assume OS for AVAL and ALGLU is the same. The ERG assume a survival benefit of HR of 0.85 for AVAL vs. ALGLU (i.e., a HR of 0.35 between AVAL and no treatment) (LOPD only);
- **Duration of treatment effect for FVC / 6MWT**: the company model assumes that duration of treatment effect for FVC% predicted is [redacted] for ALGLU and [redacted] for AVAL. The duration of treatment effect for 6 MWT was [redacted] for ALGLU and [redacted] for AVAL. The ERG considers there is no evidence of a differential

treatment effect for AVAL vs ALGLU and assumes the [redacted] treatment effect for both treatments (LOPD only).

The ERG's preferred assumptions have a large impact on the model results. For the ERG's base case for IOPD, AVAL has an [redacted] vs ALGLU. For the ERG's base case for LOPD, AVAL has an ICER of £398,367 per QALY vs ALGLU.

7 END OF LIFE

The CS does not mention whether or not AVAL would be suitable for consideration as an end-of-life treatment for NICE appraisal. The ERG considers that AVAL does not meet the NICE criteria to be considered an end-of-life treatment, as patients currently treated with ERT would be expected to have a life expectancy greater than 24 months on average.

8 References

1. Simon NJ, Richardson J, Ahmad A, et al. Health utilities and parental quality of life effects for three rare conditions tested in newborns. *J Patient Rep Outcomes* 2019;3(1):4. doi: 10.1186/s41687-019-0093-6 [published Online First: 2019/01/24]
2. Kishnani PS, Hwu WL, Mandel H, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* 2006;148(5):671-76. doi: 10.1016/j.jpeds.2005.11.033 [published Online First: 2006/06/02]
3. Hahn A, Schanzer A. Long-term outcome and unmet needs in infantile-onset Pompe disease. *Ann Transl Med* 2019;7(13):283. doi: 10.21037/atm.2019.04.70 [published Online First: 2019/08/09]
4. Association for Glycogen Storage Disease UK. Pompe Disease (GSD2) [updated 01/01/2022. Available from: https://agsd.org.uk/all-about-gsd/gsd-variants/pompe-disease-gsd2/
5. Peruzzo P, Pavan E, Dardis A. Molecular genetics of Pompe disease: a comprehensive overview. *Ann Transl Med* 2019;7(13):278. doi: 10.21037/atm.2019.04.13 [published Online First: 2019/08/09]
6. National Organization for Rare Disorders (NORD). National Organization for Rare Disorders (NORD). Rare Disease Database. Pompe Disease. [Available from: https://rarediseases.org/rare-diseases/pompe-disease/. accessed 01/02/2022.
7. Broomfield A, Fletcher J, Davison J, et al. Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy. *J Inherit Metab Dis* 2016;39(2):261-71. doi: 10.1007/s10545-015-9898-5 [published Online First: 2015/10/27]
8. Chan J, Desai AK, Kazi ZB, et al. The emerging phenotype of late-onset Pompe disease: A systematic literature review. *Mol Genet Metab* 2017;120(3):163-72. doi: 10.1016/j.ymgme.2016.12.004 [published Online First: 2017/02/12]
9. Patel TT, Banugaria SG, Case LE, et al. The impact of antibodies in late-onset Pompe disease: a case series and literature review. *Mol Genet Metab* 2012;106(3):301-9. doi: 10.1016/j.ymgme.2012.04.027 [published Online First: 2012/05/23]
10. Hagemans ML, Winkel LP, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain* 2005;128(Pt 3):671-7. doi: 10.1093/brain/awh384 [published Online First: 2005/01/22]
11. Department of Health. NHS reference costs 2018-2019. *https://wwwenglandnhsuk/publication/2018-19-national-cost-collection-data-publication/* 2020
12. European Medicines Agency. Myozyme Summary of product Characteristics (SmPC): European Medicines Agency.
13. Kronn DF D-SD, Hwu WL, Jones SA, Nakamura K, Okuyama T,. Management of Confirmed Newborn-Screened Patients With Pompe Disease Across the Disease Spectrum. . 2017;140(Suppl 1):S24-S45. *Pediatrics* 20178;140
14. National Health Service (NHS). National Health Service (NHS) Lysosomal storage disorders (LSD) specialised service. 2013 [Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf. accessed 01/02/2022.
15. Kishnani PS, Corzo D, Leslie ND, et al. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. *Pediatr Res* 2009;66(3):329-35. doi: 10.1203/PDR.0b013e3181b24e94 [published Online First: 2009/06/23]
16. van der Ploeg AT, Kruijshaar ME, Toscano A, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. *Eur J Neurol* 2017;24(6):768-e31. doi: 10.1111/ene.13285 [published Online First: 2017/05/10]

