NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avalglucosidase alfa for treating Pompe disease [ID3737]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avalglucosidase alfa for treating Pompe disease [ID3737]

Contents:

The following documents are made available to consultees and commentators:

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

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2. **Clarification questions and company responses**
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   b. Gemma Seyfang – patient expert, nominated by the Association of Glycogen Storage Disease UK
   c. James Davison, consultant paediatric metabolic medicine – clinical expert nominated by Sanofi
   d. Robin Lachmann, consultant in inherited metabolic disease – clinical expert, nominated by the Royal College of Physicians
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avalglucosidase alfa for treating Pompe disease [ID3737]

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
ID3737_AVAL_Pompe Disease_STA Document B	2	Yes	14th January 2022

Contents

Tables and figures

Abbreviations

Acronym	Definition
AE	Adverse event
AIC	Akaike's Information Criteria
ALGLU	Alglucosidase alfa
AVAL	Avalglucosidase alfa
BIC	Bayesian Information Criteria
BMI	Body mass index
CDSR	Cochrane Database for Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CRIM	Cross-reactive immunological material
CSR	Clinical study report
DPAS	Difficulty Physical Activity Score
EPOC	European Pompe Consortium
ERT	Enzyme replacement therapy
ETP	Extended treatment period
FVC	Forced vital capacity
GAA	Acid α-glucosidase
GLI	Global lung initiative
GMFCS-E&R	Gross Motor Function Classification System - Expanded & Revised
GMFM-88	Gross Motor Function Measure-88
HHD	Hand held dynamometry
HR	Hazard ratio
HRQoL	Health-related quality of life
IAR	Infusion-associated reaction
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G
IOPD	Infantile-onset Pompe disease
IPFD	Interpalpebral fissure distance
IQR	Interquartile range
IV	Intravenous
IVFS	Invasive ventilation-free survival
KM	Kaplan-Meier
LOPD	Late-onset Pompe disease
LSD	Lysosomal storage disorder
LSM	Least squares mean
LVM	Left ventricular mass
LVMI	Left ventricular mass index
MCID	Minimum clinically important difference
MCS	Mental component score
MEP	Maximum expiratory pressure

Acronym	Definition
MIP	Maximum inspiratory pressure
mITT	Modified intention-to-treat
MMRM	Mixed Model Repeated Measures
MPD	Margin pupil distance
MRD-1	Margin to reflex distance 1
MTD	Maximally tolerated dose
M6P	Mannose-6-phosphate
NHS	National Health Service
OS	Overall survival
PAP	Primary analysis period
PAS	Patient access scheme
PCS	Physical component score
PD	Pharmacodynamics
PDIS	Pompe disease impact scale
PDSS	Pompe disease symptom scale
PedsQL	Pediatric Quality of Life Inventory
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
Pompe-PEDI	Pompe-Pediatric Evaluation of Disability
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QMFT	Quick motor function test
QoL	Quality-of-life
qow	Once weekly
RCT	Randomised controlled trial
R-PAct	Rasch-built Pompe-specific Activity scale
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SFN	Small fibre neuropathy
SF-12	Short form health survey – 12 questions
SF-36	Short form health survey – 36 questions
SLR	Systematic literature review
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSS	Total symptom score
UK	United Kingdom
uRTI	Upper respiratory tract infection
US	United States
VAS-OBS	Observational visual analogue scale
VFS	Ventilation-free survival
6MWT	Six-minute walk test

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

Pompe disease

- Pompe disease is an inherited lysosomal storage disorder. It is chronic, progressive, and very debilitating. The disease is caused by mutation of the *GAA* gene, which results in reduced or absent activity of acid α-glucosidase (GAA) protein (1). GAA is responsible for the degradation of lysosomal glycogen into glucose, which is particularly important in muscle cells across various tissues (2-4). Multiple systems are thus impaired including the cardiovascular, respiratory, musculoskeletal, and gastrointestinal. The condition is chronic and severely disabling and results in substantially reduced quality of life (5) and often lower life expectancy than that in the general population (6, 7).
- The disease can be defined as having two main subtypes, late-onset Pompe disease (LOPD) and infantile-onset Pompe disease (IOPD).
- IOPD typically manifests during the first weeks of life, with the most common symptoms in untreated patients being cardiomegaly (enlarged heart), hypotonia (decreased muscle tone), hypertrophic cardiomyopathy (abnormally thick heart muscle), respiratory distress, and rapidly progressive muscle weakness (particularly of the upper and lower limbs) (5, 8, 9). In untreated IOPD patients life expectancy is often below 12 months (7).
- LOPD is more heterogeneous than IOPD, comprising juvenile and adult patients who present with more slowly progressing phenotypes which typically spare the cardiovascular system (10). While the mean age of symptom onset is between 30–50 years, LOPD may first present as early as infancy, or as late as the seventh decade of life (5).
- This irreversible functional loss and resulting severe disability eventually leads to dependency on wheelchair use and invasive ventilation, and premature death (6).

- Patients experience significantly reduced quality of life (QoL) in the domains of physical functioning, general health, vitality and social functioning (11). The disease also impacts day-to-day life for families and friends of patients, putting strain on relationships. Many family members give up jobs or leisure time to help care for patients, contributing to an increased psychological, societal and economic burden (12, 13).

Unmet need

- Enzyme replacement therapy (alglucosidase alfa [ALGLU; Myozyme®]) has transformed the course of Pompe disease by extending overall survival and slowing disease progression, however, after a period of improvement and stabilisation, the disease progression can resume; in addition response to treatment can vary between patients, reflecting the heterogeneous nature of the disease (14, 15). There is therefore a need for improved treatment options that can offer greater benefit and longer duration of response than the current standard-of-care.
- Without treatment, patients with IOPD typically die from cardiorespiratory complications before two years of age, with a median age of death at 8.7 months (6). Furthermore, even with ERT enabling survival to adulthood, outcomes are poor for patients with IOPD, particularly for those who are CRIM-negative (who produce no or a radically truncated endogenous enzyme) (16) and require additional immune tolerance induction to enhance ERT efficacy (7). In LOPD, treatment with ALGLU reverses or minimises the disease progression, however patients may eventually begin to decline again and will require an alternative treatment.

Avalglucosidase alfa

- Avalglucosidase alfa (AVAL) is a next-generation, recombinant human GAA enzyme replacement therapy for the treatment of patients with IOPD and LOPD.
- Compared with ALGLU, AVAL has a 15-fold increase in mannose 6-phosphate moieties, which enhance its receptor-mediated uptake (17, 18), leading to increased glycogen clearance in muscle tissues. This is expected

to lead to long-term benefits in muscle function (including cardiac, respiratory and skeletal), improved outcomes for patients and delay in the onset of disability.

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

The company submission is consistent with the final NICE scope (19) and the NICE reference case (20), with differences outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Children and adults with Pompe disease	As per final scope	NA
Intervention	Avalglucosidase alfa	As per final scope	NA
Comparator(s)	Alglucosidase alfa	As per final scope	NA
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 • immunogenicity response • adverse effects of treatment • health-related quality of life (for patients and carers)	As per final scope	NA
Economic analysis	The reference case (20) 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 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.	A conservative cost-comparison approach is presented in the base-case.	• **LOPD:** In the pivotal phase 3 COMET trial, AVAL demonstrated non-inferiority vs ALGLU in the primary endpoint of FVC% predicted at Week 49, however there was a trend for improvement across a broad range of outcomes related to respiratory and musculoskeletal health, as well as patient reported outcomes including QoL (Section B.2.6.1). • **IOPD:** Despite trends for improvement or stabilisation with AVAL across several clinical outcomes in the phase 2 Mini-COMET trial

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			(Section B.2.6.2), extrapolation of outcomes in a cost-effectiveness analysis would require multiple assumptions and be associated with a significant amount of uncertainty. • Given that AVAL offers greater health benefits than ALGLU [redacted], a cost-comparison approach is considered the most appropriate basis for decision making. This is both a pragmatic and conservative approach that should enable rapid access to AVAL. • A cost-effectiveness analysis is presented for reference in Appendix L, and also shows AVAL to be a cost-effective and cost-saving option.

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC, forced vital capacity; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

B.1.2 Description of the technology being appraised

The draft Summary of Product Characteristics is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Avalglucosidase alfa (Nexviadyme®)
Mechanism of action	Pompe disease is a rare progressive metabolic muscle disorder resulting in severe disability and a reduced life expectancy compared with the general population. It is inherited in an autosomal recessive manner and defined by a deficiency of GAA (Section B.1.3). Avalglucosidase alfa is a recombinant human, next-generation ERT. It replaces the deficient GAA enzyme in patients with Pompe disease, enabling degradation of glycogen within lysosomes. Cellular uptake is primarily mediated by binding to cell surface M6P receptors (21). Compared with ALGLU (Myozyme®), AVAL has a 15-fold increase in M6P levels, which enhance its receptor-mediated uptake (17, 18). Preclinical studies using *in vivo* Pompe models have demonstrated that, compared with ALGLU, AVAL has a 1000-fold higher binding affinity to M6P receptors (17, 18), leading to greater glycogen clearance from muscles at one-fifth of the dose of ALGLU (18).
Marketing authorisation/CE mark status	AVAL received promising innovative medicine designation from the MHRA in September 2020, and an EAMS positive scientific opinion was awarded on 5th March 2021 (EAMS number: 04425/0004) for the following indications, which are more limited than the anticipated licensed indication and the population addressed in this appraisal: • 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. In early October 2020, the EMA accepted for review the MAA for AVAL. Final CHMP positive opinion was received in November 2021, with MHRA and EMA marketing authorisation anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated licensed indication is for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).
Method of administration and dosage	IV administration. Single-use vial containing 100 mg AVAL. After reconstitution, the solution contains 10 mg of AVAL per mL. Each vial contains 10.3 mL reconstituted solution and a total extractable volume of 10.0 mL at 10 mg/mL.

	AVAL is to be administered IV at a dose of 20 mg/kg of body weight once every 2 weeks for patients with LOPD and IOPD. For patients with IOPD who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg qow should be considered in the absence of safety concerns (e.g. severe hypersensitivity, anaphylactic reactions, or risk of fluid overload).
Additional tests or investigations	It is not anticipated that any additional tests or investigations will be required.
List price and average cost of a course of treatment	The list price for AVAL is [redacted]. The cost of a year's treatment for a typical adult weighing 78.5 kg is [redacted]. The cost of a year's treatment for a child weighing 22.3 kg is [redacted].
Patient access scheme (if applicable)	A PAS has been agreed with NHS England and NHS Improvement. This scheme is a simple discount. The PAS price for AVAL is [redacted].

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CHMP, Committee for Medicinal Products for Human Use; EAMS, Early Access to Medicines Scheme; ERT, enzyme replacement therapy; EMA, European Medicines Agency; GAA, acid α-glucosidase; IOPD, infantile-onset Pompe disease; IV, intravenous; kg, kilogram; LOPD, late-onset Pompe disease; M6P, mannose 6-phosphate; MAA. Marketing Authorisation Application; mg, milligram; MHRA, Medicines and Healthcare Products Regulatory Agency; mL, millilitre; NHS, National Health Service; PAS, patient access scheme; qow, every other week.

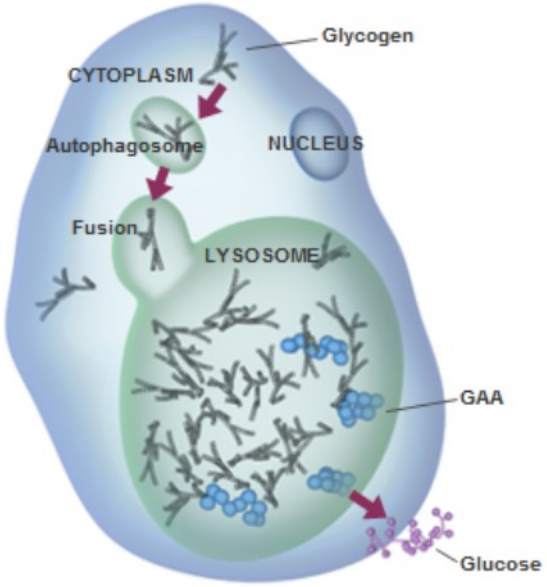
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Pathogenesis

Pompe disease is a progressive metabolic muscle disorder resulting in severe disability and a reduced life expectancy compared with the general population (6, 7). It is a lysosomal storage disorder (LSD), which stems from mutation in the *GAA* gene. Pathogenic mutations result in the production of a lysosomal enzyme (acid α-glucosidase; GAA) with little to no enzymatic activity, or very low levels of the wild-type GAA protein (1).

GAA is responsible for the degradation of lysosomal glycogen into glucose, cleaving alpha-1,4 and alpha-1,6 linkages in glycogen molecules under the acidic conditions of the lysosome. Its function is particularly important in muscle cells where, second only to the liver, the majority of glycogen is found (Figure 1) (Appendix C).

Figure 1: Endogenous GAA pathway



Adapted from Raben 2002 (22).
Abbreviations: GAA, acid alpha-glucosidase.

Deficiency of GAA results in the intra-lysosomal accumulation of glycogen in various tissues (2-4), which significantly impairs the function of muscle tissue. Therefore, Pompe disease affects multiple systems, including the cardiovascular, gastrointestinal, musculoskeletal and respiratory systems in which the normal functioning of muscle cells is essential (5).

In the earlier stages of Pompe disease, small lysosomes filled with glycogen molecules begin to accumulate between healthy myofibrils; the affected lysosomes becoming swollen and distorted over time. This disrupts the muscle tissue architecture and function and initiates the early clinical signs of muscle weakness. Eventually, lysosomes rupture and release glycogen, along with lytic enzymes, into the cell cytoplasm (Figure 2). The release of lytic enzymes results in the loss of contractile force as myofibrils are degraded via autophagy, resulting in irreversible cellular damage (3, 4, 23). Loss of muscle tissue and its replacement by fat tissue is observed, and a corresponding irreversible loss of function is experienced by the patient.

Figure 2: Progression of Pompe disease

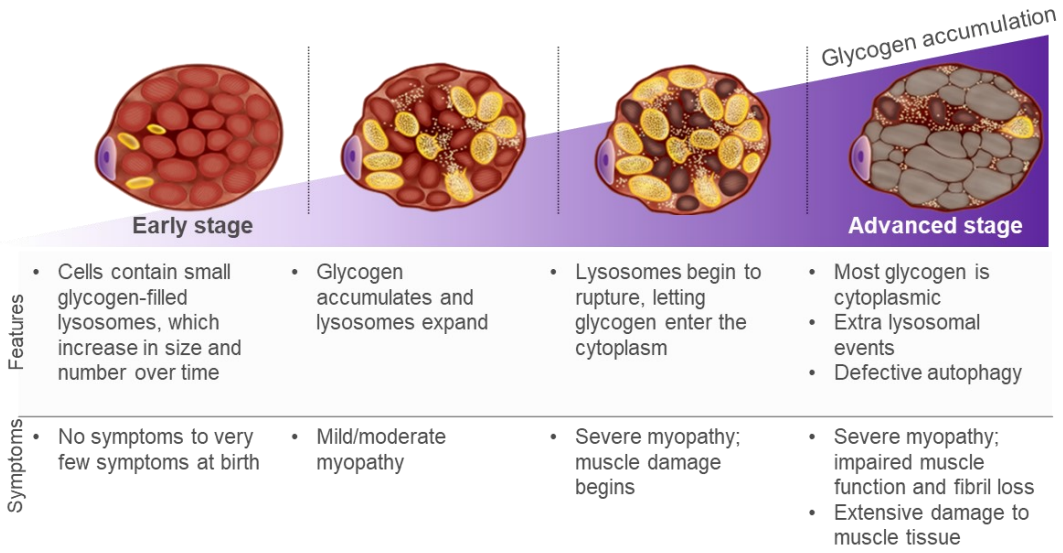


Illustration from Thurberg 2006 (3).

B.1.3.2 Genetics of Pompe disease

Pompe disease is an autosomal recessive disorder, meaning that in general, both parents will be asymptomatic carriers of the disease and likely unaware of the presence of the pathogenic gene. Like other lysosomal storage disorders, Pompe disease presents with significant genetic heterogeneity. Over 560 pathogenic *GAA* mutations have been reported, with more being discovered each year. These include missense, nonsense and splice-site variants, partial deletions, and insertion mutations (24), and thus a wide spectrum of disease severity results.

Despite associations between particular mutations and specific phenotypes, considerable clinical variation is observed between patients with the same mutation and haplotype (25). Even between siblings with identical genetic mutations, the age of symptom onset and clinical course of Pompe disease can be variable, indicating a likely influence of genetic background and environmental factors on *GAA* gene expression (2, 26).

In general, patients with IOPD harbour mutations that completely halt the expression of all forms of the GAA protein or lead to a low expression of mutant forms of GAA that fail to retain essential levels of enzymatic activity (1).

B.1.3.3 Pompe disease classification

Although Pompe disease represents a wide spectrum of clinical phenotypes, it is broadly classified into two subgroups, related to clinical presentation and levels of GAA activity. Infantile-onset Pompe disease (IOPD) is characterised by onset of symptoms such as cardiomyopathy, hypotonia and respiratory distress by one year of age and their rapid progression (5, 6, 8, 9). Patients generally have ≤1% GAA activity compared with normal range. Patients with late-onset Pompe disease (LOPD) generally present later in life than those with IOPD (mean age of symptom onset is between 30–50 years) (5), although in some cases the disease can become apparent as early as in infancy. The most common symptoms include muscle weakness and respiratory difficulties (8, 9), with the cardiovascular system typically spared (10). In patients with LOPD 1–30% of normal GAA activity can be observed (27).

Depending on whether endogenous GAA protein is present or absent, patients are categorised into cross-reactive immunological material (CRIM)-positive (GAA is present), or CRIM-negative (GAA is absent). Therefore, all LOPD patients are CRIM-positive, as are those IOPD patients with certain missense mutations. However, infants who have inherited biallelic *GAA* variants which produce no enzyme (null variants) are CRIM-negative (28). CRIM-negative patients typically have poorer outcomes compared with the CRIM-positive patients (16) and require immune tolerance induction to initiate ERT (7).

B.1.3.4 Symptoms and disease progression

B.1.3.4.1 *IOPD*

IOPD typically manifests during the first weeks of life, with the most common symptoms in untreated patients being cardiomegaly, hypotonia, hypertrophic cardiomyopathy, respiratory distress, and rapidly progressive muscle weakness (particularly of the upper and lower limbs) (5, 8, 9). Table 3 presents the frequency of presenting signs and symptoms, and the average age of onset, in untreated patients with IOPD.

Table 3: Frequency of presenting signs and symptoms, and mean and median ages at onset of first symptoms

Sign/symptom	Frequency (%) (N=168)	Age at presentation, months	
		Mean (SD)	Median
Cardiomegaly	154 (91.7)	4.1 (3.1)	4.0
Hypotonia	148 (88.1)	3.9 (2.7)	4.0
Cardiomyopathy	147 (87.5)	4.2 (4.7)	3.8
Respiratory distress	131 (78.0)	4.3 (4.4)	4.0
Muscle weakness	105 (62.5)	4.5 (3.1)	4.0
Feeding difficulties	96 (57.1)	3.4 (2.7)	3.7
Failure to thrive	89 (53.0)	4.2 (2.6)	4.0
Congestive heart failure	84 (50.0)	5.1 (2.4)	4.5
Gastroesophageal reflux	16 (9.5)	5.3 (5.6)	4.3
Sleep apnoea	6 (3.6)	4.0 (2.4)	3.5
Other symptoms	60 (35.7)	3.9 (2.7)	4.0

Adapted from Kishnani 2006 (6).
Abbreviations: N, number; SD, standard deviation.

Musculoskeletal abnormalities, leading to failure to thrive and poor motor development, typically appear between 1.6–2 months of age (29), while respiratory insufficiency, caused by diaphragmatic and intercostal muscle weakness (6), leads to respiratory distress and frequent infections. Respiratory distress often results in the need for assisted ventilation by 6 months of age, also limiting mobility and leading to mortality in patients who are untreated (8).

Since the approval of ALGLU, it has become clear that IOPD is a multisystemic disorder, and that individuals develop clinical symptoms not known in the pre-ERT era (7). Features of this new IOPD phenotype include cardiac, speech, hearing, musculoskeletal, respiratory, swallowing, and neurocognitive symptoms (7).

B.1.3.4.1.1 IOPD treated with ALGLU

While the disease is often fatal within 12 months for untreated patients, ALGLU has transformed IOPD from a rapidly progressive disease into a chronic condition (7). In the pivotal US-based clinical trial by Kishnani et al. (30), ALGLU improved overall survival (OS) of patients with IOPD (24-month survival rate of 94.4%), and at 52 weeks, motor and functional scores using the Alberta Infant Motor Scale were improved in 72% of patients. Treatment with ALGLU also improved markers of cardiac impairment, reducing left ventricular mass index (LVMI) by 55% (30).

A UK-based retrospective study (conducted between January 2000 and June 2014) by Broomfield 2015 (16) reported that 60% of patients with IOPD treated with ERT were still alive at the end of data collection (median duration of ERT use was 3 years and 10 months; range 6 months to 13 years and 7 months). ERT has been transformative for these patients, and of those with up to 42 months data, 54% were alive and 30.6% were ventilation-free. The study included patients with CRIM-negative and CRIM-positive status; CRIM-negative status was significantly related to poorer overall survival (p=0.03).

Survival rates in patients treated with ALGLU are in stark contrast with survival rates in untreated patients. A chart review, focussing on the natural history of IOPD in 168 infants, reported a median age of death of 8.7 months, with 144 deaths reported. Survival rates at 12 months of age were 25.7% overall, while ventilator-free survival was 16.9%.(6). Thus, treatment with ALGLU has transformed IOPD from rapidly progressing fatal disease to a chronic, manageable condition.

In many patients, progressive skeletal muscle weakness results in loss of acquired motor milestones, and patients eventually require support with orthopaedic devices and wheelchairs (7). Patients also have weakness of both inspiratory and expiratory muscles (7). Mucus accumulation, lung collapse, and pulmonary infection arise from reduced ability to cough due to expiratory muscle weakness (7). Inspiratory muscle weakness reduces exercise tolerance and predisposes to ventilatory failure during respiratory tract infections and chronic ventilatory fatigue that ultimately results in the need for ventilation (7).

ALGLU improves cardiac function within a few months in most patients, however some patients who start treatment late experience reduced exercise tolerance and chronic heart failure during follow-up (7).

B.1.3.4.2 *LOPD*

LOPD is more heterogeneous than IOPD, comprising juvenile (1+ years old) and adult patients who present with more slowly progressing phenotypes which typically spare the cardiovascular system (10). While the mean age of symptom onset is between 30–50 years, the diverse severity of LOPD means it may first present as early as infancy, or as late as the seventh decade of life (5).

As with IOPD, multiple systems are affected in patients with LOPD. Table 4 presents the common symptoms of LOPD classed by system; this is not an exhaustive list owing to the wide heterogeneity of the disease.

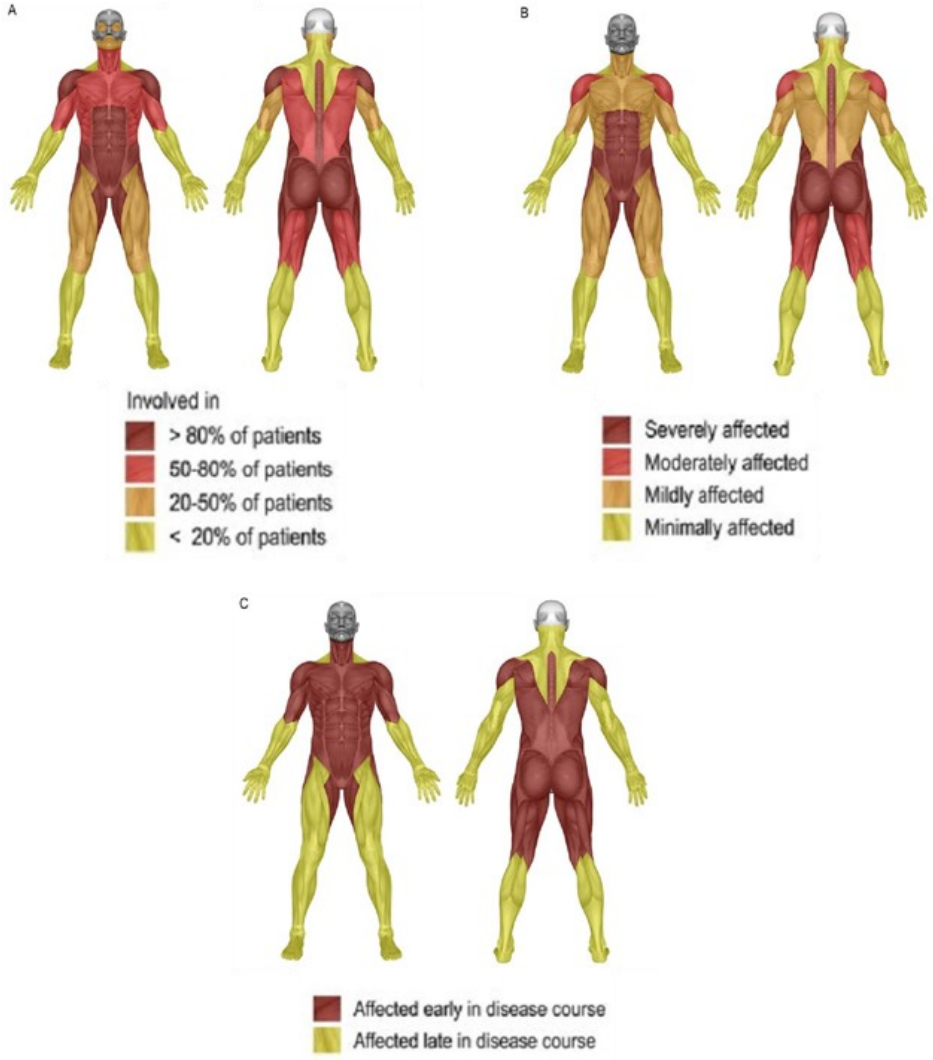
Table 4: Common clinical manifestations and systems affected in LOPD

System Symptoms
Respiratory
Respiratory failure/insufficiency, diaphragm weakness, sleep-disordered breathing, orthopnoea, dyspnoea, fatigue
Musculoskeletal
Limb-girdle muscle weakness, muscle pain, frequent falls, gait abnormalities, difficulty walking/climbing stairs, scoliosis/scapular winging
Cardiac
Rhythm disturbances
Gastrointestinal
Difficulty chewing/jaw muscle fatigue, poor weight gain/maintenance, swallowing difficulties/weak tongue, gastrointestinal reflux
Neurological
Small-fibre neuropathy – leading to painful paraesthesia of the extremities
Urinary
Incontinence, post-void dribbling

Abbreviations: LOPD, late-onset Pompe disease.
Adapted from Laforet 2008; Wokke 2008; Hirschhorn 2014 and Hobson-Webb 2015 (5, 31-33).

The LOPD subtype is characterised by progressive muscle weakness, particularly within the proximal lower extremity and trunk muscles, as well as upper limbs, such as shoulder girdle and neck flexors, alongside respiratory insufficiency and gastrointestinal upset (Figure 3) (8, 9, 34). One prospective LOPD cohort study reported that proximal muscle weakness in the lower extremities was the presenting symptom in 93.1% of patients (32).

Figure 3: Muscle weakness in adults with LOPD



Distribution of skeletal muscle weakness (A), severity of muscle weakness of the individual muscle groups (B), and involvement of the individual muscles over time (C) in 94 adults with Pompe disease. Adapted from Van der Beek 2012 (35).

Other symptoms which may present in patients with LOPD include pain, fatigue, neuropathy, vascular, and urinary symptoms (36-38).

In a cross-sectional survey of 124 individuals with Pompe disease, nearly half (45%) reported experiencing pain in the previous 24 hours, compared with 27% of a control population of 111 individuals (p=0.004) (39). The back (50%), the shoulders (48%), and the upper legs/thighs (46%) were the most affected, and the most common word used to describe the pain was ‘exhausting’ (70%). Pulling/tearing pains were also frequent in patients (57%). Relative to patients without pain, those with pain had lower scores for physical and mental health, and higher levels of depression and anxiety (39). There may be multiple contributors to pain in Pompe disease, including postural problems due to muscle weakness and muscle pain (39).

Patients may also develop small-fibre neuropathy (SFN), a possible consequence of glycogen accumulation in peripheral nerves which results in painful paraesthesia of the extremities (40). One prospective study conducted in 44 patients with Pompe disease demonstrated that 50% of patients may have comorbid SFN (33).

Up to 76% of patients across the LOPD clinical spectrum report fatigue, appearing to result from respiratory muscle weakness (38). During interviews investigating patient experience with Pompe disease, one patient described how fatigue was a "*major aspect of Pompe disease*", stating "*general fatigue and muscle fatigue mean I have to be careful about what I choose to take on*" (41).

Patients with LOPD who are reliant on wheelchair use and/or respiratory support have significantly higher Fatigue Severity Scale scores compared with patients who do not rely on such support (37). In addition, patients with LOPD frequently suffer from urinary symptoms such as incontinence and post-void dribbling (54% and 46% of patients, respectively) (42). The impact of incontinence may be compounded in those with mobility issues by being socially limiting and further impacting QoL.

The impact of the late-onset disease on patient's daily life is often substantial and commences with initial signs and symptoms such as difficulty in walking, rising from a chair or climbing stairs (43). Patients may also experience general decline in physical capabilities, change in gait and falls (44). Over time, most patients become wheelchair-bound (43). Patients value their independence, and the increasing reliance on mobility aids as their disease progresses diminishes it (43, 45). Loss of proximal muscle strength means simple tasks such as getting out of bed and getting up off the toilet become increasingly difficult, and while adaptions may be made at home, leaving the house becomes progressively more challenging, further impacting the quality of life of the individual and the family (45).

Initial respiratory clinical manifestations may be related to sleep apnoea and include disturbed sleep resulting in daytime somnolence (sleepiness) and morning headache; breathlessness and fatigue adds substantially to the psychosocial burden of Pompe disease (46).

As the disease progresses, many patients eventually require non-invasive or invasive ventilation (comprising an endotracheal tube and a mechanical ventilator

(47)), and ultimately progress to respiratory failure; the leading cause of death in patients with LOPD (22, 48). Wokke 2008 reported that 65.5% of patients with LOPD had FVC sitting values of <80%, indicating varying degrees of restrictive respiratory disease, ranging from mild to very severe (32). Loss of independence is a real fear for patients; some resist the use of a ventilator at night, fearing being unable to breathe unaided and increased breathing difficulties and resultant death (49). In a review of studies on non-invasive ventilation experiences in adults with hypercapnic respiratory failure, several studies highlighted fear of the ventilation machine and feelings of being out of control and reliant on technology for survival (50).

B.1.3.4.2.1 LOPD treated with ALGLU

In LOPD, treatment with ALGLU, particularly when administered close to the time of disease onset, can slow disease progression and promote clinically meaningful patient outcomes (15). In the LOTS randomised controlled trial (RCT), treatment with ALGLU significantly increased both the distance walked during the 6MWT (ALGLU: 25.13 m improvement; placebo: 2.99 m decrease; p=0.03) and the percentage of the predicted FVC in the upright position (ALGLU: 1.20% improvement; placebo: 2.20% decrease; p=0.006) (51, 52). In the extension phase, patients treated with ALGLU for up to 104 weeks maintained the improved walking distance and stabilisation in pulmonary function (53).

In a long-term study including 189 patients followed up for a median of five years, treatment with ALGLU reduced the risk of wheelchair dependence (HR 0.36; 95% CI 0.17–0.75) (54). Another study included 174 patients who had previously experienced a decline in their quality of life, with SF-36 physical component score decreasing by a mean of 0.73 per year (95% CI: -1.07, -0.39). During the first two years of treatment with ALGLU the SF-36 physical component score of these patients improved by a mean of 1.49 (95% CI: 0.76, 2.21). In addition, the study showed a positive effect of ALGLU treatment on the ability to participate in everyday activities (as measured by the Rotterdam handicap scale score) which was declining prior to ERT and then stabilised in the first two years following the initiation of treatment (55).

In another 9-year observational study, ERT was positively associated with survival in patients with LOPD (hazard ratio [HR]: 0.41; 95% CI: 0.19, 0.87) demonstrating its effectiveness in the wider population (56).

B.1.3.5 Epidemiology

Due to its rarity and complexity, Pompe disease presents a unique challenge with regards to estimating the number of patients affected. Lack of awareness, variation in presentation and symptomatic overlap with other more common diseases can result in missed and delayed diagnoses (57). As a result, and due to underlying variation between countries, birth prevalence estimates of Pompe disease vary considerably.

No study investigating the prevalence of Pompe disease within the UK has been completed. However, the Association for Glycogen Storage Disease estimates approximately 200 patients in the UK have Pompe disease (58). This is consistent with the analysis from The Clinical Practice Research Datalink (CPRD); the point prevalence in December 2019 was estimated to be 1 in 308,642 (95% CI: 1 in 252,5251, 1 in 383,142), equating to approximately 183 patients in England (59). The CPRD analysis also estimated the incidence of Pompe disease between January 2000 and December 2019 to be 1 in 5,882,352 person-years (95% CI: 1 in 4,761,905, 1 in 7,142,857), with approximately five patients diagnosed each year (59).

Table 5 presents a list of studies reporting the estimated birth prevalence of Pompe disease by stage of onset.

Table 5: Birth prevalence estimates of Pompe disease

Country	Birth prevalence estimate	Source
Estimates using traditional enzymatic assays		
Australia†	1 in 146,000 (all types)	Meikle 1999 (60)
Czech Republic	1 in 435,679 (infantile) 1 in 694,655 (juvenile)	Poupětová 2010 (61)
Netherlands†	1 in 101,000 (infantile) 1 in 720,000 (juvenile) 1 in 53,000 (adult)	Ausems 1999 (62)
	1 in 76,336 (infantile) 1 in 142,857 (juvenile and adult)	Poorthuis 1999 (63)

Country	Birth prevalence estimate	Source
	1 in 50,000 (all types)	
Portugal†	1 in 588,235 (all types)	Pinto 2004 (64)
Estimates using newborn bloodspot screening		
Austria	1 in 8,684 (all types)	Mechtler 2012 (65)
Taiwan	1 in 57,000 (infantile)	Yang 2014 (66)
	1 in 18,108 (all types) 1 in 57,343 (infantile) 1 in 26,466 (late-onset)	Chien 2011 (67)
United States	1 in 27,800 (late-onset)	Scott 2013 (68)
	1 in 5,463 (all types)	Hopkins 2015 (69)

†Estimates include prenatal and postnatal diagnoses.

B.1.3.6 Burden of Disease

B.1.3.6.1 *Impact on patients with IOPD*

Patients with IOPD become wheelchair- and ventilation-dependent; untreated patients require invasive ventilation by six months of age, never learn to sit, crawl or walk, and usually die from cardiorespiratory failure within one year (6). ALGLU has been available in clinical practice since 2006 (70) and has allowed numerous patients who would have otherwise died in infancy to experience childhood and adolescence. In addition, as experience with ALGLU continues, it may be expected that the lives of at least some IOPD patients will continue beyond adolescence. Although the longer life has been of huge meaning to the patients and their families, QoL in IOPD is often severely impaired when compared with other children their age.

B.1.3.6.1.1 Impact on education

Children with IOPD who reach school-age can attend specialist schools with the necessary adaptations in place but require additional support and care. The disease can also impact their academic performance. One study in children with IOPD who were treated with ERT reported that patients with below average academic skills demonstrated average non-verbal cognitive abilities but had weakness in speech and language skills. These observations were consistent with a learning disability diagnosis compared with an intellectual disability (71).

B.1.3.6.1.2 Impact on wellbeing and mental health

The impact of Pompe disease on children's wellbeing and mental health is high, particularly due to the inability to take part in activities other children enjoy. In

caregiver interviews, one parent of a child with IOPD stated *"he is in a wheelchair most of the time… he faces why he is having this condition and his siblings are not, so he is kind of very angry at the moment… he is very, very upset"* (41).

One study investigated the experience of children with a broad range of inborn errors of metabolism, including Pompe disease, in which life transition, including the challenges related to having a social life, and coping with uncertainty were common themes amongst parents who were interviewed (72). One parent described the limitations imposed by a progressive metabolism disorder and the challenges it may introduce for sustaining long-term, meaningful friendships, "*kids are really good with him, but no one will come over and play… they're at an age where they talk really quick and they do things really quickly and [he's] in a wheelchair now… so like I said, they're always incredibly friendly but there's nobody who would come over and watch a movie with him"* (72).

B.1.3.6.1.3 Impact of mechanical ventilation

The need for invasive ventilation related to disease progression is more common in IOPD than LOPD (73). Based on clinical expert advice, once respiratory function starts to deteriorate, patients decline quickly and often need invasive ventilation within a couple of years of starting NIV. The process of initiating invasive ventilation is difficult for patients and caregivers. Patients are initially admitted to ICU to have the tracheostomy tube surgically inserted (74). Following this, in accordance with expert advice, they often need to stay in hospital for several months while their home is adapted to their needs. Patients are equipped with a second backup ventilator and a battery operated one that can be attached to a wheelchair and used in case of power cuts. Caregivers require comprehensive training to support an invasively ventilated child (75). Common procedures that may have to be carried out by parents include for example changing the tracheostomy tapes, ventilator care, or infection control (76).

The need for invasive ventilation increases the risk of complications. In accordance with a survey carried out in patients with Duchenne muscular dystrophy (77), [redacted]

[redacted]. It also causes anxiety about the potential failure of the ventilator for both the patient and their family, as well as the need to have a carer present at all times.

B.1.3.6.2 *Impact on patients with LOPD*

Due to the number of symptoms and associated morbidity of Pompe disease, QoL is significantly reduced compared with the general population (including in the domains of physical activity, perceived health, vitality, and social activity) (11, 45). Disease progression causes irreversible loss of physical functionality and may subsequently lead to dependency on mobility aids (e.g. wheelchair use), home assistance, home adaptations, rehabilitation and physiotherapy (78, 79), while reducing ability to attend school or the workplace and socialise.

B.1.3.6.2.1 Impact on mental health

Pompe disease impacts mental health, with patients commonly experiencing anxiety and depression and requiring psychological support (Appendix M). In addition to their physical abilities making some activities of everyday living harder and their 'world smaller,' some describe consciously withdrawing from friends, especially while coming to terms with the diagnosis to avoid talking about it and to avoid the need to ask for help.

The Pompe PROM study (41, 80), which consisted of interviews with patients with Pompe disease and their carers, reported that patients described suffering from fear, worry, frustration, depression, and uncertainty. When asked about living with Pompe disease, one patient stated, "*Life with Pompe disease for me is difficult, because of the progressive muscle weakness and the fact I'm using a wheelchair and ventilator pretty much 24 hours a day. I also have care needs; I need help with everything, transferring in and out of bed, using the toilet and other activities of daily life… I'm relying on other people all of the time and when I'm alone, I am more vulnerable to accidental falls. If I fall from my wheelchair, I will likely not survive because I cannot breathe… With relationships with family and friends, it definitely has an effect. I can't go out as much and meet people"* (41).

The Pompe PROM study (41, 80) reported that 18% of patients experienced depression, compared with 4.5% of the general UK population (81). Moreover, 22%

of patients experienced frustration, and 21% had coping issues. Pompe disease is associated with a high prevalence of pain, which has a negative impact on mental wellbeing (39).

B.1.3.6.2.2 Impact on daily activities

The impact of LOPD on daily activities is profound and reflects the multi-system nature of the disease. Patients with the disease frequently experience their lives being limited by symptoms such as mobility problems, fatigue, breathlessness, disturbed sleep, gastrointestinal and urinary symptoms, difficulties swallowing, muscle pain, or anxiety and depression (44). As their condition deteriorates, patients need to adjust their lifestyle to the limitations imposed by their disease, allow more time for everyday activities (82), and rely increasingly on their family members and carers. This can also mean having to reduce hours or stop working, experiencing negative changes to family relationships, limitations to social life, or being unable to go on holiday (44). Over time patients need to introduce numerous modifications to their homes to adapt to the progressing disability (83). The process can be costly and the available funding insufficient to cover all the expenses. In some cases, moving home may be necessary, for example to ensure wheelchair access (41).

This is reflected in a subgroup analysis of a large international study including 51 patients with untreated LOPD showed they had significantly lower SF-36 scores compared with the general population in the domains of physical functioning, general health, vitality, and social functioning. Differences on the physical functioning scale were most profound, with patients with LOPD reporting three-times lower physical functioning compared with the general population (score of 29.3 vs. 83.1) (11). This further demonstrates the broad impact of Pompe disease with its effects being far greater than that of the muscle biology.

Fatigue is a common life-limiting factor which greatly impacts patients' QoL, with up to 76% of patients with LOPD reporting that they are troubled by fatigue (38). Patients have described the significance of fatigue associated with Pompe disease, stating "*one of the major aspects is fatigue; general fatigue and muscle fatigue, so I have to be quite careful about what I choose to take on…"* and *"I'm very tired after the day, I [have] no energy until the next day… I'm drained because of [Pompe*

disease]" (41). Fatigue may impact capacity to perform adequately in daily life; at school or work, to do household chores or take part in social activities (45).

Pompe disease may also lead to impaired speech, ability to chew and swallow food (84). In addition, through the weakening of gastrointestinal musculature, patients may develop significant gastrointestinal upset. Stool urgency and diarrhoea are more common in adults with Pompe disease (55% and 56%, respectively) compared with age- and gender-matched controls (20% and 18%, respectively). Moreover, 20% of patients rely on over-the-counter medications such as loperamide to help control symptoms (85).

B.1.3.6.2.3 Impact of ventilation

Weakening of the diaphragm and other respiratory muscles over the course of LOPD is a major cause of respiratory failure and often results in the eventual dependence on night-time or full-time respiratory support or invasive ventilation; this pivotal moment in the course of the disease has a substantial impact on the everyday lives of patients and their relatives (51, 86), including their social lives and education/employment. Many patients are reluctant to initiate or remain on mechanical ventilation due to the psychological aspects of the therapy; the introduction of, and reliance on, a noisy machine, sleep disturbance and discomfort (87). [redacted] (77). In ERT-naïve patients, home ventilatory support is associated with lower physical health-related quality of life (HRQoL) and activities of daily living (88).

B.1.3.6.3 *Caregiver burden*

Pompe disease symptoms and diagnosis may be frightening for both the patients and their carers. It also impacts day-to-day life for families and friends of patients, having the potential to significantly affect personal relationships and family activities. One patient described the effects of Pompe disease on relationships, stating *"A life changer for me is that I've separated from my wife, I think she found it harder to deal with than I did. She went into quite a severe depression. I'm looking to date again, but it's hanging over me that at some point, I'm going to need to broach the subject with any new potential partner"* (41).

One study reported that 73% of patients were recipients of informal care. For adult patients, partners most often provide care for the patient (92%), while parents make up the majority of caregivers (94%) providing informal care for patients under the age of 18 (13). Many caregivers give up jobs or leisure time to help care for patients, contributing to an increased societal and economic burden (12, 13).

Both patients and carers have discussed how the disease results in care dependence. One patient said **"***I can't walk, I have to use a wheelchair unless I'm in my own house, where I use a Zimmer frame. There are lots of things I can't do… I have a cleaner that comes for me twice a week… I have to leave things until I can ask my dad, friends or neighbours to come and give me a hand"* (41). [redacted]

Three carers discussed the impact the care they provide for their loved ones has on their own wellbeing (41). A parent of two LOPD patients stated *"It was quite consuming when the boys were at school… I worried every day, really... I couldn't work, it was too much to think about".* Caring for a child with IOPD was described by one parent who stated "*He couldn't sleep at night… I had to put him on my shoulder, all night sitting on a chair or a sofa, because if I put him down, he couldn't breathe. As a single mother, it is very, very hard. [I have] physical exhaustion, I was quite healthy before".* When support is provided to patients by friends, their wellbeing is also affected: "*Caring with someone with Pompe disease presents challenges. I feel I have to keep myself fit and organised to meet the challenges ahead".*

B.1.3.7 Clinical pathway of care

B.1.3.7.1 *Enzyme replacement therapy*

ALGLU is a recombinant, purified form of the human lysosomal GAA enzyme that aims to replace the missing or malfunctioning enzyme (89). It is the current standard-of-care therapy for patients with Pompe disease, funded as part of the Highly Specialised National Health Service (NHS) LSD service (90). The licensed dose of

ALGLU is 20 mg/kg (91), however in patients with IOPD 40 mg/kg is used for the first three months in order to resolve cardiomyopathy (Appendix M). In addition, according to clinical advice, the dose may be escalated in IOPD patients experiencing decline on ERT.

Two publications studying UK-specific Pompe disease cohorts registered in England and Wales have found that all IOPD and virtually all LOPD patients were treated with ALGLU (only 3 untreated patients in a cohort of >60 patients) (16, 79), making it a recognised therapy for Pompe disease. Its use is supported by several clinical guidelines published in different regions worldwide (92-95).

B.1.3.7.2 *LOPD treatment guidelines*

Due to the variety of symptoms, patients usually require care from a multidisciplinary team of professionals (Section B.1.3.7.4).

The decision to commence treatment with ERT is usually based on the European Pompe Consortium (EPOC) 2017 guidelines, which recommend ERT immediately following diagnosis in patients meeting all the following criteria:

- Confirmed diagnosis of Pompe disease
- The patient should be symptomatic
- The patient and clinician should commit to regular treatment and regular monitoring
- The patient should have residual skeletal and respiratory muscle function, which is considered functionally relevant and clinically important for the patient to maintain or improve
- Absence of another life-threatening illness that is in an advanced stage (96).

The EPOC guidelines also provide recommendations for stopping ERT, which should be considered for any one of the following reasons:

- The patient suffers from severe infusion-associated reactions which cannot be managed

- High antibody titres are detected which significantly counteract the effect of ERT
- The patient wishes to stop ERT
- The patient does not comply with regular infusions or yearly clinical assessments
- The patient has another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate
- There is no indication that skeletal muscle function and/or respiratory function have stabilised or improved in the first 2 years of receiving ERT (96).