17. Kuperus E KM, Wens SCA, de Vries JM, Favejee MM, van der Meijden JC, . Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study. Neurology. 2017;89(23):2365-73. *Neurology* 2017;89(23):2365-73.
18. Schoser B, Stewart A, Kanters S, et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. *J Neurol* 2017;264(4):621-30. doi: 10.1007/s00415-016-8219-8 [published Online First: 2016/07/04]
19. Van der Ploeg AT KM, Willemsen R, Brons NH, Reuser AJ,. Intravenous administration of phosphorylated acid alpha-glucosidase leads to uptake of enzyme in heart and skeletal muscle of mice. 1991;87(2):513-8. *J Clin Invest* 1991;87(2):513-8.
20. Zhu Y, Li X, Kyazike J, et al. Conjugation of mannose 6-phosphate-containing oligosaccharides to acid alpha-glucosidase improves the clearance of glycogen in pompe mice. *J Biol Chem* 2004;279(48):50336-41. doi: 10.1074/jbc.M409676200 [published Online First: 2004/09/24]
21. Zhu Y, Jiang JL, Gumlaw NK, et al. Glycoengineered acid alpha-glucosidase with improved efficacy at correcting the metabolic aberrations and motor function deficits in a mouse model of Pompe disease. *Mol Ther* 2009;17(6):954-63. doi: 10.1038/mt.2009.37 [published Online First: 2009/03/12]
22. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. 2013
23. Sanofi data on file. Pediatric open-label, ascending dose cohort study (Mini-COMET). Clinical Study Report. 2020., 2020.
24. Diaz-Manera J, Kishnani PS, Kushlaf H, et al. Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial. *The Lancet Neurology* 2021;20(12):1012-26. doi: https://doi.org/10.1016/S1474-4422(21)00241-6
25. Diaz-Manera J, Kishnani PS, Kushlaf H, et al. Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial. *The Lancet Neurology* 2021;20(12):1012-26.
26. Sanofi. COMparative Enzyme replacement Trial with neoGAA versus rhGAA (COMET) (interim Clinical Study Report): Sanofi.
27. Sanofi. An open-label, multicentre, multinational extension study of the long-term safety and pharacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease (NEO-EXT) (interim Clinical Study Report): Sanofi, 2020.
28. Sanofi. An open-label, multicenter, multinational, ascending dose study of the safety, tolerability, pharacokinetics, pharmacodynamics, and exploratory efficacy of repeated biweekly infusions of neoGAA in naive and alglucosidase alfa treated late-onset Pompe disease patients (NEO1 Clinical Study Report): Sanofi, 2015.
29. Pena LDM, Barohn RJ, Byrne BJ, et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naive and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. *Neuromuscul Disord* 2019;29(3):167-86. doi: 10.1016/j.nmd.2018.12.004 [published Online First: 2019/02/17]
30. Ditters IAM, Huidekoper HH, Kruijshaar ME, et al. Effect of alglucosidase alfa dosage on survival and walking ability in patients with classic infantile Pompe disease: a multicentre observational cohort study from the European Pompe Consortium. *Lancet Child Adolesc Health* 2022;6(1):28-37.
31. Clinicaltrials.gov. Clincial study for IOPD participants less than or equal to 6 months of age to evaluate efficacy and safety of enzyme replacement therapy (ERT) with avalglucosidase alfa (Baby-COMET): Clinicaltrials.gov; 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT04910776 accessed 7th February 2022.

32. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi: 10.1136/bmj.l4898 [published Online First: 2019/08/30]
33. Cochrane Effective Practice and Organisation of Care (EPOC). Suggested risk of bias critieria for EPOC reviews. EPOC Resources for review authors, 2017 2017 [Available from: epoc.cochrane.org/resources/epoc-resources-review-authors accessed 02/02/2022.
34. Acmg Work Group on Management of Pompe Disease, Kishnani PS, Steiner RD, et al. Pompe disease diagnosis and management guideline. *Genet Med* 2006;8(5):267-88. doi: 10.1097/01.gim.0000218152.87434.f3 [published Online First: 2006/05/17]
35. van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med* 2010;362(15):1396-406. doi: 10.1056/NEJMoa0909859 [published Online First: 2010/04/16]
36. Arlegui H, Nachbaur G, Praet N, et al. Using Discretely Integrated Condition Event Simulation To Construct Quantitative Benefit-Risk Models: The Example of Rotavirus Vaccination in France. *Clin Ther* 2020;42(10):1983-91.e2. doi: 10.1016/j.clinthera.2020.08.013 [published Online First: 2020/09/30]
37. Genzyme S. Pompe Registry Report, 2017.
38. van der Beek NA dVJ, Hagemans ML, Hop WC, Kroos MA, Wokke JH, et al.,. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis* 2012;7(88)
39. Kishnani PS CD, Nicolino M, Byrne B, Mandel H, Hwu WL, et al.,. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology. . *Neurology* 2007;68(2):99-109.
40. Sanofi Genzyme. Economic model Avalglucosidase Alfa for Late-Onset Pompe Disease: Technical report. Unpublished: Sanofi, 2021.
41. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. *NICE, London* 2013
42. Kishnani PS, Corzo D, Nicolino M, et al. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. *Neurology* 2007;68(2):99-109. doi: 10.1212/01.wnl.0000251268.41188.04 [published Online First: 2006/12/08]
43. <Diaz-Manera 2021.pdf>.
44. Statistics OfN. National life tables.
45. Gungor D, de Vries JM, Hop WC, et al. Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. *Orphanet J Rare Dis* 2011;6:34. doi: 10.1186/1750-1172-6-34 [published Online First: 2011/06/03]
46. Güngör D, Kruijshaar ME, Plug I, et al. Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study. *Orphanet J Rare Dis* 2013;8:49. doi: 10.1186/1750-1172-8-49 [published Online First: 2013/03/28]
47. van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med* 2010;362(15):1396-406.
48. van Kooten HA, Harlaar L, van der Beek N, et al. Discontinuation of enzyme replacement therapy in adults with Pompe disease: Evaluating the European POmpe Consortium stop criteria. *Neuromuscul Disord* 2020;30(1):59-66. doi: 10.1016/j.nmd.2019.11.007 [published Online First: 2020/01/09]
49. Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Health Qual Life Outcomes* 2009;7:27. doi: 10.1186/1477-7525-7-27 [published Online First: 2009/04/02]
50. Kanters TA, Redekop WK, Kruijshaar ME, et al. Comparison of EQ-5D and SF-6D utilities in Pompe disease. *Qual Life Res* 2015;24(4):837-44. doi: 10.1007/s11136-014-0833-2 [published Online First: 2014/10/25]
51. Ara RW, A.;. NICE DSU technical support document 12: The use of health state utility values in decision model. http://www.nicedsu.org.uk, 2011.

52. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. *Health Soc Care Community* 2006;14(6):508-22. doi: 10.1111/j.1365-2524.2006.00639.x [published Online First: 2006/10/25]
53. Curtis LB, A. Unit Costs of Health and Social Care 2020. *https://wwwpssruacuk/project-pages/unit-costs/unit-costs-2020/* 2020
54. Dretzke J, Blissett D, Dave C, et al. The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation. *Health Technol Assess* 2015;19(81):1-246. doi: 10.3310/hta19810 [published Online First: 2015/10/17]
55. Age UK. Disability equipment and home adaptations. Available at: www.ageuk.org.uk/globalassets/age-uk/documents/factsheets/fs42_disability_equipment_and_home_adaptations_fcs.pdf. 2020
56. NRS Healthcare. Sunlift Mini Mobile Hoist. Available at: https://www.nrshealthcare.co.uk/mobility-aids/moving-transferring-handling-aids/mobile-hoists/sunlift-mini-mobile-hoist (last accessed 10th September 2021).
57. Clinical Practice Research Datalink (CPRD). Incidence and prevalence of Pompe disease.: Sanofi, 2019.
58. Castro-Jaramillo HE. The cost-effectiveness of enzyme replacement therapy (ERT) for the infantile form of Pompe disease: comparing a high-income country's approach (England) to that of a middle-income one (Colombia). *Rev Salud Publica (Bogota)* 2012;14(1):143-55. doi: 10.1590/s0124-00642012000100012 [published Online First: 2012/12/20]
59. Kanters TA, van der Ploeg AT, Kruijshaar ME, et al. Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in adult patients with Pompe disease. *Orphanet J Rare Dis* 2017;12(1):179. doi: 10.1186/s13023-017-0731-0 [published Online First: 2017/12/15]
60. Cooper K, Brailsford SC, Davies R. Choice of modelling technique for evaluating health care interventions. *Journal of the Operational Research Society* 2007;58(2):168-76. doi: 10.1057/palgrave.jors.2602230

9 Appendices

9.1 Appendix 1 Rationale for clinical effectiveness risk of bias judgements

Table 55 provides supplementary detail to section 3.2.2 of this report, expanding on the company's and the ERG's respective risk of bias judgments for the Mini-COMET trial and the COMET trial, respectively. The critical appraisal instrument used is version 2 of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2).[32] Rob 2 is designed to be applied to one or more individual study outcomes in an RCT. We chose the designated primary outcome measure for study:

- Mini-COMET trial: safety and tolerability at week 25
- COMET trial: change from baseline to week 49 in FVC% predicted measured in the upright position

Table 55 The company's and the ERG's respective risk of bias assessments of the Mini-COMET and the COMET trials

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
DOMAIN 1: Risk of bias arising from the randomization process				
1.1 Was the allocation sequence random?	Yes	Yes	Yes	Yes
Rationale	The site accessed the interactive response technology system to obtain a treatment assignment and patient number.	[redacted] (CSR section 8.4.3)	Treatment assignment and randomisation of eligible patients were performed using a centralised treatment allocation system/interactive response technology.	[redacted] (CSR section 8.4.3) "The random treatment assignments for eligible patients were done using a centralised treatment allocation system (interactive response technology). This system generated the patient

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
				randomisation list and allocated the patient identification number and corresponding treatment kit to patients accordingly" (p. 1014) (Diaz-Manera et al., 2021) [24]
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	Yes	Yes	Yes
Rationale	The site accessed the interactive response technology system to obtain a treatment assignment and patient number.	An interactive response technology (IRT) system was used for randomisation, consequently allocation was concealed	Treatment assignment and randomisation of eligible patients were performed using a centralised treatment allocation system/interactive response technology.	A centralised treatment allocation system/IRT was used for randomisation, consequently allocation is concealed
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no	Probably no	Probably no	Probably yes
Rationale	There were some imbalances in demographics and	Baseline imbalances in demographics and values of key efficacy parameters	Overall, baseline demographic characteristics were well balanced between	Participants allocated to AVAL had a shorter mean period of time between being diagnosed