If after stopping ERT the disease deteriorates faster than it did during treatment, then restarting ERT can be considered.

At present, there is insufficient evidence to support starting ERT in pre-symptomatic patients. The EPOC 2017 guidelines recommend that patients should be monitored every six months in the first year and once per year thereafter in attempt to identify disease progression and to commence treatment early. However, it is generally advised to commence treatment as early as possible in patients while there is functional muscle available (96).

B.1.3.7.3 *IOPD treatment guidelines*

In addition to ERT, the NHS Commissioning Board's standard contract for a lysosomal storage disorders service (97) highlights that due to the severity of Pompe disease in patients with IOPD, long-term respiratory support either by invasive or non-invasive ventilation is likely required. The NHS LSD service document recommends that early treatment intervention occurs as soon as possible in patients with IOPD, except for those requiring mechanical ventilation prior to diagnosis. Patients require recurring detailed cardiac evaluations and respiratory function testing, robust management of life-threatening cardiac arrythmias, and formal sleep studies (as indicated during course of IOPD). They also require appropriate care for insertion of a port-a-cath for ERT, and may require tracheotomy and gastrostomy (97).

Upon diagnosis, the CRIM status of patients with IOPD should be confirmed as soon as possible. An immune response is commonly observed in patients who are CRIM-negative, which leads to the development of high and sustained anti-ALGLU immunoglobulin G (IgG) antibody titres, thus leading to a poor clinical response to ERT (93). To overcome this, immunomodulatory interventions are routinely used in the UK to induce immune tolerance; these frequently include rituximab, methotrexate, and intravenous immunoglobulin treatment (7).

B.1.3.7.4 *Supportive care*

For optimal care, treatment is based on an individual patient's needs and managed by a multidisciplinary team (MDT) of professionals familiar with the disorder. For this reason, care is coordinated by one of the specialist treatment centres within the UK. The MDT includes, but is not limited to, the medical disciplines such as metabolic specialists, cardiologists, pulmonologists, sleep consultants, gastroenterologists, neurologists, and orthopaedics. In addition, adjuvant disciplines such as physiotherapists, psychologists, genetic counsellors, occupational therapists, dieticians and speech therapists are periodically involved (8, 98). This highly extensive and comprehensive team reflects the systemic nature of Pompe disease and the various body systems impacted by the disorder. The magnitude of care input required reflects the severity of this inherited chronic metabolic condition.

For patients who have a degree of respiratory dysfunction, respiratory physical therapy may be used to strengthen respiratory muscles and retain lung volumes, but eventually, respiratory assistance through mechanical ventilation will be required. Mechanical ventilation, via non-invasive or invasive techniques (e.g. Bi-level Positive Airway Pressure [biPAP] or volume ventilators), can support patients' breathing during the night and/or periods of the day (99).

Occupational therapy, physiotherapy, dietary advice and speech and language therapy are important parts of the holistic care package as the disease advances (94, 99). Occupational therapists assist with home adaptations necessary to enable patients to live in their own homes. The provision of walking aids and wheelchairs becomes necessary due to loss of mobility and the heightened risk of falls as the disease advances. These accessory aids require regular review and assessment. Physiotherapy is employed to maintain functionality and comfort for as long as

possible; treatment maximises the range of movement, helps with posture and retains remaining muscle strength. In addition, dietary advice and speech and language therapy help to ensure functional swallowing, secretion clearance and clarity of speech.

B.1.3.8 Unmet need

B.1.3.8.1.1 IOPD

The current standard-of-care, ALGLU, has transformed the course of the disease by slowing progression and extending OS in IOPD, enabling patients to survive infancy (14). For patients with rapidly progressing IOPD, clinicians have highlighted a significant unmet need for effective treatments (Appendix M). Outcomes for these patients are poor, with a substantial proportion unable to walk at 4–5 years of age due to residual muscle weakness (88). Early treatment intervention improves mobility and delays dependence on mechanical ventilation at a crucial time for the patients' development and their families. However, one study indicated that patients with IOPD developed gradual muscle weakness over the pelvic girdle after two years of age, while ptosis (drooping eyelids) and speech disorders were common even with a median treatment time of 63 months (16, 100).

The unmet need for further treatment options in IOPD is particularly evident in patients who are CRIM-negative, as these patients require additional immune tolerance induction to enhance ERT efficacy. Even with treatment, their outcomes are generally much poorer than their CRIM-positive peers. Unfortunately in the UK, the proportion of CRIM-negative IOPD patients is higher (up to 45%) (16, 100) compared with many other countries (e.g. approximately 32% in the US (101)), thus highlighting an even greater need for improved therapy.

B.1.3.8.1.2 LOPD

ALGLU slows the progression of disease in LOPD and reduces mortality (30, 52, 102). Response to treatment can vary between patients, likely reflecting the heterogenous nature of the disease. Treatment improves patients' HRQoL, however it remains significantly lower than that of the general population, reflecting the progressive physical disability inherent with the disease (15, 103).

Following initial improvement or stabilisation of symptoms, the benefits of ALGLU treatment may diminish over time (53). A number of patients who receive ERT will still progress to wheelchair-dependency or ventilatory support. Nevertheless, this must be viewed in the context of Pompe disease being a progressive illness; without ERT patients experience a significant decline in muscle strength, respiratory muscle function, walking distance and daily life activities (14). In a prospective cohort study of 102 adult patients, measures of pulmonary function and skeletal muscle strength and function were significantly higher at 5 years post-ERT initiation compared with their extrapolated natural course (30).

At an advisory board, three metabolic consultants and two clinical nurse specialists who specialise in treating patients with Pompe disease agreed that most patients eventually decline on ALGLU, with most patients experiencing a peak in clinical improvements (e.g. muscle strength, pulmonary function, daily life activities) during the first two to three years of treatment (104). There is therefore a well-recognised need for an alternative treatment for patients with Pompe disease.

B.1.3.9 Avalglucosidase alfa

Avalglucosidase alfa (AVAL) is a recombinant human, next-generation ERT. It replaces the deficient GAA enzyme in patients with Pompe disease, enabling degradation of glycogen within lysosomes.

Cellular uptake is mediated by binding to cell surface mannose 6-phosphate (M6P) receptors (21). Compared with ALGLU, AVAL has a 15-fold increase in M6P levels, which enhance its receptor-mediated uptake (17, 18). Preclinical studies using *in vivo* Pompe models have demonstrated that, compared with ALGLU, AVAL has a 1000-fold higher binding affinity to M6P receptors (17, 18), leading to greater glycogen clearance from muscles at one-fifth of the dose of ALGLU (18).

It is anticipated that AVAL will offer an additional, improved treatment option for new patients and existing patients already receiving ALGLU.

B.1.4 Equality considerations

No equality issues are anticipated.

B.2 Clinical effectiveness

Avalglucosidase alfa has been investigated in a robust clinical trial programme, comprising paediatric and adult patients across the spectrum of both IOPD and LOPD, including patients with LOPD who were treatment-naïve and ERT-experienced

- The clinical evidence base for AVAL consists of a phase 3, randomised controlled trial with an extended treatment phase (COMET), a phase 2 study with an extended treatment phase (Mini-COMET), and a phase 1 study (NEO1) (105), with an extended, long-term phase 2 component (NEO-EXT).
- Across the four clinical trials 118 adults with LOPD and [redacted] paediatric patients ([redacted], 22 patients with IOPD) were treated with AVAL (Appendix C).

Patients with LOPD

- The phase 3 RCT COMET investigated the efficacy and safety of AVAL compared with ALGLU in patients with LOPD who were ERT-naïve.
- Patients treated with AVAL had a 2.4-point greater improvement in FVC% predicted compared with patients treated with ALGLU at Week 49, meeting the measurement of non-inferiority (p=0.0074; 95% CI, –0.13, 4.99).
- Superiority was tested for, but barely missed (p=0.06); due to the hierarchical trial design, all secondary and tertiary endpoint significance is reported at the nominal level without multiplicity adjustment.
- [redacted](106).
- Patients treated with AVAL had a 30.01 metre greater improvement in 6MWT (distance walked in metres) from baseline to Week 49 compared with ALGLU, with an LSM CFB of 32.21 (SE: 9.93) in the AVAL group vs. 2.19 (SE: 10.40) in the ALGLU group.

- Compared with ALGLU, in patients treated with AVAL there was an improvement across a broad range of outcomes related to respiratory and musculoskeletal health, as well as patient reported outcomes including QoL.
- [redacted]
- [redacted]
    - [redacted]
- In NEO-EXT, stabilisation of clinical outcomes was maintained in the long-term (6 years). Therefore, AVAL is likely to delay disease progression milestones such as wheelchair and ventilator use.

Patients with IOPD

- The phase 2 trial, Mini-COMET, investigated the efficacy of 20 mg/kg and 40 mg/kg doses of AVAL in patients with clinical decline or suboptimal response to ERT.
- The trial included a randomised arm (Cohort 3), where patients were allocated to receive either AVAL 40 mg/kg or ALGLU (current stable dose).
- In patients with IOPD with clinical decline or suboptimal response to ERT, treatment with AVAL was associated with a trend for improvement or stabilisation across several clinical outcomes.
- Treatment with AVAL decreased biomarkers of disease burden, and stabilised or improved clinical efficacy outcomes measuring motor function (GMFM-88, QMFT and Pompe-PEDI), and cardiovascular hypertrophy (LVM Z-score).
- During the ETP, changes in outcomes such as GMFM-88 and QMFT generally followed a similar trajectory at the patient level as they had done during the PAP.

Safety

- In COMET and Mini-COMET (Cohort 3), AVAL had a safety and tolerability profile that appeared to be more favourable than ALGLU.
- A pooled safety analysis from the four clinical studies included 118 adults and [redacted] paediatric patients ([redacted], 22 patients with IOPD) treated with AVAL (Appendix C).
- Serious adverse reactions reported in patients treated with AVAL were headache, dyspnoea, respiratory distress, nausea, skin discolouration, chills, chest discomfort, pyrexia, increased blood pressure, increased body temperature, heart rate increase, and decreased oxygen saturation.
- [redacted]
- IARs were reported in 26.1% of patients. Most IARs were assessed as mild to moderate.
- Adverse drug reactions reported in clinical trials in the paediatric population [redacted] were similar to those reported in adults.

B.2.1 Identification and selection of relevant studies

B.2.1.1 Identification of studies

A single systematic literature review (SLR) was undertaken to address the following research questions:

1) What is the efficacy and safety of ALGLU and AVAL compared with any other treatment including none?
2) What is the HRQoL of patients with Pompe disease and their caregivers?
3) What are the economic outcomes of treatment of Pompe disease?
4) What are the costs and resource use in Pompe disease?

Studies relevant to at least one of the research questions were included in the review. The approach is briefly summarised in Table 6 and full details are provided in Appendix D.

Table 6: Summary of systematic review methodology

Task	Methodology
Protocol	A protocol was developed to identify studies in Pompe disease to address questions on: 1) efficacy and safety of alglucosidase alfa and avalglucosidase alfa, 2) HRQoL, 3) economic outcomes, 4) costs and resource use
Searches	Electronic databases, bibliographies of recently published systematic reviews and meta-analyses, and grey literature were searched
Title and abstract screening	Screening of all titles and abstracts by two independent investigators; discrepancies resolved by a third reviewer
Full-text screening	Screening of all full-text articles by two independent investigators; discrepancies resolved by a third reviewer
Study mapping	Mapping identified studies to review questions (1-4)
Data extraction	• Conducted by one reviewer using standardised data extraction form • All extracted data validated by a second reviewer
Quality assessment	• Cochrane risk-of-bias tool for RCTs (Version 2 (107)) – extracted by one reviewer and quality checked by a second reviewer • Drummond's checklist for economic evaluations (108)
Data synthesis	• Narrative summary, as meta-analysis not feasible

Abbreviations: HRQoL, health-related quality of life; RCT, randomised controlled trial.

Relevant published and unpublished studies which were identified are listed in Table 7. The key studies that provide evidence comparing AVAL with the comparator of interest (ALGLU) are presented in **bold** text.

Table 7: List of relevant studies

Study name (acronym)	Primary study reference	Population	Intervention	Comparator
Unpublished studies				
NCT03019406 (Mini-COMET)	Mini-COMET CSR (109)	Patients <18 years old with IOPD previously treated with ALGLU	Cohort 1: AVAL IV 20 mg/kg qow (N=6) Cohort 2: AVAL IV 40 mg/kg qow (N=5) Cohort 3: AVAL IV 40 mg/kg qow (N=5)	Cohort 1: No comparator Cohort 2: No comparator Cohort 3: ALGLU at current stable dose [redacted]
NCT02032524 (NEO-EXT)	NEO-EXT CSR (110)	Patients who previously completed the NEO1 study (see below)	**Group 1 (treatment-naïve):** • Patients received AVAL dose assigned during NEO1 until dose switching to 20 mg/kg IV qow (N=8)† **Group 2 (previously treated):** • Patients received AVAL dose assigned during NEO1 until dose switching to 20 mg/kg IV qow (N=11)†	No comparator
Published studies				
NCT02782741 (COMET)	COMET CSR (111) Diaz-Maera et al 2021 (112)	Patients >3 years old with LOPD who are treatment-naïve	AVAL IV 20 mg/kg qow (N=51)‡	ALGLU IV 20 mg/kg qow (N=49)
NCT01898364 (NEO1)	Pena et al 2019 (105)	Patients ≥18 years old with LOPD (ERT-naïve or previously treated with ALGLU)	Group 1 (ERT-naïve): • AVAL IV 5 mg/kg qow (N=4) • AVAL IV 10 mg/kg qow (N=3) • AVAL IV 20 mg/kg qow (N=3)	No comparator

Study name (acronym)	Primary study reference	Population	Intervention	Comparator
			Group 2 (ERT-experienced): • AVAL IV 5 mg/kg qow (N=4) • AVAL IV 10 mg/kg qow (N=4) • AVAL IV 20 mg/kg qow (N=6)	

†Following selection of the 20 mg/kg dose in 2016, patients who were initially receiving 5 mg/kg or 10 mg/kg doses in NEO1 were required to consent to switch to the 20 mg/kg qow regimen for duration of the study; ‡[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; IV, intravenous; kg, kilogram; LOPD, late-onset Pompe disease; mg; milligram; qow, every other week.

B.2.2 List of relevant clinical effectiveness evidence

An overview of the trials that informed the clinical evidence base is provided in Table 8–Table 10. Reported outcomes in **bold** text are reported in the economic analysis.

Table 8: Clinical effectiveness evidence (COMET)

Study	A phase 3 randomised, multicentre, multinational, double-blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment-naïve patients with late-onset Pompe disease				
Study design	Phase 3, randomised, multicentre, multinational, double-blind, active-controlled study				
Population	Treatment-naïve patients with LOPD				
Intervention(s)	Avalglucosidase alfa (AVAL) 20 mg/kg qow				
Comparator(s)	Alglucosidase alfa (ALGLU) 20 mg/kg qow				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	Source of comparative efficacy data for AVAL and ALGLU (Section B.4.2)				
Reported outcomes specified in the decision problem **(outcomes incorporated in the model marked in bold)**	• change in respiratory function • change in motor function • change in muscular function • immunogenicity response • adverse effects of treatment • health-related quality of life				
All other reported outcomes	• pharmacokinetics • pharmacodynamics • pharmacogenetics				

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; kg, kilogram; LOPD, late-onset Pompe disease; mg, milligram; qow, every other week.

Table 9: Clinical effectiveness evidence (Mini-COMET)

Study	An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa (neoGAA, GZ402666) in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response
Study design	Phase 2, multi-stage, open-label, multicentre, ascending dose study
Population	• Stage 1: Patients with IOPD who experienced clinical decline on ERT • Stage 2: patients with IOPD experiencing suboptimal response to ERT
Intervention(s)	AVAL 20 mg/kg qow or 40 mg/kg qow

Comparator(s)	ALGLU current stable dose				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	
	No			No	X
Rationale for use/non-use in the model	Mini-COMET does not provide adequate long-term data for modelling time-to-event outcomes directly (Section B.5.2)				
Reported outcomes specified in the decision problem	• change in respiratory function • change in cardiac function • change in motor function • change in muscular function • immunogenicity response • adverse effects of treatment • health-related quality of life				
All other reported outcomes	• pharmacokinetics • pharmacodynamics • pharmacogenetics				

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; kg, kilogram; IOPD, infantile-onset Pompe disease; mg, milligram; qow, every other week.

Table 10: Clinical effectiveness evidence (NEO1/NEO-EXT)

Study	**NEO1:** An open-label, multicentre, multinational, ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of repeated biweekly infusions of neoGAA in naïve and alglucosidase alfa treated late-onset Pompe disease patients **NEO-EXT:** An open-label, multicentre, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease				
Study design	**NEO1**: Phase 1, open-label, multicentre, ascending dose study **NEO-EXT:** Open-label, multicentre, multinational extension study				
Population	Patients with LOPD who are ERT-naïve or ERT-experienced				
Intervention(s)	**NEO1:** AVAL 5 mg/kg, 10 mg/kg or 20 mg/kg qow **NEO-EXT:** Patients received AVAL dose assigned during NEO1 until dose switching to 20 mg/kg qow[†]				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	Patient numbers are limited, and few patients had been on treatment longer than the assumed plateau period (Section B.4.2)				
Reported outcomes specified in the decision problem	• change in respiratory function • change in motor function				

	• change in muscular function • immunogenicity response • adverse effects of treatment • health-related quality of life (for patients and carers)
All other reported outcomes	• pharmacokinetics • pharmacodynamics

†Following selection of the 20 mg/kg dose in 2016, patients who were initially receiving 5 mg/kg or 10 mg/kg doses in NEO1 were required to consent to switch to the 20 mg/kg qow regimen for duration of the study.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; kg, kilogram; LOPD, late-onset Pompe disease; mg, milligram; qow, every other week.

Mini-COMET and NEO1 were not used to populate the economic model but are included in Sections B.2.2 to B.2.6.

Mini-COMET is the primary source of efficacy and safety data for AVAL in IOPD. This study was not included in the economic model because it does not provide adequate long-term data for modelling time-to-event outcomes directly (Section B.5.2).

NEO-EXT contains the longest follow up for patients with LOPD receiving AVAL. This study was included in the economic model, as the model assumed that both FVC% predicted and 6MWT plateau for durations specific to treatment. These were determined using a combination of published data on ALGLU, clinical opinion, and data from NEO-EXT.

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

B.2.3.1 COMET (Phase 3, LOPD, ERT-naïve)

COMET was a phase 3, randomised, multicentre, double-blind, active-controlled study. The trial assessed the efficacy and safety of AVAL 20 mg/kg qow vs. ALGLU 20 mg/kg qow in ERT-naïve patients with LOPD.

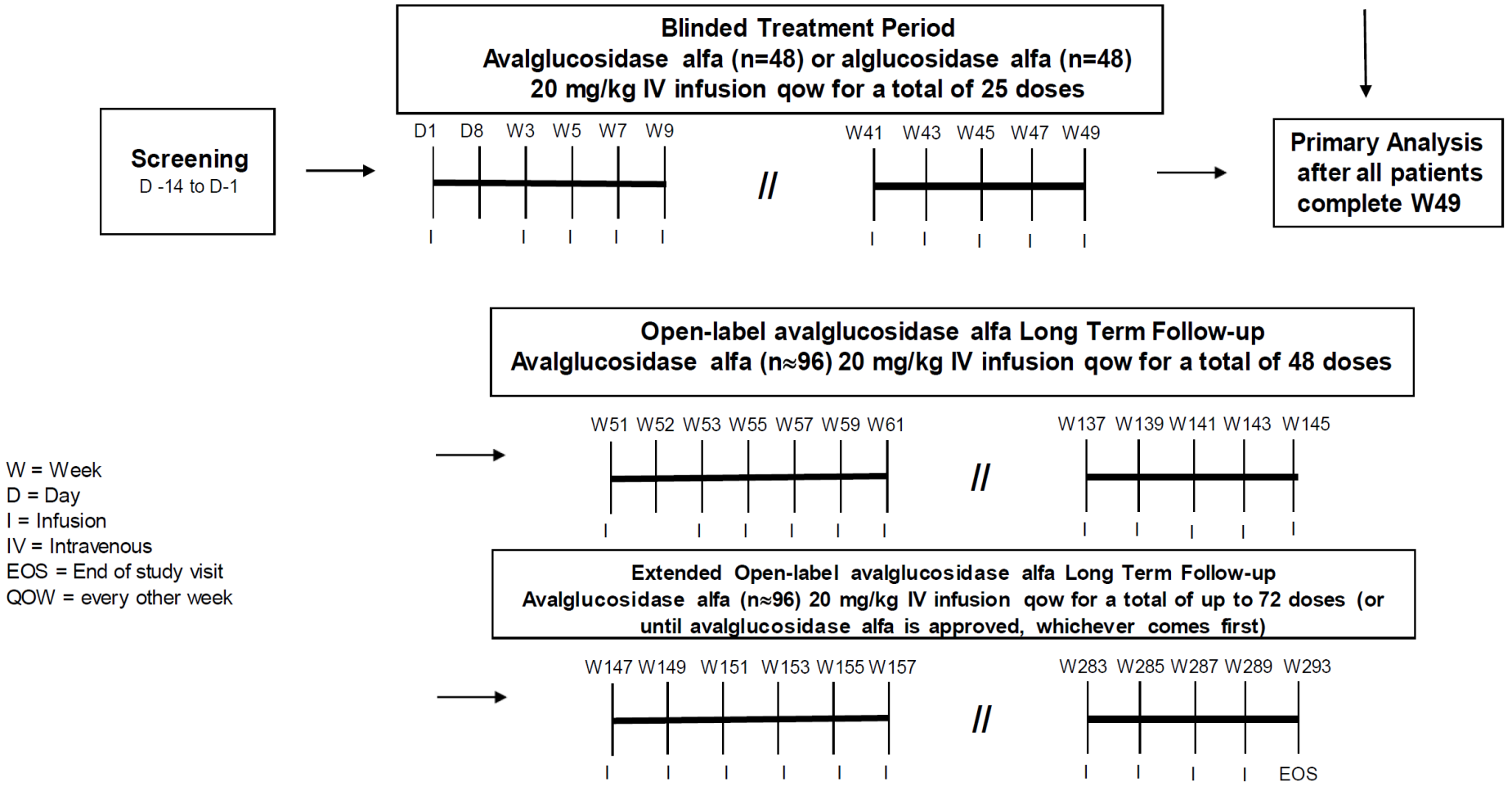
A total of 100 patients (including 5 UK patients) were randomised (1:1) to receive AVAL or ALGLU in a blinded manner, with stratification factors based on baseline FVC, gender, age (<18 vs. ≥18 years) and region (Japan vs. Ex-Japan). Randomisation was performed within each of the following six strata:

- Age <18 years
- Age ≥18 years, all genders and FVC values (% predicted), Japan
- Age ≥18 years, male and FVC (% predicted) <55%, ex-Japan
- Age ≥18 years, female and FVC (% predicted) <55%, ex-Japan
- Age ≥18 years, male and FVC (% predicted) ≥55%, ex-Japan
- Age ≥18 years, female and FVC (% predicted) ≥55%, ex-Japan.

Following the 49-week blinded primary analysis period (PAP) patients moved into an open-label extended treatment period (ETP). In the ETP, patients who were initially randomised to receive ALGLU arm were switched to receive AVAL (Figure 4).

Results in this submission are based on the interim CSR (data cut-off 19th March 2020, up to Week 97) and a more recent data cut (8th June 2021). All patients have completed the PAP, but the ETP is ongoing and data are only available at later time points for a proportion of patients.

Figure 4: COMET study design (N=100)†



W = Week
D = Day
I = Infusion
IV = Intravenous
EOS = End of study visit
QOW = every other week

†Sample size calculations determined a total sample size of 96 patients (with a 1:1 randomisation ratio) would provide approximately 80% power to demonstrate non-inferiority of AVAL in the primary effiacacy endpoint (FVC% predicted). A total of 100 patients were randomised in COMET.

B.2.3.2 Mini-COMET (Phase 2, IOPD, ERT-experienced)

Mini-COMET was a phase 2, multi-stage, open-label, multicentre, ascending dose study. The trial assessed the safety of repeated intravenous AVAL administration in paediatric patients with IOPD who were previously treated with ALGLU, and who demonstrated clinical decline or sub-optimal response.

The trial was divided into two stages:

Stage 1 – patients with clinical decline:

- Cohort 1 – patients assigned to receive AVAL 20 mg/kg qow
- Cohort 2 – patients assigned to receive AVAL 40 mg/kg qow.

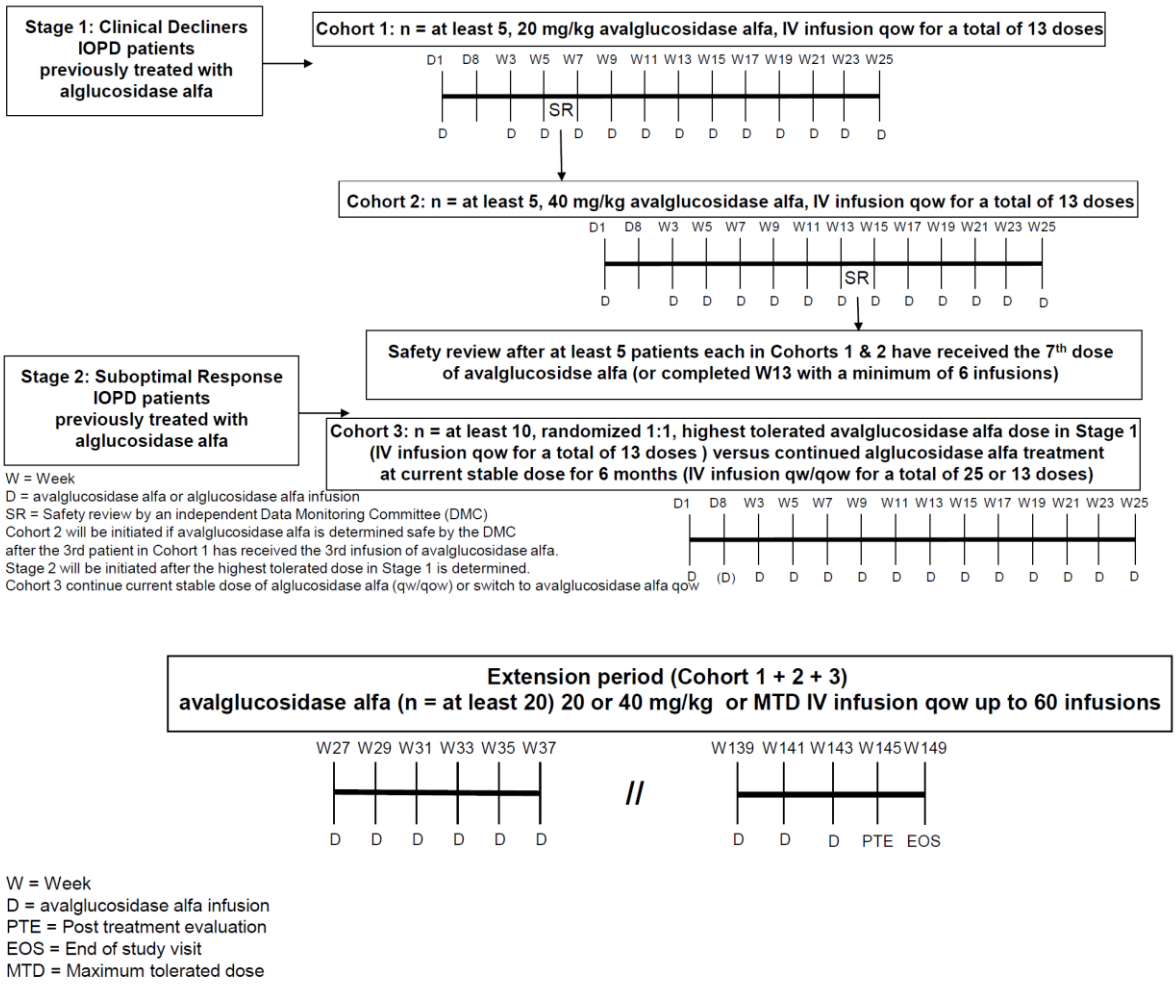
Stage 2 – patients with suboptimal response:

- Cohort 3 – patients randomised 1:1 to receive AVAL at the highest tolerated dose in Stage 1 (20 mg/kg or 40 mg/kg qow) or ALGLU at their current stable dose [redacted]

The PAP lasted six months (25 weeks), following which patients received long-term AVAL and follow-up in an ETP (Figure 5).

Results in this submission are based on the interim CSR (data cut-off 30th September 2019) and a more recent data cut (28th May 2021). All patients have completed the PAP and all patients in Cohort 3 have completed Week 97, but the ETP is ongoing and data are only available at later time points for a proportion of patients.

Figure 5: Mini-COMET study design (N=22)



NeoGAA: avalglucosidase alfa
Abbreviations: kg, kilogram; IOPD, infantile-onset Pompe disease; mg, milligram.

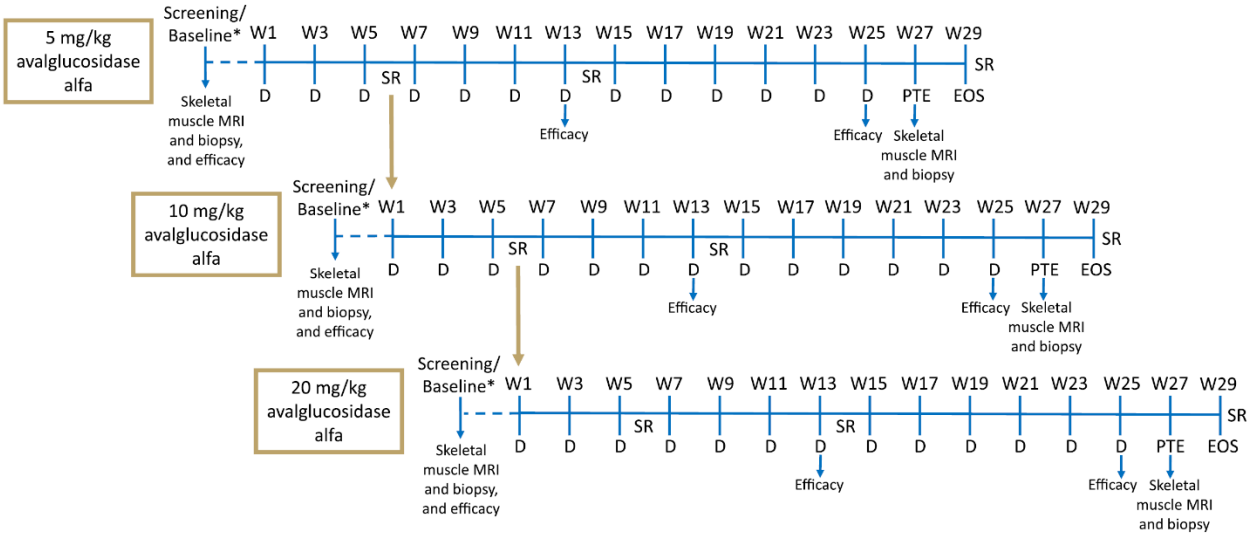
B.2.3.3 NEO1 (Phase 1, LOPD, ERT-naïve and ERT-experienced)

NEO1 was a phase 1, open-label, multicentre, ascending dose study which assessed the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of AVAL. The study recruited patients with LOPD who were either ERT-naïve or had been previously treated with ALGLU.

Patients were analysed in two groups (Group 1 [ERT-naïve] and Group 2 [previously treated for a minimum of nine months with ALGLU; ERT-experienced]). The first dose of AVAL administered to patients was 5 mg/kg. For both Group 1 and Group 2, the AVAL doses were planned to be administered in an ascending manner. For each dose escalation step, the increment was two-fold (10 mg/kg and 20 mg/kg) and was supported by the monitoring of potential treatment-related adverse events. The

groups were initiated simultaneously, with each group receiving AVAL for 24 weeks (Figure 6).

Figure 6: NEO1 study design (N=24)



Abbreviations: D, avalglucosidase alfa infusion; EOS, end of study; kg, kilogram; mg, milligram; PTE, post-treatment evaluation; SR, safety review; W, week.

This study has been completed. Results in this submission are based on the final CSR and study publication (105).

B.2.3.4 NEO-EXT (Phase 2, LOPD, completed NEO1)

NEO-EXT is an open-label, multicentre, multinational extension study which aims to determine the long-term safety and pharmacokinetics of repeated fortnightly infusions of AVAL in patients with LOPD who completed the NEO1 study.

Upon study entry, patients continued to receive the same dose as received in NEO1. Following selection of the 20 mg/kg dose in 2016, patients who were initially receiving 5 mg/kg or 10 mg/kg doses in NEO1 were required to consent to switch to the 20 mg/kg qow regimen for duration of the study, at which point patients entered a 'rebaseline' timepoint.

Results in this submission are based on the interim CSR (data cut-off 27th February 2020) and include the two periods of treatment from NEO1 and NEO-EXT. NEO-EXT is ongoing.

B.2.3.5 Comparative summary of trial methodology

A summary of trial methodology is presented in Table 11.

Table 11: Comparative summary of trial methodology

Study	COMET (NCT02782741)	Mini-COMET (NCT03019406)	NEO1 (NCT01898364) and NEO-EXT (NCT02032524)
Location	International (Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Japan, South Korea, Mexico, The Netherlands, Poland, Portugal, Russia, Spain, Switzerland, Taiwan, Turkey, UK, USA)	International (France, Japan, Taiwan, UK and US)	International (US, Belgium, France, Germany, The Netherlands, Denmark, and the UK)
Trial design	Phase 3, randomised, multicentre, double-blind, active-controlled study	Phase 2, multi-stage, open-label, multicentre, ascending dose study	**NEO1:** Phase 1, open-label, multicentre, ascending dose study **NEO-EXT:** Phase 2, open-label, multicentre, multinational extension study
Key inclusion criteria	• Patients ≥3 years old with confirmed GAA enzyme deficiency from any tissue source and/or two confirmed GAA gene mutations	• <18 years old with a documented GAA enzyme deficiency from blood, skin or muscle tissue for confirmed diagnosis of IOPD • Cardiomyopathy at the time of diagnosis, i.e. LVMI equivalent to mean age-specific LVMI plus 2 standard deviations • Receiving stable dose of ALGLU regularly for a minimum of 6 months immediately prior to study entry For patients participating in Stage 1 (clinical decliners cohorts 1 and 2): evidence of clinical decline in at least one of the following parameters related to Pompe disease:	**NEO1:** **Group 1 (ERT-naïve) and Group 2 (ERT-experienced):** • ≥18 years old with confirmed GAA enzyme deficiency from any tissue source and/or confirmed GAA gene mutation, and without known cardiac hypertrophy • Able to ambulate 50 metres without stopping and without an assistive device. Use of assistive device for community ambulation was permitted • FVC in upright position ≥50% predicted

Study	COMET (NCT02782741)	Mini-COMET (NCT03019406)	NEO1 (NCT01898364) and NEO-EXT (NCT02032524)
		• respiratory function [redacted] • motor skills [redacted] • muscle weakness [redacted] • cardiac parameters [redacted] For patients participating in Stage 2 (suboptimal responders cohort 3): evidence of suboptimal clinical response in at least one of the following parameters related to Pompe disease: • respiratory function [redacted] • motor skills [redacted] • new onset of ptosis (drooping eyelids)	**Group 2 (ERT-experienced) only:** • Previous treatment with ALGLU for ≥9 months NEO-EXT: • Previously completed an AVAL study (NEO1)

Study	COMET (NCT02782741)	Mini-COMET (NCT03019406)	NEO1 (NCT01898364) and NEO-EXT (NCT02032524)
Key exclusion criteria	• Known Pompe-specific cardiac hypertrophy • Wheelchair dependency • Unable to ambulate 40 meters without stopping and without an assistive device • Dependent on invasive ventilation • Unable to perform repeated FVC measurements in upright position of ≥30% predicted and ≤85% predicted • Previous treatment with ALGLU or any other investigational therapy for Pompe disease • Known history of drug or alcohol abuse within 6 months prior to screening • Clinically significant organic disease (except for symptoms relating to Pompe disease) • Prior or current use of immune tolerance induction therapy	• High antibody titre (anti-ALGLU ≥1:25600 at two consecutive time points not <1 month apart) • [redacted] • Previous treatment in any cohort of Mini-COMET • Clinically significant organic disease • High risk for allergic reaction to AVAL • Requirement for any prohibited concomitant medications during study	**Group 1 (ERT-naïve) and Group 2 (ERT-experienced):** • Wheelchair-dependency • Requires invasive ventilation • Participating in another clinical study using investigational treatment • Clinically significant organic disease **Group 1 (ERT-naïve) only:** • Previous treatment with ALGLU or any other ERT for Pompe disease **Group 2 (ERT-experienced) only:** • High risk for severe allergic reaction to AVAL **NEO-EXT:** • Concurrently participating in another clinical study using investigational treatment • Unable to adhere to the requirements of the study • Clinically significant organic disease, except for symptoms relating to Pompe disease
Settings and locations where the data were collected	Patients were screened across 69 sites, globally (including the UK)	Patients were screened across 10 sites, globally (including the UK)	Patients were screened across 17 sites, globally (including the UK)

Study	COMET (NCT02782741)	Mini-COMET (NCT03019406)	NEO1 (NCT01898364) and NEO-EXT (NCT02032524)
Trial drugs (the interventions for each group with sufficient details to allow replications, including how and when they were administered) Intervention(s), n; comparator(s), n	100 patients were randomised (1:1) to receive: **Intervention** AVAL 20 mg/kg administered intravenously qow (N=51) **Comparator** ALGLU 20 mg/kg administered intravenously qow (N=49)	[redacted] patients were enrolled in the study. In Cohort 3, [redacted] patients were randomised (1:1): **Intervention** Cohort 1: AVAL IV 20 mg/kg qow (N=6) Cohort 2: AVAL IV 40 mg/kg qow (N=5) Cohort 3: AVAL IV 40 mg/kg qow (N=5) **Comparator** Cohort 1: No comparator Cohort 2: No comparator Cohort 3: ALGLU, IV at current stable dose (N=6) [redacted]	**NEO1:** **Group 1 (ERT-naïve)** • AVAL IV 5 mg/kg qow (N=4) • AVAL IV 10 mg/kg qow (N=3) • AVAL IV 20 mg/kg qow (N=3) **Group 2 (ERT-experienced)** • AVAL IV 5 mg/kg qow (N=4) • AVAL IV 10 mg/kg qow (N=4) • AVAL IV 20 mg/kg qow (N=6) **NEO-EXT:** **Group 1 (treatment-naïve):** • Patients received AVAL dose assigned during NEO1 until dose switching to 20 mg/kg IV qow (N=8)[†] **Group 2 (previously treated):** • Patients received AVAL dose assigned during NEO1 until dose switching to 20 mg/kg IV qow (N=11)[†]
Permitted and disallowed concomitant medication	Some patients could be pre-treated with antihistamines, antipyretics, and/or corticosteroids at the discretion of the study investigator for management of IARs. However, pre-treatment was not recommended, particularly in patients with previous IgE-mediated hypersensitivity reaction		
	The use of immunomodulatory treatments (e.g. methotrexate, rituximab, immunoglobulins, and other immunosuppressants) was prohibited during the course of the study	The use of immunomodulatory treatments (e.g. methotrexate, rituximab, immunoglobulins, and other immunosuppressants), and beta blockers, were prohibited during the course of the study	–

Study	COMET (NCT02782741)	Mini-COMET (NCT03019406)	NEO1 (NCT01898364) and NEO-EXT (NCT02032524)
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint was CFB to Week 49 in FVC (% predicted) in the upright position. FVC was reported in litres and as percent of predicted normal values based on age, gender, race (Caucasian, Asian, African-American and Other/Mixed), and height	The primary objective of the study was to evaluate the safety profile of AVAL in patients with IOPD previously treated with ALGLU	The primary objective of the study was to assess the safety and tolerability of AVAL in patients with LOPD
Other outcomes used in the economic model/specified in the scope	The key secondary efficacy endpoint was the total distance (meters) walked during 6MWT Additional secondary efficacy endpoints were CFB to Week 49 in: • Pulmonary function using MEP and MIP (% predicted) in the upright position • Lower extremity muscle strength, measured by HHD • Motor function, measured by QMFT • HRQoL, measured with the 12-item short form health survey (SF-12) • Safety	Secondary objectives included evaluation of the preliminary efficacy of AVAL in comparison to ALGLU, CFB to Week 25 in: • Creatinine kinase • GMFM-88 and GMFCS-E&R to evaluate motor function • QMFT • Pompe-PEDI • LVM and LVMI Z-score • Eyelid position (IPFD, MRD1 and MPD)	Other secondary outcomes included: • Exploratory efficacy, CFB in: • Pulmonary function (FVC, FEV_1, MIP, MEP and PEF) • 6MWT • GSGC • GMFM-88 • QMFT • HHD • PedsQL – adult report
Pre-planned subgroups	Planned subgroup analyses for the primary efficacy endpoint of FVC% predicted in the upright position and key secondary endpoint 6MWT were performed for the following subgroups:	Planned subgroup analyses were conducted for the secondary and selected tertiary efficacy endpoints by: • Race • Ethnicity • Gender	Results for NEO1/NEO-EXT are presented for patients who were naïve to treatment (Group 1) and those who were previously treated with ALGLU (Group 2). No further subgroup analyses were performed in NEO1/NEO-EXT

Study	COMET (NCT02782741)	Mini-COMET (NCT03019406)	NEO1 (NCT01898364) and NEO-EXT (NCT02032524)
	• age group (<18 years; ≥18 years and <45 years; ≥45 years old) • gender • baseline FVC groups (<55% or ≥55%) • region • baseline walking device at 6MWT • baseline 6MWT • duration of disease at baseline • race	• Prior ALGLU treatment duration • Age at first ALGLU infusion • Age at first infusion of AVAL or ALGLU in the study • Baseline use of non-invasive ventilatory support • Baseline status on invasive ventilatory support • Assistive device use • CRIM status • Baseline GMFCS level • ACE genotype • Status of inhibitory antibody • Quartiles of peak IgG antibody titre • Baseline LVM Z-Score • Duration of Pompe disease at start of Mini-COMET • Prior use of ALGLU dose regimen	

[†]Following selection of the 20 mg/kg dose in 2016, patients who were initially receiving 5 mg/kg or 10 mg/kg doses in NEO1 were required to consent to switch to the 20 mg/kg qow regimen for duration of the study.

Abbreviations: Abbreviations: ACE, angiotensin I-converting enzyme; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; FEV1, forced expiratory volume; FVC, forced vital capacity; GAA, acid α-glucosidase; GMFCS-E&R, Gross Motor Function Classification System – Expanded & Revised; GMFM-88; Gross Motor Function Measure-88; GSGC, Gait, Stair, Gower's Maneuver, and Chair; HHD, hand-held dynamometry; Hex4, glucose tetrasaccharide; HRQoL, health-related quality of life; IgE, immunoglobulin E; IgG, immunoglobulin G; IOPD, infantile-onset Pompe disease; IPFD, interpalpebral fissure distance; IV, intravenous; kg, kilogram; LOPD, late-onset Pompe disease; LVM, left ventricular mass; LVMI, left ventricular mass index; MEP, maximum expiratory pressure; mg, milligram; MIP, maximum inspiratory pressure; MPD, margin pupil distance; MRD1, margin reflex distance; MRI; magnetic resonance imaging; NA, not applicable; PD, pharmacodynamics; PedsQL, Paediatric Quality of Life Inventory; PEF, peak expiratory flow; PFT, pulmonary function test; PK, pharmacokinetics; Pompe-

PEDI, Pompe-Paediatric Evaluation of Disability Inventory; QMFT, quick motor function test; qow, every other week; qw, every week; UK, United Kingdom; US, United States; 6MWT, six-minute walk test.

B.2.3.6 Baseline characteristics

Summaries of key demographics and baseline characteristics in the trials are presented in Table 12 for LOPD and Table 13 for IOPD.

Table 12: Baseline demographics and disease characteristics, COMET and NEO1/NEO-EXT

	COMET			NEO1/NEO-EXT	
Parameter	**AVAL N=51**	**ALGLU N=49**	**Total N=100**	**Group 1 (ERT-naïve) N=10**	**Group 2 (ERT-experienced) N=14**
Baseline demographics					
Age (years) Mean (SD) Median Min, Max	 46.0 (14.5) 47.7 16, 78	 50.3 (13.7) 48.9 20, 78	 48.1 (14.2) 48.5 16, 78	 44.8 (20.26) 38.3 19.8, 78.3	 46.7 (14.11) 46.2 20.5, 67.5
Gender, N (%) male	27 (52.9)	25 (51.0)	52 (52.0)	7 (70.0)	5 (36.0)
Disease characteristics					
Age at diagnosis, years Mean (SD) Median Min, Max	 44.73 (14.74) 47.05 10.8, 77.7	 48.16 (14.64) 47.34 17.1, 76.7	 46.41 (14.72) 47.14 10.8, 77.7	 43.3 (23.79)[†] 36.4 15.8, 78.2	 36.3 (16.39)[‡] 34.2 3.4, 62.9
Age at first symptoms, years Mean (SD) Median Min, Max	 32.94 (16.58) 32.35 3.8, 66.3	 37.73 (15.74) 39.42 6.1, 73.2	 35.31 (16.27) 38.89 3.8, 73.2	 [redacted]	 [redacted]
Baseline values of key efficacy parameters					
Predicted FVC (%), upright, N Mean (SD) Median Min, Max	51 62.5 (14.4) 65.5 32, 85	49 61.6 (12.4) 60.8 39, 85	100 62.1 (13.4) 63.2 32, 85	10 68.3 (19.58) 58.9 50.7, 109.8	14 75.4 (17.05) 72.7 49.6, 117.2

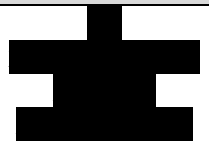
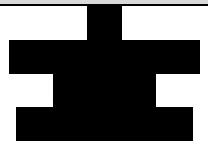
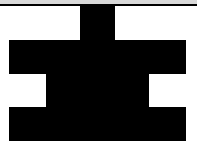
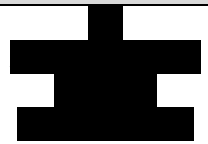
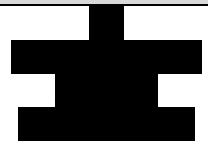
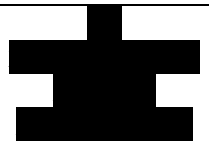
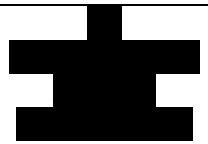
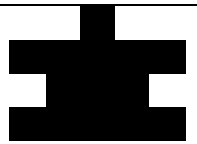
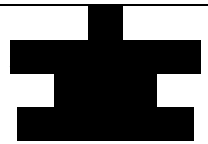
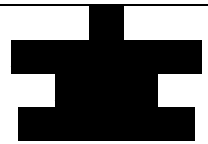
	COMET			NEO1/NEO-EXT	
Parameter	**AVAL N=51**	**ALGLU N=49**	**Total N=100**	**Group 1 (ERT-naïve) N=10**	**Group 2 (ERT-experienced) N=14**
Distance walked from 6MWT (m), N Mean (SD) Median Min, Max	51 399.3 (110.9) 415.7 118, 630	49 378.1 (116.2) 387.0 138, 592	100 388.9 (113.5) 403.5 118, 630	10 449.2 (118.36) 488.5 208.0, 593.0	14 440.4 (141.02) 439.0 201.0, 657.0

†n=8; ‡n=9; ¶n=1

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; FVC, forced vital capacity; m, metres; NR, not reported; SD, standard deviation; 6MWT, six-minute walk test.