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
	patient characteristics at baseline, namely younger age of patients and more patients from minorities (2 Black or African American and 1 Hispanic or Latino out of 6 patients) in the ALGLU arm; growth parameters were normal across the treatment arms.	probably due to chance given the small number of patients (n=11) randomised (CS Table 13). We do not expect these differences would impact on the study's primary outcome of safety and tolerability. However, the differences could potentially bias clinical efficacy findings from the study.	groups in the primary analysis period except that Hispanic or Latino ethnicity was more frequent in the ALGLU (24.5%) than in the AVAL group (5.9%) due to the higher number of patients coming from Latin America (14.3% in ALGLU group and 3.9% in AVAL group) and North America (40.8% in ALGLU group and 27.5% in AVAL group).	and starting ERT treatment than those allocated to ALGLU. The participants assigned to AVAL also had better median predicted FVC % predicted and 6MWT scores at baseline than those assigned to ALGLU. Clinical expert advice to the ERG is that, taken together, this suggests that the AVAL group might have started treatment earlier in the course of their disease and that this might mean that they had a greater chance of showing benefit.
1.0 Algorithm result	Low risk	Low risk	Low risk	Some concerns
1.0 Assessor's Judgement	Low risk	Low risk	Low risk	Some concerns
1.0 General note	None	None	None	None
DOMAIN 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)				
2.1 Were participants aware of their assigned intervention during the trial?	Yes	Yes	No	Probably No
Rationale	This was an open-label study, with the primary objective of assessing	[redacted]	Study patients, investigators, and study site personnel (except for the unblinded	"Participants, investigators, and study site personnel (except for the unmasked pharmacist or

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
	safety of increasing doses of AVAL and using multiple doses of ALGLU. It was not blinded at the site level from an operation perspective. However, measures were taken to reduce bias for some observations where feasible, such as the central reading of echocardiograms in a blinded manner and the testing of laboratory parameters (except for pharmacokinetic and immunogenicity measurements) without a knowledge of the treatment.	[redacted] (CSR section 8.4.6)	pharmacist or the unblinded designee) remained blinded to the randomised treatment until after the database was locked and the primary analysis completed.	the unmasked designee) remained unaware of study treatment assignments and did not have access to the randomisation schedule" (p. 1014) (Diaz-Manera et al., 2021) [24]
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes	Probably yes	No	Probably No

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
Rationale	This was an open-label study, with the primary objective of assessing safety of increasing doses of AVAL and using multiple doses of alglucosidase alfa. It was not blinded at the site level from an operation perspective. However, measures were taken to reduce bias for some observations where feasible, such as the central reading of echocardiograms in a blinded manner and the testing of laboratory parameters (except for pharmacokinetic and immunogenicity measurements) without a knowledge of the treatment.	[redacted] (CSR section 8.4.6)	Study patients, investigators, and study site personnel (except for the unblinded pharmacist or the unblinded designee) remained blinded to the randomised treatment until after the database was locked and the primary analysis completed.	[redacted] (CSR section 8.4.6)
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention	No	No information	Not applicable	Not applicable

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
that arose because of the experimental context?				
Rationale	No withdrawal	CSR section 9.2 gives insufficient details of protocol deviations to determine if there were deviations from the intended intervention that arose because of the experimental context	Not applicable	Not applicable
2.4 If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable	Not applicable	Not applicable	Not applicable
Rationale	Not applicable	Not applicable	Not applicable	Not applicable
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable	Not applicable	Not applicable	Not applicable
Rationale	Not applicable	Not applicable	Not applicable	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes	Yes	Yes

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
Rationale	The modified intention-to-treat population was defined as all randomised patients in Cohort 3 who received at least one infusion and with evaluable baseline efficacy assessment. Patients were analysed in the treatment group to which they were randomised. The modified intention-to-treat population was the primary population for Cohort 3 (Stage 2) efficacy analysis.	"[redacted]" (CSR section 8.7.2)	Modified intention-to-treat analysis performed, and the authors claimed "If the pure intention-to-treat (all randomised patients) population is different from the modified intention-to-treat population, we plan to perform a sensitivity analysis in this population as well to assess the robustness of the results."	"For efficacy analyses, participants were analysed by modified intention to treat (mITT). This population (referred to as the primary analysis population) consisted of participants who received at least one infusion (partial or full) of the assigned treatment" (p. 1017)(Diaz-Manera et al., 2021). [24]
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable	Not applicable	Not applicable	Not applicable
Rationale	Not applicable	Not applicable	Not applicable	Not applicable
2.0 Algorithm result	Low risk	Some concerns	Low risk	Low risk

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
2.0 Assessor's Judgement	Low risk	Some concerns	Low risk	Low risk
2.0 General Notes	None	Concerns are in relation to 2.3	None	None
DOMAIN 3: Risk of bias due to missing outcome data				
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes	Yes	Yes	No
Rationale	The number of patients for which data outcomes are reported matches the number of patients at baseline.	All randomised participants (N = 11) were included in the mITT population safety analyses (CS Table 21).	The number of patients for which data outcomes are reported matches the number of patients at baseline.	Data were available for < 95% of participants in the ALGLU arm on the FVC % predicted outcome between Weeks 25 and 49 (the end of the PAP) (see CS Figure 10). Specifically, data appear to be missing for 9% to 18% of the participants in this treatment arm on this outcome during this period. As interim data are presented for the ETP, there is incomplete participant data for the FVC % predicted outcome during the ETP period.
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased	Not applicable	Not applicable	Not applicable	Probably Yes