Table 13: Baseline demographics and disease characteristics, Mini-COMET

Parameter	**Cohort 1 N=6**	**Cohort 2 N=5**	**Cohort 3**		
			AVAL N=5	**ALGLU N=6**	**Total N=11**
Baseline demographics					
Gender, N (%) male	5 (83.3)	3 (60.0)	2 (40.0)	2 (33.3)	4 (36.4)
Age at study entry (years) Mean (SD) Median Min, Max	 7.6 (3.4) 8.2 2, 11	 8.1 (4.1) 9.8 1, 12	 6.9 (2.7) 8.0 4, 10	 4.7 (3.2) 3.6 1, 10	 5.7 (3.0) 4.5 1, 10
Disease characteristics					
Age at diagnosis of Pompe disease (months) Mean (SD) Median Min, Max	 1.93 (2.07) 1.10 0.3, 5.5	 4.29 (3.75) 4.47 0.3, 8.7	 1.54 (1.49) 1.84 0.0, 3.5	 5.12 (5.46) 3.45 0.3, 15.9	 3.49 (4.39) 3.12 0.0, 15.9
Age at first symptoms of Pompe disease (months) Mean (SD) Median Min, Max	 1.23 (1.70) 0.34 0.0, 4.4	 3.33 (2.93) 4.40 0.1, 6.5	 0.18 (0.41) 0.00 0.0, 0.9	 1.79 (1.72) 1.79 0.0, 3.7	 1.06 (1.50) 0.13 0.0, 3.7

Parameter	Cohort 1 N=6	Cohort 2 N=5	Cohort 3		
			AVAL N=5	ALGLU N=6	Total N=11
Age at first treatment of Pompe disease (months)[a] Mean (SD) Median Min, Max	 2.85 (2.35) 2.41 0.4, 5.7	 5.32 (4.76) 4.63 0.5, 10.4	 2.12 (2.22) 1.94 0.2, 5.7	 6.19 (6.65) 4.44 0.3, 19.4	 4.34 (5.35) 4.01 0.2, 19.4
Baseline values of key efficacy parameters					
Predicted FVC (%), upright, N Mean (SD) Median Min, Max					
Distance walked from 6MWT (m), N Mean (SD) Median Min, Max					
Prior ALGLU treatment dose, N					
20 mg/kg qow 20 mg/kg qw 25 mg/kg qw 30 mg/kg qw 35 mg/kg qw 40 mg/kg qow 40 mg/kg qw 42.6 mg/kg qw					

a First alglucosidase alfa dose ever.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC, forced vital capacity; kg, kilogram; m, metres; mg, milligram; NA, not applicable; NC, not calculated; NR, not reported; qow, every other week; qw, every week; SD, standard deviation; 6MWT, six-minute walk test.

B.2.3.6.1 *COMET (Phase 3, LOPD, ERT-naïve)*

Fifty-one patients were randomised to the AVAL group and 49 patients were randomised to the ALGLU group in the PAP. Gender was well balanced between the groups, and mean weight, height, and body mass index (BMI) were similar between groups.

In terms of age, patients in the AVAL and ALGLU group are regarded as balanced. Mean age at Pompe diagnosis and at first symptom onset were similar between treatment arms. The mean time from Pompe disease diagnosis to first infusion of study drug was 15.60 (SD: 32.06) and 26.52 (SD: 59.86) months in the AVAL and ALGLU groups, respectively. There was one paediatric patient in the AVAL arm. [redacted]

Most patients in COMET were white. There was a higher proportion of Hispanic patients in the ALGLU treatment arm (24.5%) compared with the AVAL arm (5.9%), likely linked to the proportion of patients from Latin America and North America in each arm. [redacted]

Overall, key efficacy parameters in the PAP were well balanced between AVAL and ALGLU groups.

B.2.3.6.2 *Mini-COMET (Phase 2, IOPD, ERT-experienced)*

Twenty-two patients were enrolled in Mini-COMET. Due to the small patient population and differences in inclusion criteria between study stages, baseline imbalances between cohorts and treatment arms in patient characteristics were evident, most notably with respect to younger age of Cohort 3 in the ALGLU treatment arm (median age 3.6, compared with 8.2, 9.8 and 8.0 years in Cohort 1, Cohort 2, and the AVAL of Cohort 3, respectively). Cohort 1 (AVAL 20 mg/kg qow) and 2 (AVAL 40 mg/kg qow) included patients with the most severe disease, while less severe motor dysfunction was observed in Cohort 3 (AVAL 40 mg/kg qow vs ALGLU). Imbalances in demographics and patient characteristics at baseline were evident between cohorts and treatment arms, most notably with respect to younger age of Cohort 3 patients in the ALGLU arm, who were mostly selected due to a new occurrence or worsening of ptosis while patients were mostly selected due to a

decline or insufficient response on motor or respiratory function in the other groups. Therefore, as the ALGLU arm was younger and healthier it is difficult to compare between Cohort 3 and Cohorts 1 and 2.

Alglucosidase alfa was administered to Cohort 3 patients randomised to ALGLU for 25 weeks at their current stable dose (defined by dose of ALGLU administered regularly for a minimum of 6 months immediately prior to study entry. [redacted] Functional levels were consequently heterogeneous at baseline across all patients.

B.2.3.6.3 *NEO1/NEO-EXT (Phase 1/2, LOPD, ERT-naïve and ERT-experienced)*

Due to the small patient population, baseline imbalances in demographics and patient characteristics were evident. In NEO1, the mean age of Pompe disease diagnosis was 43.3 and 36.3 years for all patients in Groups 1 and 2, respectively. Most patients assigned to Group 1 were female (70%), compared with 36% assigned to Group 2. At baseline, patients had a mean FVC% predicted in the upright position of 68.3 (SD: 19.58) and 58.3 (SD: 17.44) in Group 1 and Group 2, respectively.

Most patients were white (Group 1: 80%; Group 2: 93%), and age at study enrolment, height and BMI were well balanced between groups. Overall, Pompe disease characteristics were similar between both groups.

B.2.3.7 Overview of endpoints in key AVAL trials

B.2.3.7.1 *Forced vital capacity (FVC) [COMET]*

The primary efficacy endpoint of COMET was FVC% predicted in the upright position, an established measure of lung capacity. Respiratory insufficiency is a major source of morbidity and mortality in patients with Pompe disease (8, 38) (Section B.2.6.1.2). This measure (alongside MIP and MEP) has also been used as a surrogate marker to predict thresholds for daytime and nighttime ventilation in LOPD (113).

One study, which focused on the association between FVC and other LOPD outcomes, determined that FVC is positively associated with LOPD measures and

outcomes across multiple domains, including 6MWT and SF-36 (114). The study identified the importance of measuring respiratory function in patients with Pompe disease to delineate the benefits of ERT.

[redacted]. This is consistent with an analysis of changes in FVC% predicted in relation to changes in the Patient Global Impression of Change (PGIC) in COMET, which suggest that an improvement of 1.7 units or greater in FVC% predicted corresponds to minimal patient relevant change. There was minimal change in FVC in patients who reported “no change” in their PGIC (FVC% predicted median IQR, 0.66 [–2.3, 5.7]) (115). In contrast, FVC increased in ascending order of magnitude for the three PGIC improvement definitions (FVC% predicted median [IQR] of 1.7 [–2.1, 5.4]; 2.1 [–2.1, 6.0]; and 4.1 [–2.1, 7.6], respectively).

Absolute FVC values and FVC% predicted were measured in both the upright and supine position during the blinded treatment period. The FVC% predicted was calculated using the Global Lung Initiative (GLI) 2012 reference equation (116), based on absolute FVC (in litres), gender, race (classified as Caucasian, Asian, African-American, and Other/Mixed), age (at least one decimal place in years), and height (in cm).

The FVC% predicted value was calculated as:

*(absolute FVC measurement/predicted value of FVC) * 100%*

B.2.3.7.2 *Six-minute walk test (6MWT) [COMET and Mini-COMET]*

The 6MWT assesses functional capacity; it is a multidimensional marker of health, measuring mobility, stability, and muscle endurance together with cardiorespiratory function (117). Distance walked in metres in 6 minutes was recorded, and percent predicted values were calculated based on normal reference equations covering the age range of the study population (118, 119) (Table 14). For analysis purposes, the age at each assessment was calculated based on:

(assessment date - birth date + 1)/365.25

Height was assessed annually for patients with age ≥18 years and every three months for patients with age <18 years and the calculation used the most recent valid value at or prior to the assessment date.

Table 14: Equations for calculating reference value for % predicted total distance walked in 6MWT

Age at baseline	Gender	Equation
≥18 years	Male and female	868.8 – 2.99 * age – 74.7 * sex
<18 years	Male	196.72 + 39.81 * age – 1.36 * age^2 + 132.28 * height
<18 years	Female	188.61 + 51.50 * age – 1.86 * age^2 + 86.10 * height

Sex: 0 if male and 1 if female; height in meters.

B.2.3.7.3 *Maximum expiratory/inspiratory pressure (MEP and MIP) [COMET and Mini-COMET]*

Maximum expiratory pressure (MEP) and maximum inspiratory pressure (MIP) are direct, sensitive measures of respiratory muscle strength which serve as screening parameters for several muscular disorders, including Pompe disease (120, 121).

In COMET and Mini-COMET, raw values of MEP and MIP were summarised descriptively, while the percent predicted values for MIP and MEP in the upright and supine positions were calculated using reference values based on age, gender and weight (121, 122) (Table 15).

For each patient, the same equations were used to calculate the predicted values at baseline and at each timepoint (e.g. if a patient commenced the trial at ≤17 years of age and turned 18 during the study, the paediatric formula would still be applied).

Table 15: Normal reference values applied in the assessment of MEP and MIP

Test/age at baseline	Male	Female
MEP		
≥18 years	174 – 0.83 * age	131 – 0.86 * age
7–17 years old	35 + 5.5 * age	24 + 4.8 * age
MIP		
≥18 years	120 – 0.41 * age	108 – 0.61 * age
7–17 years old	44.5 + 0.75 * weight	40 + 0.57 * weight

Age in years; weight in kg.

For analysis purposes, the percent predicted value is defined as:

*(absolute measurement/normal reference value)*100%*

Since the reference values were only available for patients of age 7 years or older, % predicted MIP and MEP were not derived for patients aged <7 years.

B.2.3.7.4 *Hand-held dynamometry (HHD) [COMET]*

Assessment of lower extremity muscle strength, measured by hand-held dynamometry (HHD), was completed before each infusion. To complete the test, the examiner holds the dynamometer stationary while the patient exerts maximal force against the dynamometer. The patient makes a gradual increase in force and then completes an isometric hold for 4–5 seconds. Lower extremity strength in the following muscle groups was also examined by the same physical therapist or trained assessor (where possible) to minimise inter-operator variability:

- Hip flexion
- Hip extension
- Hip abduction
- Hip adduction
- Knee flexion
- Knee extension
- Ankle dorsiflexion
- Ankle plantar flexion.

Limb tests were completed bilaterally to account for differences in generated force for the dominant and non-dominant limb.

A summary score of lower extremity strength was calculated, as the sum of the 12 measurements from six muscle groups. The percent predicted value of the total score for lower extremity strength was the average of the 12 percent predicted values from the six muscle groups. If any of the 12 measurements from the six muscle groups were missing, the summary score was not recorded.

B.2.3.7.5 *Quick Motor Function Test (QMFT) [COMET and Mini-COMET]*

The QMFT is an observer-administered test comprising 16 items specifically difficult for patients with Pompe disease (e.g. raising the torso, hip and knee flexion, standing up from a chair) (123). It is a useful tool for rating clinical severity and motor function in patients (123). The items were scored separately on a five-point ordinal

scale (ranging from 0 to 4), with a total score of all items ranging between 0–64 points. Higher scores were representative of a better outcome. If any of the 16 items were missing, the total QMFT score was considered as missing.

B.2.3.7.6 *EQ-5D-5L [COMET]*

EQ-5D-5L is a standardised generic instrument used as a measure of health-related quality of life (124). It comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has five levels of health/ability (type of response could be ‘no problem’, ‘slight problem’, ‘moderate problem’, ‘severe problem’; or ‘able to perform activity’ or not; slight, moderate, severe, or extreme).

The EuroQoL-visual analogue scale (EQ-VAS) records the respondent’s self-rated health status on a vertical graduated (0–100) visual analogue scale. A score of 100 represents the best imaginable health state and 0 refers to the worst imaginable health state. Patients who were ≥18 years of age at screening/baseline completed this assessment.

B.2.3.7.7 *12-item Short-Form Survey (SF-12) [COMET]*

The 12-Item Short-Form Survey (SF-12) was administered to assess HRQoL in patients ≥18 years old at screening/baseline. The SF-12 consists of four two-item health domain scales, including, physical functioning (PF), role-physical (RP), role-emotional (RE) and mental health (MH), as well as four one-item health domain scales, including, bodily pain, general health, vitality, and social functioning. The weighted sum of the 12 item scores produces the Physical Component Summary (PCS) and Mental Component Summary (MCS) scale (125).

B.2.3.7.8 *Pompe-Paediatric Evaluation of Disability Inventory (Pompe-PEDI) [Mini-COMET]*

A disease-specific version of Paediatric Evaluation of Disability Inventory (PEDI) was developed to assess functional capabilities and performance in children with Pompe disease from two months through to adolescence.

The Pompe-PEDI is comprised of a Functional Skills Scale and Caregiver Assistance Scale; both scales have three domains: Self Care, Mobility, and Social

Function. The Pompe-PEDI includes all items from the original PEDI, as well as additional items in the Functional Skills Mobility and Self-Care domains, to reflect clinically relevant functional skills for children with Pompe disease. Norm-based scoring was developed for these new items and scoring algorithms for the PEDI were adjusted to reflect the additional normative data collected for the Pompe-PEDI.

A trained assessor administered the Pompe-PEDI Functional Skills Scale – Mobility Domain to the patient (or the patient's legal guardian if the patient was incapable of performing). The domain was selected to measure change in mobility secondary to changes in muscle strength and consisted of 160 mobility items. An increase in raw score of one point indicated the acquisition of one new skill. Results were reported as raw score, normative standard score (with standard error) and scaled score (with standard error).

Pompe-PEDI Functional Skill Scale, Mobility Domain normative scores indicate where a patient's function falls on age-based reference curves in healthy peers, as captured by performance on the Pompe-PEDI (126). A score of 50 is the expected mean at each age interval with a standard deviation of 10; 95% of healthy children are expected to score within two standard deviations of the mean of 50 (that is, between 30 and 70). Increase in normative score reflects gained skills.

B.2.3.7.9 *Left ventricular mass (index) (LVM and LVMI Z-score) [Mini-COMET]*

Hypertrophic cardiomyopathy affects most infants with Pompe disease and may be measured by left ventricular mass (LVM) (127). In Mini-COMET, two-dimensional and M-mode echocardiography were performed for all patients to measure LVM. A specified medium (e.g. videotape or digital) was sent for interpretation by a central cardiologist who was blinded to the patient and study time point. LVMI and LVM Z-score were recorded using offline review.

B.2.3.7.10 *Eyelid position measurements (Mini-COMET)*

Ptosis (drooping eyelids) is common among patients with IOPD (104), and to measure the potential impact of AVAL treatment on improving ptosis, the following eyelid position measurements were performed by a central reader: interpalpebral fissure distance (IPFD), margin reflex distance-1 (MRD-1) and margin pupil distance

(MPD). Study participants had images taken of their eyes while wearing standardised eyeglass frames as a measurement tool at pre-specified time points.

Interpalpebral fissure distance, or vertical interpalpebral fissure, measures the maximum distance between the upper and lower lid margins (128) and is recommended by the British Medical Journal Best Practice as a measurement to diagnosis ptosis (129). Margin reflex distance-1 is the distance from the pupil centre to the upper eyelid. The average MRD-1 measurement is 4 mm, with ptosis defined as an MRD-1 measurement less than 4 mm (130). Margin pupil distance measures the distance from the central upper eyelid margin to the centre of the pupil (131).

B.2.3.7.11 *Pompe disease symptom scale (PDSS) and Pompe disease impact scale (PDIS) [COMET]*

The PDSS is a newly developed 12-item patient-reported outcome designed to capture the range and severity of disease-related symptoms experienced by patient with Pompe disease. The PDSS has a 24-hour recall version and asks patients to report severity of each symptom with an 11 point-scale, from 0 (none) to 10 (as bad as I can imagine). The PDSS includes the following domains: Shortness of Breath Score (SBS), Fatigue/Pain Score (FPS), Morning Headache Score, Overall Fatigue Score (OFS), Upper Extremity Weakness Score, Pain Score, and a Total Symptom Score (TSS) (132).

The PDIS is a newly developed 15-item patient-reported outcome that includes a mood score (including depression, worry, anxiety) and a Difficulty Physical Activity Score (DPAS) which includes walking, climbing stairs, rising from a sitting position, bending over, squatting, and exercise. The PDIS has a 24-hour recall version and asks patients either about the severity of a particular item on an 11-point scale (0 to 10) (depression, worry, anxiety), or whether the patient could complete each mobility-related activity in the past 24 hours and the level of difficulty associated with the activities that were completed (0 to 10 scale (132).

B.2.3.7.12 *Rasch-built Pompe-specific activity scale (R-Pact) [COMET]*

The R-PAct is an 18-item self-administered questionnaire that quantifies the effects of Pompe disease on patients' ability to carry out daily activities and to participate in social activities. There are three response categories, ranging from unable to

perform (0), able to perform, but with difficulty (1), and able to perform without difficulty (2). At the time of the study the questionnaire was only available in English and Dutch languages, and therefore only provided to English and Dutch speaking populations.

B.2.3.7.13 *Patient Global Impression of Change (PGIC) [COMET]*

The PGIC items consist of four questions pertaining to overall disease-related symptoms, activities of daily living, as well as mobility and respiratory issues. The items range from –3 (a great deal worse), 0 (no change) to 3 (a great deal better). The PGIC items were completed at Week 49 of COMET and are also administered annually during the extension period. The data from this scale was used to support and validate additional endpoints in the trial.

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

B.2.4.1 COMET

B.2.4.1.1 *Hypothesis objective*

The primary statistical objective was to test the non-inferiority of AVAL vs. ALGLU at 5% level of significance. The null and alternative hypotheses were based on a non-inferiority margin of 1.1% and are described as H01 and Ha1 below:

$$H01: AVAL - ALGLU \leq -1.1 \text{ vs.}$$
$$Ha1: AVAL - ALGLU > -1.1$$

The study was considered to have met its primary statistical objective if the non-inferiority null hypothesis (H01) was rejected, or the lower bound of the two-sided 95% confidence interval for the least square mean difference of AVAL – ALGLU was >–1.1. After non-inferiority was demonstrated, a test for superiority of AVAL vs. ALGLU was performed with an overall 5% level of significance. If the superiority null hypothesis (no difference between AVAL and ALGLU) was rejected, and the point estimate for the difference favoured AVAL, the statistical superiority of AVAL vs. ALGLU could be claimed.

B.2.4.1.2 *Sample size and power calculation*

Sample size calculations were based on non-inferiority testing of the primary efficacy endpoint of CFB to Week 49 in FVC (% predicted) upright position, with the following assumptions:

- Normal distribution for the endpoint with a common SD of 5.1% predicted, which was estimated based on data from a previous phase 3, placebo-controlled trial (LOTS)
- Mean treatment difference of 2.0% predicted, assumed based on a conservative estimate when comparing studies LOTS (52) and NEO1 (105)
- A two-sided 5% significance level
- Expected percent of missing data of 10%
- A non-inferiority margin of 1.1%, which is based on the estimated ALGLU effect from the placebo-controlled study (LOTS). The proposed margin represents approximately 50% of the lower bound of the 80% CI for the ALGLU vs. placebo treatment effect.

A total sample size of 96 patients was estimated to provide approximately 80% power to demonstrate non-inferiority of AVAL vs. ALGLU, when the true difference (AVAL–ALGLU) in the primary efficacy endpoint (FVC% predicted) is 2.0% predicted. If the NI criterion was met, a test for superiority was then performed. If the true difference between AVAL and ALGLU was 3.5% predicted (as suggested based on cross-study comparisons between the LOTS (52) and NEO1 (105)) clinical trials, the study would have at least 85% power to demonstrate superiority of AVAL to ALGLU.

B.2.4.1.3 *Statistical analysis of primary endpoint*

The primary efficacy endpoint was a change from baseline to Week 49 in FVC (% predicted) in the upright position. It was analysed in an mITT population (defined as all randomised patients who received at least one partial or total infusion), and modelled using an MMRM approach, including randomisation strata, age, gender, treatment, visit and treatment-by-visit interaction as fixed effects.

An unstructured covariance matrix shared across treatment groups was used to model the within-patient errors, and the Kenward-Roger approximation was used to estimate degrees of freedom. The model was fitted using restricted maximum likelihood, and the difference between groups was estimated based on least squares mean (LSM) at Week 49. Missing data was not imputed and was assumed to be missing at random.

B.2.4.1.4 *Statistical analysis of secondary endpoints*

Secondary efficacy endpoints were summarised descriptively at each study visit, and analyses were performed in an mITT population using an MMRM approach, like the primary endpoint analysis (Section B.2.4.1.3).

B.2.4.1.5 *Multiplicity issues*

A sequential test strategy for the primary and key secondary endpoints was used to control the Type 1 error rate at 5%. Testing proceeded according to the following order and stopped if there was a non-significant comparison:

- The primary efficacy endpoint of FVC% predicted was tested for non-inferiority of AVAL vs ALGLU
- If non-inferiority was demonstrated, the superiority of AVAL vs ALGLU in FVC% predicted was tested with the same overall 5% significance level
- If the superiority of AVAL vs ALGLU is demonstrated, the hypothesis testing for the secondary efficacy endpoints proceeded according to the following order:
- CFB to Week 49 in 6MWT (a superiority test with a two-sided alpha of 0.05)
- CFB to Week 49 in MIP% (a superiority test with a two-sided alpha of 0.05)
- CFB to Week 49 in MEP% (a superiority test with a two-sided alpha of 0.05)
- CFB to Week 49 in summary score of lower extremity strength by HHD (a superiority test with a two-sided alpha of 0.05).

B.2.4.1.6 *Data management and patient withdrawals*

Patients could withdraw from the study before study completion if they decided to do so, at any time and irrespective of any reason. Withdrawal of consent for treatment was distinguished from withdrawal of consent for follow-up visits and from non-patient contact follow-up (e.g. medical record check). Patients who withdrew from the study were explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited was documented.

A sensitivity analysis was conducted to assess the robustness of the primary efficacy analysis results with regards to missing data. This included a tipping point analysis.

B.2.4.2 Mini-COMET

B.2.4.2.1 *Hypothesis objective*

The primary objective of the study was to evaluate the safety profile of AVAL in patients with IOPD previously treated with ALGLU.

B.2.4.2.2 *Sample size and power calculation*

No formal sample size calculations were performed. Sample size for Mini-COMET was based upon empirical considerations.

B.2.4.2.3 *Statistical analysis of the primary endpoint*

The primary endpoint of Mini-COMET was to evaluate the safety profile of AVAL in patients with IOPD previously treated with ALGLU. It was analysed in a safety population, defined as all randomised patients who received at least one partial or total infusion.

B.2.4.2.4 *Statistical analysis of secondary endpoints*

All efficacy endpoints were summarized descriptively by dose cohort and treatment group.

B.2.4.3 NEO1/NEO-EXT

B.2.4.3.1 *Hypothesis objective*

The objectives of the study were:

- To determine in treatment-naïve patients LOPD (Group 1):
    - The safety and tolerability of AVAL
    - The PK parameters of AVAL
    - The PD effects of AVAL on skeletal muscle and other exploratory biomarkers
    - The effect of AVAL on exploratory efficacy endpoints.
- To determine in ALGLU-treated patients with LOPD (Group 2):
    - The safety and tolerability of AVAL
    - The PK parameters of AVAL
    - The PD effects of AVAL on skeletal muscle and other exploratory biomarkers
    - The effect of AVAL on exploratory efficacy endpoints.

B.2.4.3.2 *Sample size and power calculation*

No formal sample size calculations were performed. Sample size for NEO-1 was based upon empirical considerations.

B.2.4.3.3 *Statistical analysis of endpoints*

The Full Analysis Set study population was used for all data analyses, including demographic, safety, and PD/efficacy. This analysis set consisted of all patients who received at least one complete infusion of AVAL. Descriptive statistics were presented for each efficacy endpoint in NEO1/NEO-EXT.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

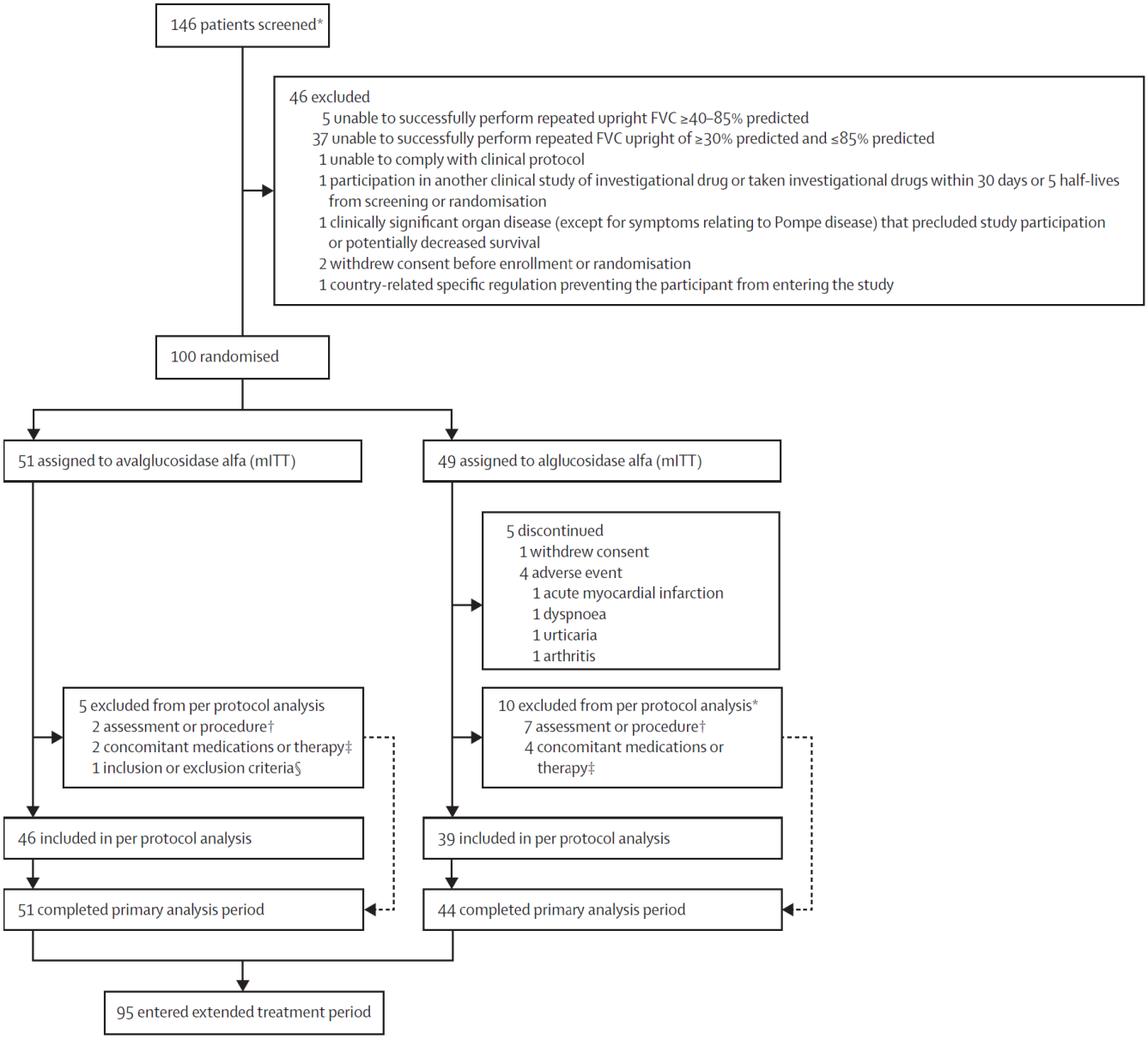
Appendix D presents the quality assessment of each of the trails identified in the SLR.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 COMET

B.2.6.1.1 *Patient disposition*

Figure 7: COMET study population



*A participant in the mITT population could have multiple reasons resulting in exclusion from the per protocol analysis and might be included in each reason;†Did not undergo assessment or Week 49 assessment during the ETP; ‡Received prohibited medication (immunomodulator), one discontinued participant in the ALGLU group was also excluded for that reason and is included twice; §Inclusion criterion not confirmed at time of randomisation.
Abbreviations: FVC, forced vital capacity; mITT, modified intention-to-treat.

Table 16: Analysis populations, COMET

Analysis population, n (%)	AVAL (N=51)	ALGLU (N=49)	Total (N=100)
Randomised	51 (100.0)	49 (100.0)	100 (100.0)
mITT†	51 (100.0)	49 (100.0)	100 (100.0)
PP	46 (90.2)	39 (79.6)	85 (85.0)
Safety	51 (100.0)	49 (100.0)	100 (100.0)

†This was identical to the ITT population.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ITT, intention-to-treat; mITT, modified intention-to-treat; PP, per protocol.

B.2.6.1.2 *Primary endpoint – FVC% predicted in upright position*

Primary analysis period (to Week 49)

In COMET, the primary endpoint was a CFB in FVC% predicted in the upright position to Week 49, which was analysed in the mITT population. The LSM CFB at Week 49 in FVC% predicted was 2.89 (SE: 0.88) in the AVAL arm, and 0.46 (SE: 0.93) in the ALGLU arm, with an LSM difference of 2.43 (95% CI: –0.13, 4.99) (

Table 17). The lower boundary of the 95% CI was well above the predefined non-inferiority margin of –1.1, thus achieving statistical non-inferiority (p=0.0074) and the primary study objective. The p-value for the superiority test was 0.0626, just missing superiority at the 5% significance level defined in the study protocol.

Table 17: Observed FVC% predicted at baseline and Week 49, and CFB based on MMRM

	AVAL (N=51)	ALGLU (N=49)	Difference
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 (SE)† 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

†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.
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.

When the observed changes from baseline to Week 49 in in FVC% predicted are represented as a cumulative probability function, a clear right shift of the AVAL curve compared with the ALGLU curve is observed (Figure 8). These curves show a clear and consistent separation between AVAL and ALGLU over the full range of possible FVC responder thresholds. The proportion of responders in the AVAL arm is

consistently higher than in the ALGLU arm, irrespective of the threshold used. Approximately 70% of patients treated with AVAL improved their FVC from baseline to Week 49.

Figure 8: Plot of the cumulative probability function of CFB to Week 49 in FVC% predicted in upright position, PAP

Abbreviations: FVC, forced vital capacity; mITT, modified intention-to-treat; PAP, primary analysis period.

Pre-specified responder analyses were conducted as per study plans. Overall, approximately twice as many patients had an improvement above a given value, [redacted] in the AVAL group compared with ALGLU. [redacted] approximately 20% (10/51) a relative increase of 15% or more.

Figure 9: FVC % predicted responder analysis, PAP

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC, forced vital capacity; PAP, primary analysis period.

Extended treatment period (to Week 97)

During the ETP,

Figure 10: LSM (SE) CFB in FVC% predicted to Week 97

Abbreviations: CFB, change from baseline; FVC, forced vital capacity; LSM, least squares mean; No, number; PAP, primary analysis period; SE, standard error.

B.2.6.1.2.1 Post-hoc analysis: removing an extreme outlier

A sensitivity post-hoc analysis was conducted by excluding an extreme outlying patient in the AVAL group. This patient, depicted at the extreme left of the blue curve in Figure 8, had a low baseline value and an atypical trajectory of respiratory function testing. They also had the largest worsening at every visit in the context of concomitant poorly controlled asthma, chronic obstructive pulmonary disease, and corresponding treatment.

After excluding this patient, the variance decreased, and the difference in FVC% predicted between AVAL and ALGLU at Week 49 was [redacted].

[redacted]

B.2.6.1.3 *Key secondary endpoints*

B.2.6.1.3.1 6MWT

Primary analysis period (to Week 49)

There was a nominally statistically significant improvement in 6MWT in patients treated with AVAL compared with those treated with ALGLU. The LSM CFB in 6MWT (distance walked in meters) at Week 49 was 32.21 (SE: 9.93) in the AVAL arm, and 2.19 (SE: 10.40) in the ALGLU treatment arm; the LSM difference was 30.01 (95% CI: 1.33, 58.69) (Table 18).

Table 18: Observed 6MWT at baseline and Week 49, and CFB based on MMRM

	AVAL (N=51)	ALGLU (N=49)	Difference
Baseline mean (SD)	399.3 (110.9)	378.1 (116.2)	–
Week 49 mean (SD)	441.31 (109.774)	383.56 (141.086)	–
CFB to Week 49 (SE)[†] 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

[†]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 meter), age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.
Abbreviations: 6MWT, 6-minute walk test; 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.

Extended treatment period (to Week 97)

During the ETP, patients treated with AVAL maintained the trend for improvement ([redacted] in the AVAL arm compared with [redacted] in patients who switched from ALGLU to AVAL) (Figure 10).

Figure 11: LSM (SE) CFB in 6MWT distance (m) to Week 97

Abbreviations: CFB, change from baseline; LSM, least squares mean; No, number; PAP, primary analysis period; SE, standard error; 6MWT, six-minute walk test.

In the pre-specified responder analysis, a greater proportion of patients in the AVAL arm had an improvement above a given value, whatever the responder threshold. At Week 49, 23.5% of patients in the AVAL arm had an improvement of ≥54 m, compared with 12.2% of patients in the ALGLU arm (

Figure 12).

Figure 12: 6MWT responder analysis, PAP

Abbreviations: 6MWT, 6-minute walk test; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PAP, primary analysis period.

B.2.6.1.3.2 MIP and MEP (% predicted)

The primary analysis included four patients with non-physiologic MIP and MEP values of 200 cm H_2O at baseline that were likely due to errors in data entry. During the PAP, data from these four patients (two patients in each of the AVAL and ALGLU groups) were included, but a post-hoc sensitivity analysis was also conducted during the PAP which excluded the four patients with implausible values.

Primary analysis period – including patients with physiologic values only

The results of the sensitivity analysis showed that LSM CFB in MIP% predicted at Week 49 was 8.70 (SE: 2.09) in the AVAL arm and 4.29 (SE: 2.19) in the ALGLU arm, with an LSM difference of 4.40 (95% CI: –1.63, 10.44).

The LSM CFB in MEP% predicted at Week 49 was 10.89 (SE: 2.84) in the AVAL arm and 8.38 (SE: 2.96) in the ALGLU treatment arm; the LSM difference was 2.51 (95% CI: –5.70, 10.73).

Primary analysis period – including patients with implausible values

The LSM CFB in MIP% predicted at Week 49 was –0.29 (SE: 3.84) in the AVAL arm and –2.87 (SE: 4.04) in the ALGLU arm, with an LSM difference of 2.58 (95% CI: –8.54, 13.71).

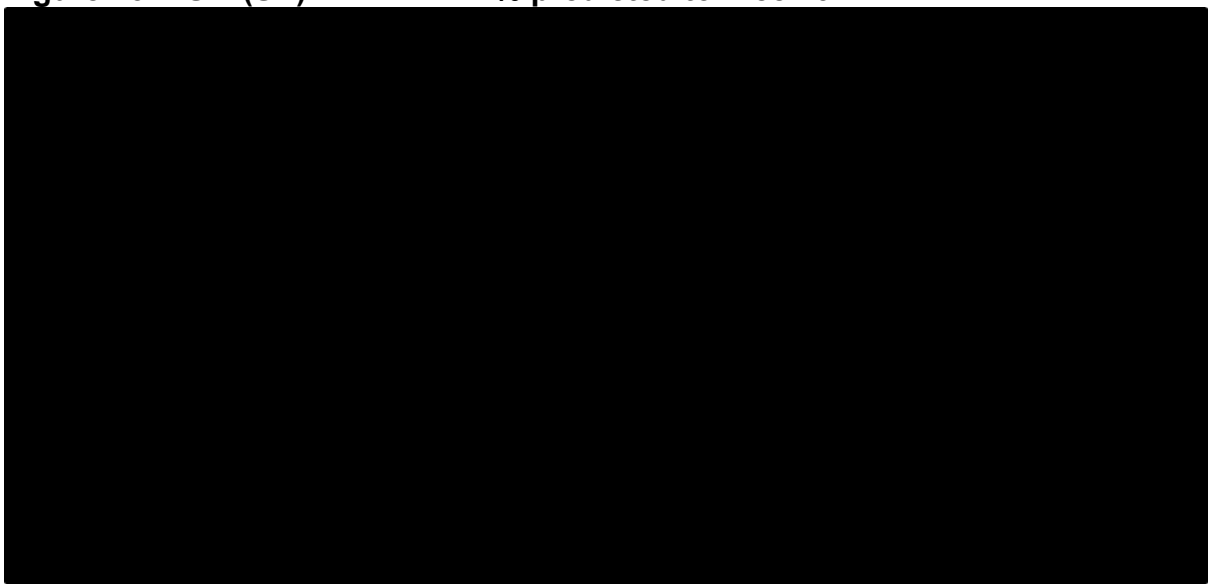
The LSM CFB in MEP% predicted at Week 49 was 2.39 (SE: 4.00) in the AVAL treatment arm and 5.00 (SE: 4.20) in the ALGLU arm; the LSM difference was –2.61 (95% CI: –14.22, 9.00).

Extended treatment period (to Week 97)

Patients who were treated with AVAL or who switched from ALGLU to AVAL continued to show a trend for improvement in MIP % predicted and MEP % predicted to Week 97.

The LSM CFB in MIP % predicted was [redacted] in the AVAL treatment arm and [redacted] in patients who switched treatment at Week 49 (Figure 13). The LSM CFB in MEP % predicted was [redacted] in the AVAL arm and [redacted] in patients who switched treatment (Figure 14).

Figure 13: LSM (SE) CFB in MIP % predicted to Week 97



Abbreviations: CFB, change from baseline; LSM, least squares mean; MIP, maximum inspiratory pressure; No, number; PAP, primary analysis period; SE, standard error.

Figure 14: LSM (SE) CFB in MEP % predicted to Week 97

Abbreviations: CFB, change from baseline; LSM, least squares mean; MEP, maximum expiratory pressure; No, number; PAP, primary analysis period; SE, standard error.

B.2.6.1.3.3 Lower extremity muscle strength by HHD

Primary analysis period (to Week 49)

The LSM CFB in HHD (lower extremity muscle strength, composite score) at Week 49 was 260.69 (SE: 46.07) in the AVAL treatment arm and 153.72 (SE: 48.54) in the ALGLU arm, with an LSM difference of 106.97 (95% CI: –26.56, 240.50) (Table 19).

Table 19: Observed HHD (lower extremity muscle strength, composite score) at baseline and Week 49, and CFB based on MMRM

	AVAL (N=51)	ALGLU (N=49)	Difference
Baseline mean (SD)	1330.45 (625.44)	1466.16 (604.91)	–
Week 49 mean (SD)	[redacted]	[redacted]	–
CFB to Week 49 (SE)[†] 95% CI	260.69 (46.07) [redacted]	153.72 (48.54) [redacted]	106.97 [redacted] –26.56, 240.50

[†]Based on an MMRM model so does not equal difference between observed values; the model adjusts for summary HHD lower extremity score at baseline, baseline FVC%, age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects. Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; CI, confidence interval; FVC, forced vital capacity; HHD, hand-held dynamometry; MMRM, mixed-effects model with repeated measures; SD, standard deviations; SE, standard error.

Extended treatment period (to Week 97)

Patients treated with AVAL maintained the trend for improvement in lower extremity HHD composite score during the ETP, with a LSM of [redacted] in the AVAL

arm and [redacted] in patients who switched from ALGLU to AVAL, at Week 97 (Figure 15).

Figure 15: LSM (SE) CFB in lower extremity HHD composite score to Week 97

Abbreviations: CFB, change from baseline; LSM, least squares mean; HHD, hand-held dynamometry; No, number; PAP, primary analysis period; SE, standard error.

B.2.6.1.3.4 QMFT

Primary analysis period (to Week 49)

The LSM CFB in the motor function scale specific for Pompe disease, quick motor function test (QMFT; total score) at Week 49 was 3.98 (SE: 0.63) in the AVAL treatment arm and 1.89 (SE: 0.69) in the ALGLU arm; the LSM difference was 2.08 in favour of AVAL (95% CI: 0.22, 3.95).[redacted]

Table 20[redacted]

Table 20: Observed QMFT at baseline and Week 49, and CFB based on MMRM

	AVAL (N=51)	ALGLU (N=49)	Difference
Baseline mean (SD)	41.29 (10.15)	42.30 (10.58)	–
Week 49 mean (SD)	[redacted]	[redacted]	–
CFB to Week 49 (SE)† 95% CI	3.98 (0.63) 2.72, 5.23	1.89 (0.69) 0.52, 3.26	2.08 (0.94) 0.22, 3.95

†Based on an MMRM model so does not equal difference between observed values; the model adjusts for total QMFT score at baseline, baseline FVC%, age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.
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; QMFT, quick motor function test; SD, standard deviations; SE, standard error.

Extended treatment period (to Week 97)

During the ETP, the LSM CFB in QMFT total score at Week 97 was [redacted] in the AVAL treatment arm and [redacted] in patients who switched from ALGLU to AVAL (Figure 16).

Figure 16: LSM (SE) CFB in QMFT total score to Week 97

Abbreviations: CFB, change from baseline; LSM, least squares mean; No, number; PAP, primary analysis period; QMFT, quick motor function test; SE, standard error.

B.2.6.1.4 *HRQoL*

B.2.6.1.4.1 SF-12

Relative to the normative mean PCS and MCS scores of 50.00 (SD: 10.00) obtained from the general population, the study population as a whole rated their ability to perform basic activities of daily living, as assessed by the PCS, at a level well below that of healthy individuals. The mean PCS score at baseline was 35.95 (SD: 7.82) in the AVAL treatment group and 36.76 (SD: 9.40) in the ALGLU treatment group.

Primary analysis period (to Week 49)

A greater improvement in PCS and MCS SF-12 scores from baseline to Week 49 was observed in patients treated with AVAL compared with ALGLU. The LSM CFB to Week 49 in the PCS score was 2.37 (SE: 0.99) in the AVAL arm and 1.60 (SE: 1.07) in the ALGLU treatment arm; the difference was 0.77 (95% CI: –2.13, 3.67). For the MCS score, the LSM CFB to Week 49 was 2.88 (SE: 1.22) in the AVAL arm and 0.76 (SE: 1.32) in the ALGLU arm; the LSM difference was 2.12 (95% CI: –1.46, 5.69).

Extended treatment period (to Week 97)

Patients treated with AVAL maintained a trend for improvement in SF-12 PCS score to Week 97, with an LSM CFB of [redacted] in the AVAL arm, and [redacted] in patients who switched from ALGLU to AVAL (Figure 17).

Patients who switched from ALGLU and AVAL had an improvement in SF-12 MCS score from baseline to Week 97, with an LSM CFB of [redacted]. Patients assigned to the AVAL arm had an LSM CFB of [redacted] at Week 97 (Figure 18).

Figure 17: LSM (SD) CFB in SF-12 PCS score to Week 97

Abbreviations: CFB, change from baseline; LSM, least squares mean; No, number; PAP, primary analysis period; PCS, physical component score; SE, standard error; SF-12, 12-item short form survey.