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
by missing outcome data?				
Rationale	Not applicable	Not applicable	Not applicable	[redacted] (CSR section 10.1.2)
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable	Not applicable	Not applicable	Not applicable
Rationale	Not applicable	Not applicable	Not applicable	Not applicable
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable	Not applicable	Not applicable	Not applicable
Rationale	Not applicable	Not applicable	Not applicable	Not applicable
3.0 Algorithm result	Low risk	Low risk	Low risk	Low risk
3.0 Assessor's Judgement	Low risk	Low risk	Low risk	Low risk
3.0 General Notes	None	None	None	None
DOMAIN 4: Risk of bias in measurement of the outcome				
4.1 Was the method of measuring the	Probably no	Probably no	Probably no	Probably no

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
outcome inappropriate?				
Rationale	Laboratory confirmed safety assessment and commonly accepted efficacy measurements.	[redacted] (CSR section 8.5.2)	Laboratory confirmed safety assessment and commonly accepted efficacy measurements.	[redacted] (CSR section 8.5.1)
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no	Probably no	Probably no	Probably no
Rationale	Regular site monitoring ensured the quality of trial conduct. Monitoring	[redacted]	Regular site monitoring ensured the quality of trial conduct. Monitoring of all	[redacted]

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
	of all investigator sites was performed by Sanofi staff according to Sanofi procedures.	[redacted] (CSR section 8.6)	investigative sites was performed under Sanofi oversight according to Sanofi procedures.	[redacted] (CSR section 8.6)
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes	Yes	No	No
Rationale	Open label	This was an open label study	Double-blinded	"Participants, investigators, and study site personnel (except for the unmasked pharmacist or the unmasked designee) remained unaware of study treatment assignments and did not have access to the randomisation schedule" (p. 1014) (Diaz-Manera et al., 2021) [24]
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no	Probably yes	Not applicable	Not applicable
Rationale	None reported	Reporting of adverse events relies on judgement	Not applicable	Not applicable

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
		of patient, caregivers and healthcare professionals		
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable	Probably no	Not applicable	Not applicable
Rationale	Not applicable	AVAL and ALGU are similar drugs. The adverse event data from the trial shows, as expected, they have a similar AE profile. Therefore there is no reason to believe knowledge of the intervention influenced AE assessment	Not applicable	Not applicable
4.0 Algorithm result	Low risk	Some concerns	Low risk	Low risk
4.0 Assessor's Judgement	Low risk	Some concerns	Low risk	Low risk
4.0 General note	None	None	None	None
DOMAIN 5: Risk of bias in selection of the reported result				
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan	Yes	Yes	Yes	Probably yes

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
that was finalised before unblinded outcome data were available for analysis?				
Rationale	Not reported	"AE summaries will include number (n) and percentage of patients experiencing an AE by study cohort and treatment group" (Statistical Analysis Plan).	Not reported	[redacted] (CSR section 8.7.3) [redacted] (Statistical analysis plan)
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time	Probably no	No	Probably no	Probably no

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
points) within the outcome domain?				
Rationale	There is clear evidence that all eligible reported results for the outcome domain correspond to all intended outcome measurements.	Number (n) and percentage of patients experiencing an AE by study cohort and treatment group are reported	There is clear evidence that all eligible reported results for the outcome domain correspond to all intended outcome measurements.	There is clear evidence that all eligible reported results for the outcome domain correspond to all intended outcome measurements.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Probably no	No	Probably no	Probably no
Rationale	The trial was analysed in accordance with a statistical plan and statistical changes documented until database lock. There is clear evidence that all eligible reported results for the outcome measurement correspond to all intended analyses.	Number (n) and percentage of patients experiencing an AE by study cohort and treatment group are reported	The trial was analysed in accordance with a statistical plan and statistical changes were documented until database lock. There is clear evidence that all eligible reported results for the outcome measurement correspond to all intended analyses.	The trial was analysed in accordance with a statistical plan and statistical changes were documented until database lock. There is clear evidence that all eligible reported results for the outcome measurement correspond to all intended analyses.
5.0 Algorithm result	Low Risk	Low Risk	Low Risk	Low Risk

	Mini-COMET (IOPD)		COMET (LOPD)	
Criteria	**Company**	**ERG**	**Company**	**ERG**
5.0 Assessor's Judgement	Low Risk	Low Risk	Low Risk	Low Risk
5.0 General note	None	None	None	None
OVERALL RISK-OF-BIAS JUDGEMENT				
Algorithm's overall Judgement	Low risk	Some concerns	Low risk	Some concerns
Assessor's overall Judgement	Low risk	Some concerns	Low risk	Some concerns
6.0 General note	Assessment from clinical study report for Cohort 3 (Stage 2)	Assessment from clinical study report and statistical analysis plan	Assessment from clinical study report	Assessment from clinical study report, statistical analysis plan and primary journal article[25]
Source: partly reproduced from CS Appendix D Tables 25 and 26				