Figure 18: LSM (SD) CFB in SF-12 MCS score to Week 97

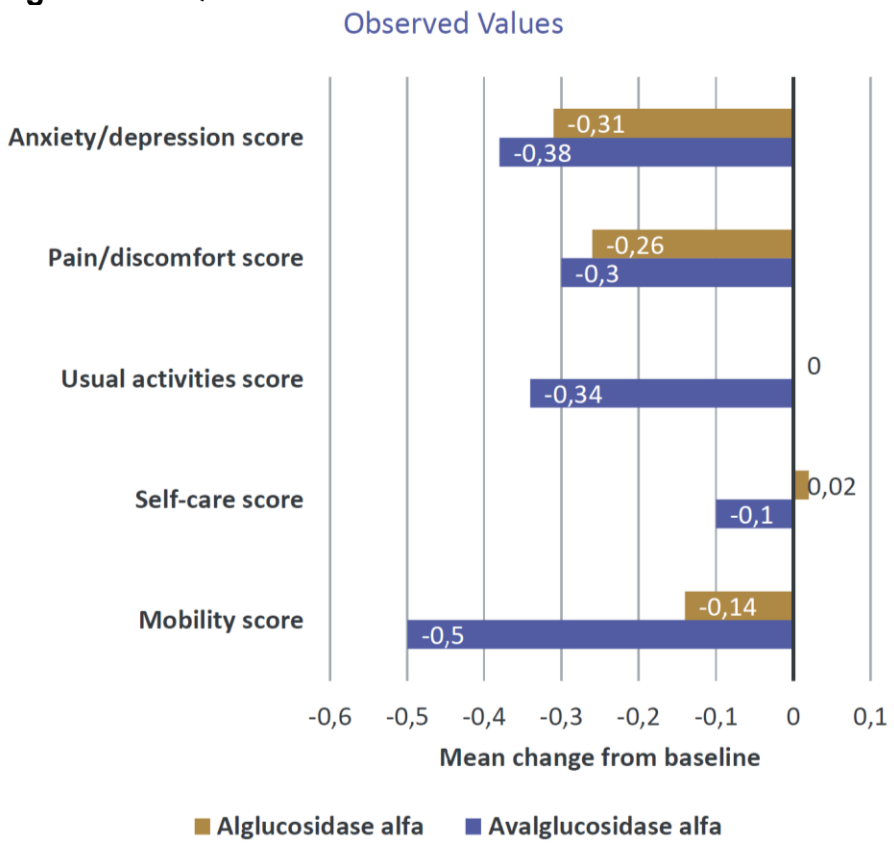
Abbreviations: CFB, change from baseline; LSM, least squares mean; MCS, mental component score; No, number; PAP, primary analysis period; SE, standard error; SF-12, 12-item short form survey.

B.2.6.1.4.2 EQ-5D-5L

Primary analysis period (to Week 49)

For EQ-5D-5L, a greater mean CFB to Week 49 was observed in the AVAL treatment arm for mobility (–0.50 [SD: 0.89] in the AVAL arm and –0.14 [SD: 0.68] in the ALGLU arm), usual activities (–0.34 [SD: 0.89] in the AVAL arm and 0.00 [SD: 0.73] in the ALGLU arm), and EQ-5D VAS (8.80 [SD: 15.01] for AVAL and –0.33 [SD: 16.13] for ALGLU) scores in comparison with the ALGLU arm, with lower scores indicating less burden. Little change and differences between treatment arms were observed in self-care, pain/discomfort, anxiety/depression scores (Figure 19).

Figure 19: EQ-5D-5L mean CFB to Week 49



Abbreviations: CFB, change from baseline.

In a post-hoc responder analysis, the proportion of patients who had improvement [redacted]

Figure 20[redacted]

Figure 20: Proportion of patients with improvement at Week 49 vs baseline in EQ-5D-5L domains

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Extended treatment period (to Week 97)

During the ETP, a greater mean CFB to Week 97 in mobility score and usual activities score . Patients also had improvements in anxiety/depression score

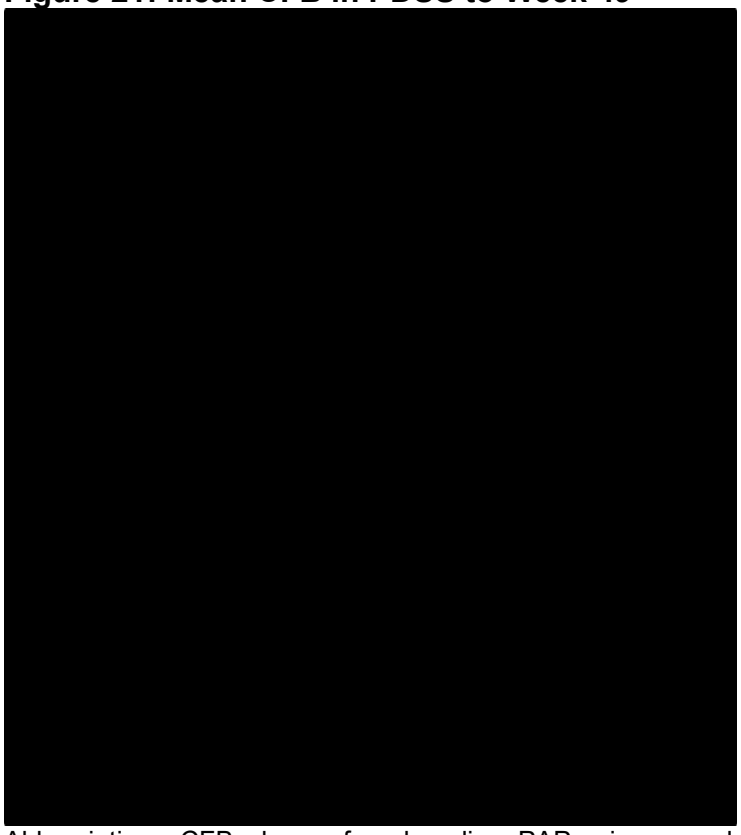
B.2.6.1.4.3 PDSS and PDIS

Primary analysis period (to Week 49)

In general, median decrease from baseline to Week 49 for all PDSS domains and TSS was greater (indicating greater improvement) for AVAL compared with ALGLU. The same trends were observed for PDIS summary score (Figure 21).

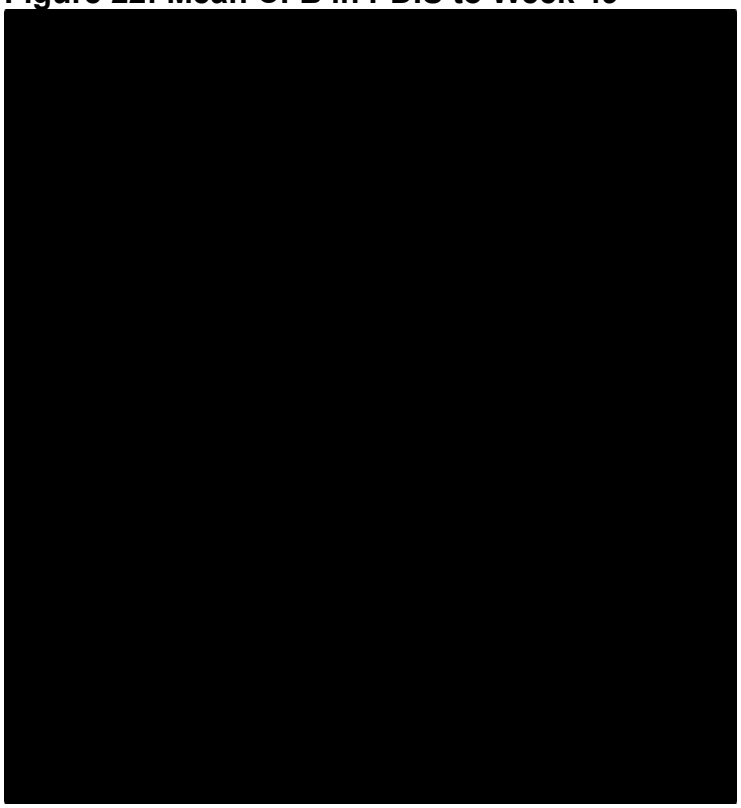
Mean decrease from baseline to Week 49 for the DPAS score of the PDIS was greater for AVAL compared with ALGLU . The same was true for the negative mood score (Figure 22).

Figure 21: Mean CFB in PDSS to Week 49



Abbreviations: CFB, change from baseline; PAP, primary analysis period; PDSS, Pompe disease symptom scale.

Figure 22: Mean CFB in PDIS to Week 49



Abbreviations: CFB, change from baseline; PAP, primary analysis period; PDIS, Pompe disease impact scale.

Extended treatment period (to Week 97)

Patients treated with AVAL and those who switched from ALGLU to AVAL had improvements in PDSS domains and total symptom score, and DPAS and negative mood score of the PDIS from baseline to Week 97.

B.2.6.1.4.4 R-PAct

Primary analysis period (to Week 49)

For the R-PAct score, there was an improvement in favour of AVAL in change from baseline to Week 49 compared with the ALGLU arm (mean change 2.37 [SD: 6.35] for AVAL vs. 1.43 [SD: 4.90] for ALGLU). This indicates that those activities which are most affected by the disease can be improved through treatment with ERT. This in turn may aid increased and sustained independence.

Extended treatment period (to Week 97)

Patients in the AVAL arm maintained improvements in R-PAct summary score to Week 97, with an LSM CFB of [redacted] (Figure 23).

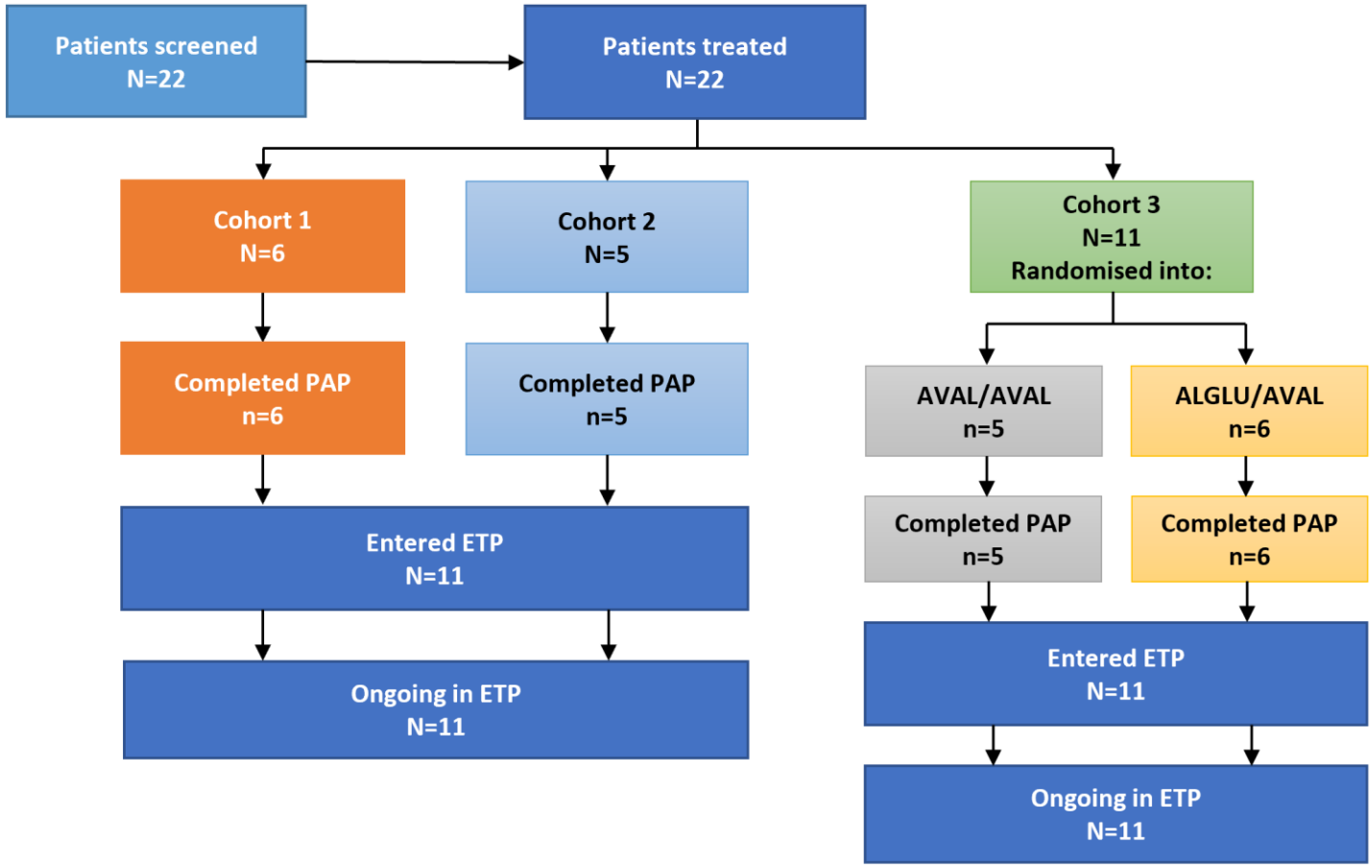
Figure 23: Mean (SD) CFB in R-PAct summary score to Week 97

Abbreviations: CFB, change from baseline; PAP, primary analysis period; PDSS, Pompe disease symptom scale.

B.2.6.2 Mini-COMET

B.2.6.2.1 *Patient disposition*

Figure 24: Patient disposition in Mini-COMET



Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ETP, extended treatment period; PAP, primary analysis period.

Table 21: Analysis populations, Mini-COMET

Analysis population, n (%)	Cohort 1 (N=6)	Cohort 2 (N=5)	Cohort 3 (N=11)
Randomised	–	–	11 (100.0)
Safety	6 (100.0)	5 (100.0)	11 (100.0)
mITT	6 (100.0)	5 (100.0)	11 (100.0)
PD	6 (100.0)	5 (100.0)	11 (100.0)
ADA population	6 (100.0)	5 (100.0)	11 (100.0)

Abbreviations: ADA, anti-drug antibody; mITT, modified intention-to-treat; PD, pharmacodynamic.

B.2.6.2.2 *Primary endpoint*

The primary efficacy endpoint for Mini-COMET was the safety and tolerability of AVAL vs ALGLU at Week 25. Safety data for Mini-COMET are presented in Section B.2.10.2.

B.2.6.2.3 *Key secondary endpoints*

B.2.6.2.3.1 GMFM-88 total score

During the PAP (to Week 25), mean GMFM-88 total percent scores increased modestly from baseline in all four treatment groups, but there was high inter-patient variability (Figure 25). During the ETP, changes in GMFM-88 largely followed the trajectory observed for each patient from baseline to Week 25.

Figure 25: GMFM-88 total percent score over time, mean (SD) CFB, safety population

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; GMFM-88, Gross Motor Function Measure-88; SD, standard deviation.

B.2.6.2.3.2 GMFCS-E&R by study visit

[redacted]

- [redacted]
- [redacted]
- [redacted]

Table 22 presents the GMFCS-E&R observed values to Week 145.

Table 22: GMFCS-E&R observed values by study visit to Week 145

Visit	GMFCS-E&R Level, n (%)	Cohort 1 N=6	Cohort 2 N=5	Cohort 3: AVAL N=5	Cohort 3: ALGLU N=6
Baseline	Number Level I Level II Level III Level IV Level V	6 1 (16.7) 1 (16.7) 1 (16.7) 2 (33.3) 1 (16.7)	5 1 (20.0) 2 (40.0) 0 2 (40.0) 0	5 2 (40.0) 1 (20.0) 1 (20.0) 0 1 (20.0)	6 3 (50.0) 0 1 (16.7) 1 (16.7) 1 (16.7)
Week 25 (PAP)	Number Level I Level II Level III Level IV Level V	[redacted]	[redacted]	[redacted]	[redacted]
Week 49 (ETP)	Number Level I Level II Level III Level IV Level V	[redacted]	[redacted]	[redacted]	[redacted]
Week 73 (ETP)	Number Level I Level II Level III Level IV Level V	[redacted]	[redacted]	[redacted]	[redacted]
Week 97 (ETP)	Number Level I Level II Level III	[redacted]	[redacted]	[redacted]	[redacted]

Visit	GMFCS-E&R Level, n (%)	Cohort 1 N=6	Cohort 2 N=5	Cohort 3: AVAL N=5	Cohort 3: ALGLU N=6
	Level IV Level V	[redacted]	[redacted]	[redacted]	[redacted]
Week 121 (ETP)	Number Level I Level II Level III Level IV Level V	[redacted]	[redacted]	[redacted]	[redacted]
Week 145 (ETP)	Number Level I Level II Level III Level IV Level V	[redacted]	[redacted]	[redacted]	[redacted]

†Patients in Cohort 3 had not reached these timepoints at the data cut-off.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa, ETP, extended treatment period; GMFCS-E&R, Gross Motor Function Classification System – Expanded and Revised; NR, not reported; PAP, primary analysis period.

B.2.6.2.3.3 QMFT

During the PAP, mean QMFT total score increased modestly from baseline to Week 25 in all patients belonging to Cohort 2 and Cohort 3 (both AVAL and ALGLU patients), but with high inter-patient variability, as presented in Figure 26. [redacted]

During the ETP, CFB in QMFT followed a similar trajectory for all patients with available data at Week 97 (Figure 26).

Figure 26: QMFT, mean (SD) CFB in total score to Week 145, safety population

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; QMFT, quick motor function test; SD, standard deviation.

B.2.6.2.3.4 Pompe-PEDI functional skills scale

An improvement in Pompe-PEDI functional skills scale, as reported by caregivers, was also observed in all groups during the initial 25-week comparative period, possibly favoured by the youngest age in the ALGLU group as shown by the spaghetti plots by age (

Figure 27). After Week 25, patients continued to improve or stabilise with AVAL 40 mg/kg qow, in opposition with a decline frequently observed with long-term treatment with ALGLU in published data (104). Between baseline and Week 25 the scaled score:

- increased in four patients and decreased in two patients in Cohort 1,
- increased in two patients from Cohort 2
- increased in three patients belonging to the AVAL arm of Cohort 3, and six in the ALGLU arm
- remained stable in three patients from Cohort 2
- decreased in two patients belonging to Cohort 1.
- Data were not available for two patients, both from the Cohort 3 AVAL arm.

[redacted]

Figure 27: Pompe-PEDI Functional Skills Scale: Mobility Domain - scaled score over time (by age), safety population

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; Pompe-PEDI, Pompe-Paediatric Evaluation of Disability Inventory.

Figure 28 presents mean CFB in Pompe-PEDI to Week 145 by cohort.

Figure 28: Pompe-PEDI Functional Skills Scale: mobility domain mean (SD) CFB in scaled score to Week 145

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; Pompe-PEDI, Pompe Paediatric Evaluation of Disability Inventory; SD, standard deviation.

B.2.6.2.3.5 Echo-LVM Z-score M-mode

At baseline, one CRIM-negative patient in Cohort 2 had an abnormal LVM Z-score (defined as higher than 2); all other patients with available baseline M-Mode echocardiography had normal scores.

All patients with available data (n=20) improved or maintained normal LVM Z-scores. The CRIM-negative patient with an abnormal baseline LVM Z-score improved to the normal range by Week 25. [redacted]

Figure 29 presents the CFB in Echo-LVM Z-score for individual patients.

Figure 29: Echo-LVM Z-score M-MODE over time, safety population

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; LVM, left ventricular mass; SD, standard deviation.

B.2.6.2.3.6 Eyelid position measurements

An improvement of the eyelid position measurement, as assessed by a central independent reader, was observed in the 40 mg/kg qow AVAL groups in Cohort 2 and Cohort 3, as compared with stabilisation or decline with AVAL 20 mg/kg qow and ALGLU (Table 23). This is meaningful to patients since ptosis is potentially amblyogenic and, if severe, may require surgical intervention. Particularly in Cohort 3 patients in the ALGLU arm, who were enrolled in the study due to a new occurrence or worsening of ptosis, it is noteworthy that eyelid position measurements did not improve, while these patients showed improvement in motor outcomes, driven by their young age and less pre-existing motor impairment. Despite some variability the

positive AVAL effect was maintained in the long-term in most patients, especially in those initially treated with AVAL 40 mg/kg qow.

Table 23: Eyelid position measurements, mean CFB at Week 25

	Stage 1		Stage 2	
	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3 AVAL 40 mg/kg N=5	Cohort 3 ALGLU current dose N=6
IFD (left flash, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
IFD (right flash, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
IFD (left non-flash, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
IFD (right non-flash, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MPD (left non-flash, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MPD (right non-flash, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MRD (left, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MRD (right, mm) Mean CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; kg, kilogram; IFD, interpalpebral fissure distance; mg, milligram; MPD, margin pupil distance; MRD, margin reflex distance; SD, standard deviation.

B.2.6.2.4 *HRQoL*

B.2.6.2.4.1 PedsQL Generic Core Scale, PedsQL Pediatric Pain Questionnaire, and Observational Visual Analogue Score

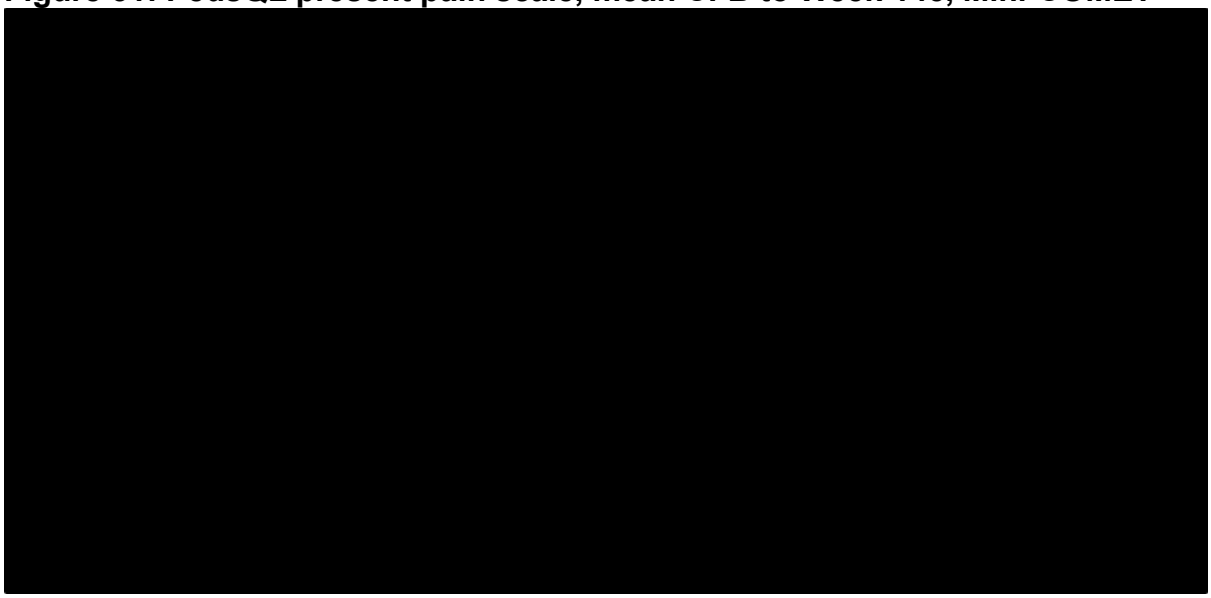
The PedsQL Generic Core Scale is an instrument designed to measure HRQoL in healthy children, as well as those with acute and chronic health conditions, covering an age spectrum between 2 and 18 years (133, 134). The PedsQL Pediatric Pain Questionnaire comprises present pain, worst pain, and the localisation of pain (the latter is not scored) (135). The Observational Visual Analogue Score (VAS-OBS) measures subjective phenomena like pain from the perspective of an observer (136). In all three scales, higher scores indicate better HRQoL.

Figure 30–Figure 33 summarise the mean change from baseline in these outcomes over time, [redacted]

Figure 30: PedsQL total score, mean CFB to Week 145, Mini-COMET

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PedsQL; Pediatric Quality of Life Inventory; SD, standard deviation.

Figure 31: PedsQL present pain scale, mean CFB to Week 145, Mini-COMET



Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; PedsQL; Pediatric Quality of Life Inventory; SD, standard deviation.