9.2 Appendix 2 ERG appraisal of systematic review methods

Table 56 Results of the ERG's critical appraisal of the company's systematic review of clinical effectiveness

Systematic review components and processes	ERG response (Yes, No, Unclear)	ERG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The review question relating to clinical effectiveness is reported in CS section B.2.1.1 and CS Appendix D, section D.1.1. The question includes all elements of the PICOD framework, except for specifying the study design of interest. Study design, however, is specified in the review's eligibility criteria (CS Appendix D, section D.1.1), so we do not consider this to be an issue.
Were appropriate sources of literature searched?	Yes	The sources searched are detailed in CS Appendix D, section D.1.1. These included MEDLINE, Embase, Cochrane Library (CENTRAL and CDSR), recent conference proceedings (2018 to present) and unpublished data held by the company from studies of AVAL.
What time period did the searches span and was this appropriate?	Yes	The searches were run from database inception to 24th August 2020. The company updated the searches on 13th August 2021. Conference abstracts were searched from 2018 to present (CS Appendix D Table 1).
Were appropriate search terms used and combined correctly?	Yes	The search strategies are provided in CS Appendix D, section D.1.1. The search terms were appropriate and we do not believe any studies would have been missed due to the terms used.

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	No – the eligibility criteria were specified, but these were not appropriate to the decision problem	CS Appendix D reports the study eligibility criteria. The criteria were broader than the decision problem. As the criteria were broader, it is unlikely that studies relevant to the decision problem would have been missed. However, because of this breadth, the review identified 103 clinical trials and observational studies for data extraction (CS Appendix D, Figure 1) and it is unclear how the four studies included in the CS were identified from these. It is therefore unclear if any of the remaining 99 studies were relevant to the decision problem.
Were study selection criteria applied by two or more reviewers independently?	Yes	The study selection process is detailed in CS Table 6 and CS Appendix D, section D.1.1. Both title and abstract and full text screening were conducted by two independent reviewers.
Was data extraction performed by two or more reviewers independently?	Unclear	The data extraction process is detailed in CS Table 6 and CS Appendix D, section D.1.1. It is stated that data were extracted by one reviewer and another reviewer validated the data. It is unclear if the reviewers did this independently of each other.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes – but only for two of the four included studies	The company provide a quality assessment of two of the four studies included in the review in CS Appendix D, section D.1.3. One study was an RCT and the other involved an RCT phase. The Cochrane Risk of Bias 2.0 tool[32] was used for the quality assessment, which was appropriate. The company did not include a critical appraisal of two

		non-randomised studies included in their review, one of which informed the economic model.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No	The quality assessment process is detailed in CS Table 6. One reviewer carried it out and another checked it. This does not appear to have been conducted independently.
Is sufficient detail on the individual studies presented?	Yes	The CS describes the methodology, outcomes and results of the studies in Sections B.2.1.1, B.2.2. B.2.3. and B.2.4.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Unclear	The company conducted a post-hoc, pooled analysis of FVC% predicted in people with LOPD at one year of receiving AVAL treatment. The ERG's commentary on the pooled analysis is available in section 3.2.6. The methods are not reported in enough detail for a full independent critical appraisal. Results of the pooled analysis are not used by the company in the cost-utility analysis.

CDSR, Cochrane Database of Systematic Reviews; CS, company submission; ITC, indirect treatment comparison; NMA, network meta-analysis; RCT, randomised controlled trial

9.3 Appendix 3 Summary of company cost minimisation models for IOPD and LOPD

The company chose to present cost minimisation models for IOPD and LOPD as their base case in the CS. The ERG considers that these models do not fully meet the NICE reference case[41] and therefore the ERG's critique concentrates on the company's cost utility models. In this appendix we present a summary of the company's cost minimisation analyses.

In response to clarification questions, the company updated their base case results. The updated base case cost results for IOPD using the AVAL PAS price are shown in Table 57 (clarification response Table 12). Compared to ALGLU, AVAL is [redacted]. Sensitivity analyses showed that the results were most sensitive to changes in the number of hours of nurse time for the administration of the treatments (clarification response Figure 5).

Table 57 Company's updated base-case results – cost minimisation, IOPD, discounted

	ALGLU	AVAL	Incremental
Primary therapy	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease			

The updated base case cost results for LOPD using the AVAL PAS price are shown in Table 58 (clarification response Table 10). Compared to ALGLU, AVAL is [redacted]. Sensitivity analyses showed that the results were most sensitive to changes in the discontinuation rate and the number of hours of nurse time for the administration of the treatments (clarification response Figure 4).

Table 58 Company's updated base-case results, discounted – cost minimisation, LOPD, discounted

	ALGLU	AVAL	Incremental
Primary therapy	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; LOPD, late-onset Pompe diseasae			

ERG's preferred assumptions

The ERG has not completed a comprehensive assessment of the cost minimisation models, however some of the ERG's assumptions related to costs for the cost utility models are also valid for the cost minimisation model. These are:

IOPD model

- **Double dosing for AVAL for the first 12 weeks:** we consider the dosing for AVAL should be the same as for ALGLU;
- **No vial sharing:** we consider that the calculated number of vials should be rounded up to the nearest whole number;

LOPD model

- **No vial sharing:** we consider that the calculated number of vials should be rounded up to the nearest whole number;

The ERG presents results below changing these assumptions. Table 59 shows the results of the ERG's preferred assumptions for the IOPD model. AVAL changes from being [redacted] to having an incremental cost of [redacted].

Table 60 shows the results of the ERG's preferred assumptions for the LOPD model. There is no change in the incremental cost for AVAL vs ALGLU. We note, however, that the results are sensitive to changes in the starting weight. For example, with a starting weight of 81 kg, the incremental cost of AVAL is [redacted] compared to ALGLU.

Table 59 ERG preferred assumptions – cost minimisation, IOPD, discounted

	ALGLU	AVAL	Incremental
Primary therapy	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, Evidence Review Group; IOPD, infantile-onset Pompe disease

Table 60 ERG preferred assumptions – cost minimisation, LOPD, discounted

	ALGLU	AVAL	Incremental
Primary therapy	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, Evidence Review Group; LOPD, late-onset Pompe diseasae

9.4 Appendix 4 ERG assessment of LOPD model stability and PSA stability

Model stability

The LOPD model is a patient-level simulation, using the DICE methodology, and includes:

- Time to reach ventilator and wheelchair thresholds,
- time of adverse events and time for time discontinuation due to the adverse effect
- time to death, general

It is necessary to perform a certain number of replications to obtain stable results. During the validation, the ERG observed issues with the stability of the model results.

The LOPD model Technical Report,[40] pages 16-18, Figures 4 and 5, describe how the company estimates the number of replications (200) for the company's base case. The methodology considers a set of runs, with a number of replications (from 1 to 700) for each run. They analysed the number of replications that are required to consider the model stable by assuming that the percentage difference in the ICER between the current replication and the average of the remaining runs should be less than 2%. The company pointed out that the stability analysis should be re-run each time the base case changes. Therefore, we consider that the number of replications used in the updated base case should have been recalculated. The ERG also considers that the company should have tested a higher number of replications to confirm the stability of the ICER.

The ERG has run a further analysis of the company's base case with an increasing number of replications (up to 3,000) to test the stability of the base case results. The incremental QALYs and life-years appear to stabilise at 200 replications. However, the incremental cost decreases as the number of replications increases (see Table 61 below). Table 62 shows changes in the confidence interval incremental cost at up to 3,000 replications, and Figure 6 shows the incremental costs for a given number of replications. After 1,000 replications, the incremental costs stabilise, and the CI is narrower than observed at 200 replications.

Table 61 Results of the company's updated base case results according to the number of replications (LOPD)

Replications	Incremental cost, £	Incremental QALYs	Incremental LY	ICER (£/QALY)
10	[redacted]	[redacted]	[redacted]	-£6,918
50	[redacted]	[redacted]	[redacted]	-£6,002
100	[redacted]	[redacted]	[redacted]	-£9,158

200*	[redacted]	[redacted]	[redacted]	**-£10,824**
500	[redacted]	[redacted]	[redacted]	-£11,154
700	[redacted]	[redacted]	[redacted]	-£12,316
800	[redacted]	[redacted]	[redacted]	-£12,608
1,000	[redacted]	[redacted]	[redacted]	-£12,830
1,500	[redacted]	[redacted]	[redacted]	-£13,418
2,000	[redacted]	[redacted]	[redacted]	-£13,231
3,000	[redacted]	[redacted]	[redacted]	-£13,471
5,000	[redacted]	[redacted]	[redacted]	-£13,195
10,000	[redacted]	[redacted]	[redacted]	-£12,997

Source: Excel LOPD company's updated CE model.
* number of replications in the CS
QALYs, quality-adjusted life years; LY, life years; ICER, incremental cost-effectiveness ratio.

Table 62 Company base case results and confidence intervals according the number of model replications (LOPD)

Number of replications	Incremental cost mean	Standard deviation	Confidence interval	% of mean
100	[redacted]	[redacted]	[redacted]	[redacted]
200	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]
800	[redacted]	[redacted]	[redacted]	[redacted]
1,000	[redacted]	[redacted]	[redacted]	[redacted]
3,000	[redacted]	[redacted]	[redacted]	[redacted]

Figure 6 LOPD company base case incremental cost vs the number of replications

The ERG also ran these analyses for the ERG base case with an increasing number of replications (up to 2,000) to test the stability of the base case results. The confidence interval was generally narrower in these analyses than for the company's base case. The incremental QALYs stabilise when using more than 200 replications, and the incremental cost stabilises after 1,000 replications (see Figure 7). The number of replications could be determined by the confidence interval required, from 200 to 1,000 replications. The ERG view that based on the confidence intervals, for the company base case there should be at least 1000 replications (CI of 11.6%, Table 62) and the ERG base case there should be at least 200 replications (CI of 3.3%, Table 63).

Figure 7 LOPD ERG preferred base case: incremental cost vs the number of replications

Table 63 ERG preferred base case results and confidence intervals for different numbers of replications

Number of replications	Incremental cost, mean	Standard deviation	Confidence interval	% of mean
100	[redacted]	[redacted]	[redacted]	[redacted]
200	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]
1,000	[redacted]	[redacted]	[redacted]	[redacted]
2,000	[redacted]	[redacted]	[redacted]	[redacted]

These two cases show us that the number of replications can vary depending on the assumptions applied in the case. Both cases stabilize the values for QALYs after 200 replications. The company base case needed more replications (1,000) to have a smaller confidence interval for the incremental cost (see Table 62). The ERG base case has a narrower confidence interval than the company base case and could run with 200 replications with a CI less than 5%.

PSA model stability

The issue of stability of the model results was also investigated for the PSA. In this case, the stability is related to a combination of the number of replications and the number of simulations. The Technical Report,[40] (pages 59-60), describes the methodology used to determine the number of simulations and replications at which the PSA becomes stable. The probability of AVAL being cost-effective at different willingness to pay thresholds was used as the outcome of interest to assess the convergence of the results. The Technical Report (Figure 14) shows the probability that AVAL is cost-effective at a different of thresholds, considering some combinations of the number of simulations and the number of replications: (400, 200), (400, 100), (300, 200), (300, 100), and (250, 100).

Due to time constraints, the ERG was not able to run a higher number of simulations (such as 600 and 900 simulations) and different combinations with the replications (100 and 200). It takes about 22 hours to complete the PSA run, with the company's suggested configuration of 300 simulations and 200 replications, and the PSA stability analysis is very time-consuming. The ERG analysed the behaviour of the company PSA by testing four different numbers of simulations (10, 50, 100, and 300) combined with the same number of replications (200). The ERG notes that the incremental ICER difference between AVAL and ALGLU reduces as the number of simulations increases.

Table 64 PSA results with different numbers of simulations using the company updated base case LOPD model

Number of PSA simulations	Incremental cost	Incremental LY	Incremental QALYS	ICER (£/QALYS)
Base case	[redacted]	[redacted]	[redacted]	-£10,824
10	[redacted]	[redacted]	[redacted]	£314,100
50	[redacted]	[redacted]	[redacted]	£285,198
100	[redacted]	[redacted]	[redacted]	£279,132
300*	[redacted]	[redacted]	[redacted]	£244,271
Source: Excel corrected LOPD CE model.				

*PSA result in the company submission.
ICER: incremental cost-effectiveness ratio; LY: life-years; ALGLU: alglucosidase alfa; AVAL: avalglucosidase alfa; QALYs: quality-adjusted life years

Figure 8 presents the PSA company base case test for 300 simulations and 200 replications and shows the mean ICER difference between AVAL and ALGLU along with the simulations. Table 65 presents the confidence interval for some number of simulations. The value of the ICER at 300 simulations has a confidence interval with 5.20% of the ICER mean.

Figure 8 LOPD company base case: ICER vs the number of simulations

Table 65 PSA company base case results and confidence intervals with various number of simulations

Number of simulations	ICER Mean (£/QALY)	Standard deviation	Confidence Interval	% of mean
10	£314,100	[redacted]	[redacted]	[redacted]
50	£285,198	[redacted]	[redacted]	[redacted]
100	£279,132	[redacted]	[redacted]	[redacted]
300	£244,271	[redacted]	[redacted]	[redacted]

The ERG also analysed the behaviour of the ERG base case PSA by testing four different numbers of simulations (10, 50, 100, and 300) combined with the same number of

replications (200) (see Table 66). We observed the same trend as in the PSA company's results in Figure 9 i.e. that the results stabilise at about 300 simulations.

Table 66 PSA results with different numbers of simulations using the ERG's base case LOPD model

Number of PSA simulations	Incremental cost	Incremental LY	Incremental QALYS	Inc. ICER (£/QALYS)
Base case	[redacted]	[redacted]	[redacted]	£398,367
10	[redacted]	[redacted]	[redacted]	£351,606
50	[redacted]	[redacted]	[redacted]	£305,939
100	[redacted]	[redacted]	[redacted]	£292,804
300*	[redacted]	[redacted]	[redacted]	£257,212

Source: Excel corrected LOPD CE model ERG base case.
*PSA result in the ERG preferred case
ICER: incremental cost-effectiveness ratio; LY: life-years; QALYs: quality-adjusted life years

Figure 9 LOPD PSA ERG base case: ICER vs the number of simulations

Table 67 LOPD PSA ERG base case results and confidence intervals with various number of simulations

Number of simulations	ICER Mean (£/QALY)	Standard deviation	Confidence Interval	% of mean
10	£351,606	[redacted]	[redacted]	[redacted]
50	£305,939	[redacted]	[redacted]	[redacted]
100	£292,804	[redacted]	[redacted]	[redacted]
300	£257,212	[redacted]	[redacted]	[redacted]

Although the ERG would have liked to explore the PSA model stability for a higher number of simulations and replications, we agree that the configuration proposed by the company (300 simulations and 200 replications) provide results with an adequate confidence interval for the company base case PSA (5.2%, see Table 65) and the ERG base case PSA (7.2%, see Table 67).

The ERG observed that the number of simulations should be at least 300 simulations and 200 replications to run the LOPD PSA, based on the results and confidence intervals for the company base case PSA and ERG base case PSA.