Figure 32: PedsQL worst pain scale, mean CFB to Week 145, Mini-COMET

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; PedsQL; Pediatric Quality of Life Inventory; SD, standard deviation.

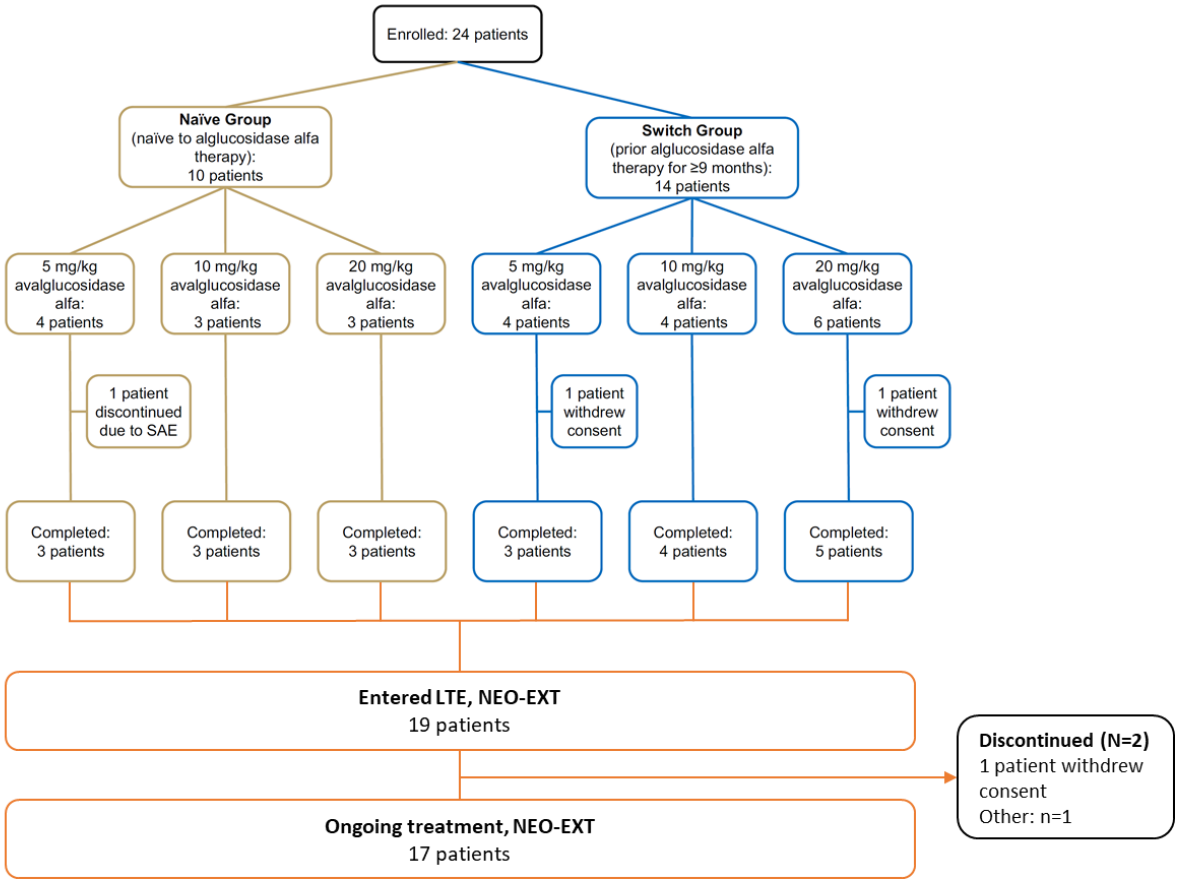
Figure 33: Pain VAS total score, mean CFB to Week 97, Mini-COMET

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; SD, standard deviation; VAS, visual analogue scale.

B.2.6.3 NEO1/NEO-EXT

B.2.6.3.1 *Patient disposition*

Figure 34: NEO1/NEO-EXT study population



Adapted from Pena 2019 (105) and NEO-EXT CSR, data on file (110).
Abbreviations: kg, kilogram; mg, milligram; SAE, serious adverse event.

B.2.6.3.2 *Primary endpoint*

The primary efficacy endpoint for NEO1/NEO-EXT was to assess the safety and tolerability of 5 mg/kg, 10 mg/kg and 20 mg/kg doses of AVAL (safety data presented in Section B.2.10.3).

B.2.6.3.3 *Secondary endpoints*

The secondary objective of NEO1/NEO-EXT was to assess the effect of AVAL on pharmacodynamics (including skeletal muscle composition), and exploratory efficacy variables, including a CFB in FVC% predicted, MEP and MIP, and 6MWT.

B.2.6.3.3.1 FVC% predicted in upright position

NEO1

In NEO1, patients in both Group 1 (ERT-naïve) and Group 2 (ERT-experienced) experienced a trend for improvement in FVC% predicted from baseline to Week 25 (Table 24).

Table 24: Observed FVC % predicted in upright position at baseline, Week 25, and change from baseline in NEO1

	Group 1 (ERT-naïve)			Group 2 (ERT-experienced)		
	AVAL 5 mg/kg n=3	AVAL 10 mg/kg n=3	AVAL 20 mg/kg n=3	AVAL 5 mg/kg n=4	AVAL 10 mg/kg n=4	AVAL 20 mg/kg n=5
Baseline mean (SD)	61.4 (13.19)	82.4 (26.74)	63.4 (17.84)	75.8 (11.66)	82.3 (23.69)	70.4 (16.40)
Week 25 mean (SD)	52.5 (10.16)	86.7 (31.64)	69.5 (20.63)	75.3 (9.35)	80.3 (22.79)	69.9 (16.92)
Change from baseline to Week 25 (SD)	–2.70 (8.81)	4.30 (4.90)	6.20 (2.15)	–0.50 (4.31)	–2.00 (2.24)	1.40 (5.71)

Abbreviations: AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; FVC, forced vital capacity; kg, kilogram; mg, milligram; n, number of patients; SD, standard deviation.

In NEO-EXT, FVC % predicted generally remained stable on treatment over time, although there was some variation between patients due to age and comorbidities (Table 25).

Table 25: Observed FVC % predicted in upright position from Week 13 to Week 312 in NEO1 and NEO-EXT

Week	Group 1 (ERT-naïve) All AVAL doses			Group 2 (ERT-experienced) All AVAL doses		
	Number of patients	Mean (SD) FVC % predicted	Mean change from baseline (SD)	Number of patients	Mean (SD) FVC % predicted	Mean change from baseline (SD)
Baseline	n=10	69.213 (19.265)		n=14	77.304 (16.450)	
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	n=9	[redacted]	2.555 (6.767)	n=13	[redacted]	0.194 (4.437)
Week 52	n=8	[redacted]	2.640 (8.199)	n=11	[redacted]	–2.510 (6.011)
Week 104	n=7	[redacted]	3.112 (11.638)	n=11	[redacted]	–3.787 (5.412)
Week 208	n=7	[redacted]	1.258 (7.012)	n=10	[redacted]	–1.705 (5.293)
Week 312	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; FVC, forced vital capacity; SD, standard deviation.

B.2.6.3.3.2 6MWT

NEO1

In NEO1, 6MWT distances were generally stable or tended to increase with AVAL, without a clear relationship to patient group or dose level (Table 26).

Table 26: 6MWT, mean CFB to Week 25, NEO1

	Group 1 (ERT-naïve)			Group 2 (ERT-experienced)		
	AVAL 5 mg/kg n=4	AVAL 10 mg/kg n=3	AVAL 20 mg/kg n=3	AVAL 5 mg/kg n=4	AVAL 10 mg/kg n=3	AVAL 20 mg/kg n=5
Baseline mean (SD)	65.8 (16.58)	69.2 (6.88)	75.2 (9.80)	54.1 (18.03)	71.9 (21.36)	72.8 (20.59)
Week 25 mean (SD)	61.4 (12.28)	67.1 (7.49)	79.1 (12.55)	52.9 (16.61)	72.6 (20.92)	65.6 (12.03)
CFB to Week 25 (SD)	2.60 (3.89)	–2.10 (2.19)	3.90 (3.45)	–1.20 (5.80)	0.70 (1.25)	–1.30 (8.94)

Abbreviations: AVAL, avalglucosidase alfa; CFB, change from baseline; ERT, enzyme replacement therapy; kg, kilogram; mg, milligram; SD, standard deviation; 6MWT, six-minute walk test.

NEO-EXT

In NEO-EXT, patients remained stable on AVAL treatment over time, with variations on performance in 6MWT due to age and comorbidities. Patients who were ERT-naïve had a greater trend improvement over time (Table 27).

Table 27: 6MWT, mean change from baseline to Week 312 in NEO1 and NEO-EXT

Week	Group 1 (ERT-naïve) All AVAL doses			Group 2 (ERT-experienced) All AVAL doses		
	Number of patients	Mean (SD) 6MWT % predicted	Mean change from baseline (SD)	Number of patients	Mean (SD) 6MWT % predicted	Mean change from baseline (SD)
Baseline	n=10	65.483 (15.540)		n=14	62.243 (17.632)	
Week 13	[redacted]	[redacted]	1.293 (3.730)	[redacted]	[redacted]	–0.312 (5.620)
Week 25	n=9			n=13		
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104						
Week 208						
Week 312						

Abbreviations: AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy; SD, standard deviation; 6MWT, six-minute walk test.

Figure 35 and Figure 36 present individual 6MWT trajectories for Group 1 and Group 2 patients, respectively.

Figure 35: 6MWT distances in Group 1 patients at baseline, Week 13, and Week 25

Abbreviations: 6MWT, 6-minute walk test; NEOGAA, avalglucosidase alfa.

Figure 36: 6MWT distances in Group 2 patients at baseline, Week 13, and Week 25

Abbreviations: 6MWT, 6-minute walk test; NEOGAA, avalglucosidase alfa.

B.2.7 Subgroup analysis

Results of subgroup analyses are presented in Appendix E.

B.2.7.1 COMET (Phase 3, LOPD, ERT-naïve)

Planned subgroup analyses for the primary efficacy endpoint of FVC% predicted in the upright position and key secondary endpoint 6MWT were performed for the following subgroups:

- age group (<18 years; ≥18 years and <45 years; ≥45 years old)
- gender
- baseline FVC groups (<55% or ≥55%)
- region
- baseline walking device at 6MWT
- baseline 6MWT
- duration of disease at baseline
- race.

Given the limited power to detect treatment differences within these subpopulations, the focus of the subgroup analysis was on assessment of the interaction between subgroup covariate and the treatment. If the p-value for the interaction term was less than 0.1, the nature of the interaction was explored to determine if there is a quantitative or qualitative interaction.

The following three mixed model repeated measure (MMRM) models for the primary efficacy endpoint were performed:

- MMRM model to include baseline FVC (% predicted, as continuous), age (as continuous), gender, treatment group, visit, treatment-by-gender interaction, and treatment-by-visit interaction as fixed effects. This was used to assess the gender interaction with the treatment.
- MMRM model to include baseline FVC (% predicted, as continuous), age (<18 years old and ≥18 years old), gender, treatment group, visit, treatment-by-age interaction, and treatment-by-visit interaction as fixed effects. This was used to assess the age interaction with the treatment. The sample size for age <18 maybe too small for this analysis.
- MMRM model to include baseline FVC (% predicted, as continuous), age (as continuous), gender, treatment group, visit, treatment-by-FVC (categorical)

interaction, and treatment-by-visit interaction as fixed effects. This was used to assess the baseline FVC interaction with the treatment.

Estimation method, covariance mix and degrees of freedom calculations were as per the primary analysis. A two-sided 95% confidence interval within each subgroup for the least square mean difference between treatment groups were provided.

B.2.7.2 Mini-COMET (Phase 2, IOPD, ERT-experienced)

Planned subgroup analyses were conducted for the secondary and selected tertiary efficacy endpoints by:

- Race
- Ethnicity
- Gender
- Prior ALGLU treatment duration
- Age at first ALGLU infusion
- Age at first infusion of AVAL or ALGLU in the study
- Baseline use of non-invasive ventilatory support
- Baseline status on invasive ventilatory support
- Assistive device use
- CRIM status
- Baseline GMFCS level
- ACE Genotype
- Status of inhibitory antibody
- Quartiles of peak IgG antibody titre
- Baseline LVM Z-Score
- Duration of Pompe disease at start of Mini-COMET
- Prior use of ALGLU dose regimen.

B.2.7.3 NEO1/NEO-EXT (Phase 1/2 LOPD, ERT-naïve and ERT-experienced)

Results for NEO1/NEO-EXT are presented for patients who were naïve to treatment (Group 1) and those who were previously treated with ALGLU (Group 2). No further subgroup analyses were performed in NEO1/NEO-EXT.

B.2.8 Pooled analysis

Given the challenges with statistically powering a comparative trial in a rare disease, a post-hoc analysis was conducted on the primary endpoint of COMET (FVC% predicted), aimed at increasing precision and power (106).

Regression analyses using a mixed model for repeated measures [redacted] were performed. Analyses were adjusted for differences in baseline characteristics and studies. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

- [redacted]
- [redacted]

[redacted]

Figure 37 [redacted]

Figure 37: Pooled analysis of FVC% predicted in patients with LOPD at one year of AVAL treatment

Note: Myozyme = alglucosidase alfa; Nexviadyme = avalglucosidase alfa.
Abbreviations: AVAL, avalglucosidase alfa; CI, confidence interval; FVC, forced vital capacity; LOPD, late-onset Pompe disease; N, number of patients; woVent, without ventilation.

[redacted]

[redacted]

[redacted]

[redacted]

B.2.9 Indirect and mixed treatment comparisons

Not applicable – see Section B.2.8.

B.2.10 Adverse reactions

B.2.10.1 COMET

B.2.10.1.1 *Primary analysis period*

From a safety perspective, AVAL was better tolerated as compared with ALGLU in the 49-week blinded comparative period of the trial as demonstrated by lower frequencies of TEAEs, SAEs, and protocol-defined IARs with AVAL. Four patients withdrew due to AEs in the ALGLU arm (including two patients with IARs), compared with none in the AVAL arm in the comparative period.

[redacted] Table 28 presents an overview of treatment-emergent adverse events during the PAP occurring within the safety population.

Table 28: Patients with at least one adverse event during PAP (to Week 49), COMET, safety population

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)

Parameter, n (%)	AVAL N=51	ALGLU N=49
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]

n (%) is the number and percentage of patients with at least one TEAE in each category.
Includes AEs up to 28 days after last infusion in PAP for patients who did not enter ETP, or up to 28 days after last infusion in PAP or date and time just prior to first infusion in ETP, whichever occurred earlier, for those who entered ETP.
[†]A serious TEAE is any untoward medical occurrence that at any dose: results in death, or is life-threatening (not referring to an event which hypothetically might have caused death if it were more severe); [‡]The term 'severe TEAE' describes the intensity or 'severity' of a specific medical occurrence; the event itself may be of relatively minor significance.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IAR, infusion-associated reaction; PAP, primary analysis period; TEAE, treatment-emergent adverse event.

The most common TEAEs were headache (21.6% AVAL arm vs. 32.7% ALGLU arm), nasopharyngitis (23.5% vs. 24.5%), back pain (23.5% vs. 10.2%), fatigue (17.6% vs. 14.3%), influenza (17.6% vs. 4.1%), diarrhoea (11.8% vs. 16.3%) and nausea (11.8% vs. 14.3%).

Table 29 presents TEAEs by preferred term occurring in ≥3% of patients by primary system organ class.

Table 29: TEAEs by preferred term occurring in ≥3% of patients by primary system organ class during PAP (to Week 49), COMET, safety population

	AVAL N=51			ALGLU N=49		
Preferred term, n (%)	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
TEAEs	[redacted]	[redacted]	6 (11.8)	[redacted]	[redacted]	7 (14.3)
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper RTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness postural	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	AVAL N=51			ALGLU N=49		
Preferred term, n (%)	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergic rhinitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Throat irritation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	AVAL N=51			ALGLU N=49		
Preferred term, n (%)	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysmenorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Feeling hot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza-like illness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion site extravasation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	AVAL N=51			ALGLU N=49		
Preferred term, n (%)	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECG abnormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin abrasion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVAL, avalglucosidase alfa; ECG, electrocardiogram; PAP, primary analysis period; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event.

The proportion of TEAEs which were potentially treatment-related was 45.1% in the AVAL treatment arm and 49.0% in the ALGLU treatment arm. Table 30 presents TEAEs potentially related to treatment in ≥2% of patients within the safety population during PAP.

Table 30: Potentially treatment-related TEAE's occurring in ≥2% patients during PAP (to Week 49), COMET, safety population

Preferred term, n (%)	AVAL N=51	ALGLU N=49
Any class	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PAP, primary analysis period; TEAE, treatment-emergent adverse event.

[redacted] Table 31 presents the anaphylactic reactions by preferred term.

Table 31: Treatment-emergent anaphylactic reactions by preferred term during PAP, (to Week 49), COMET, safety population

	AVAL N=51		ALGLU N=49	
Preferred term, n (%)	**Patients**	**Events, n**	**Patients**	**Events, n**
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Sensation of foreign body	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PAP, primary analysis period; TEAE, treatment-emergent adverse event.

B.2.10.1.2 *Extended treatment period*

During the ETP, [redacted] of patients who were originally randomised to AVAL experienced TEAEs; [redacted] experienced TESAEs potentially related to study

treatment and [redacted] discontinued study treatment due to TEAEs. [redacted]

Of the patients who switched from ALGLU to AVAL, [redacted] experienced at least one TEAE, and [redacted] had TESAEs potentially related to study treatment. [redacted]

Table 32 presents a summary of TEAEs occurring during AVAL treatment in the ETP.

Table 32: Patients with at least one adverse event during COMET (COMET, PAP and ETP, safety population)

Parameter, n (%)	Patients who received AVAL during PAP and ETP N=42	Patients who switched from ALGLU to AVAL N=34	All patients who received AVAL in either PAP or ETP N=77
TEAEs	[redacted]	[redacted]	[redacted]
TEAEs potentially related to study treatment	[redacted]	[redacted]	[redacted]
TESAEs[ǂ]	[redacted]	[redacted]	[redacted]
TESAEs potentially related to study treatment	[redacted]	[redacted]	[redacted]
Severe TEAEs[†]	[redacted]	[redacted]	[redacted]
TEAEs leading to permanent treatment discontinuation	[redacted]	[redacted]	[redacted]
TEAEs leading to death	[redacted]	[redacted]	[redacted]
Protocol-defined IARs	[redacted]	[redacted]	[redacted]
Algorithm-defined IARs	[redacted]	[redacted]	[redacted]

n (%) is the number and percentage of patients with at least one TEAE in each category.
Events in PAP and ETP: include adverse events that developed, worsen or became serious on or after the 1st infusion of AVAL in PAP, and up to 28 days after the last infusion of AVAL in ETP.
Events in ETP: include adverse events that developed, worsen or became serious on or after the 1st infusion of study drug in ETP and up to 28 days after last infusion in ETP.
[ǂ]A TESAE is any untoward medical occurrence that at any dose: results in death, or is life-threatening (not referring to an event which hypothetically might have caused death if it were more severe); [†]The term 'severe TEAE' describes the intensity or 'severity' of a specific medical occurrence; the event itself may be of relatively minor significance.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ETP, extended treatment period; IAR, infusion-associated reaction; PAP, primary analysis period; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

B.2.10.2 Mini-COMET (IOPD, ERT-experienced)

B.2.10.2.1 *Primary analysis period (up to Week 25)*

The incidence of AEs was comparable between the two treatment arms (AVAL and ALGLU) of Cohort 3. Patients assigned to Cohort 2 (AVAL 40 mg/kg) experienced more TESAEs (60.0%) than patients assigned to Cohort 1 (AVAL 20 mg/kg; 16.7%) and Cohort 3 (AVAL 40 mg/kg; 0%), respectively. No permanent withdrawals from treatment or deaths were observed in any cohort. Infusion-associated reactions were observed in 2/5 (40.0%), 1/5 (20.0%) and 1/6 (16.7%) patients in Cohort 2 (AVAL 40 mg/kg), Cohort 3 (AVAL 40 mg/kg arm), and Cohort 3 (ALGLU current dose arm), respectively.

Table 33 presents an overview of TEAEs experienced by the safety population during the PAP (to Week 25).

Table 33: Number of patients experiencing at least one TEAE (Mini-COMET, PAP, safety population)

Parameter, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
TEAEs	5 (83.3)	5 (100)	5 (100)	5 (83.3)
TEAEs potentially related to study treatment	0	2 (40)	1 (20.0)	1 (16.7)
TESAEs[ǂ]	1 (16.7)	3 (60.0)	0	2 (33.3)
TESAEs potentially related to study treatment	0	0	0	0
Severe TEAEs[†]	0	2 (40.0)	0	1 (16.7)
Severe TEAEs potentially related to study treatment	0	0	0	0
TEAEs leading to permanent treatment discontinuation	0	0	0	0
TEAEs leading to death	0	0	0	0
TEAEs leading to death potentially related to study treatment	0	0	0	0
Adverse event of	0	2 (40.0)	1 (20.0)	1 (16.7)

Parameter, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
special interest				
Protocol-defined IARs	0	2 (40.0)	1 (20.0)	1 (16.7)
Algorithm-defined IARs	0	2 (40.0)	1 (20.0)	1 (16.7)

[‡]A TESAE is any untoward medical occurrence that at any dose: results in death, or is life-threatening (not referring to an event which hypothetically might have caused death if it were more severe); [†]The term 'severe TEAE' describes the intensity or 'severity' of a specific medical occurrence; the event itself may be of relatively minor significance.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IARs, infusion-associated reaction; kg, kilogram; mg, milligram; PAP, primary analysis period; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

The highest proportion of TEAEs experienced by patients were observed in the [redacted] system organ class. During the PAP, the three most commonly reported TEAEs by preferred term were [redacted]

Table 34 presents the most common TEAEs by system organ class and by preferred term, occurring in at least two patients during the PAP.

Table 34: Proportion of patients experiencing most common TEAEs by primary system organ class and preferred term (Mini-COMET, PAP, safety population)

Preferred term, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
TEAEs (patients with at least 1)	5 (83.3)	4 (80.0)	5 (100.0)	5 (83.3)
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]
Upper RTI	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid ptosis (drooping eyelids)	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Excessive cerumen production	[redacted]	[redacted]	[redacted]	[redacted]
Middle ear effusion	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
Abdominal pain				
Toothache				
Nausea				
Skin and subcutaneous tissue disorders				
Rash				
Musculoskeletal and connective tissue disorders				
Pain in extremity				
General disorders and administration site conditions				
Pyrexia				
Injury, poisoning and procedural complications				
Fall				
Product Issues				
Device occlusion				

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; kg, kilogram; mg, milligram; PAP, primary analysis period; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

B.2.10.2.1.1 Treatment-related adverse events

Treatment-related events occurred in [redacted]. Events of [redacted] (Table 35).

Table 35: Proportion of patients experiencing a treatment-related AE by preferred term (Mini-COMET, PAP, safety population)

Parameter, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; kg, kilogram; mg, milligram; PAP, primary analysis period.

B.2.10.2.1.2 Serious adverse events

Six patients experienced TESAEs during the PAP. The most frequently reported serious adverse event by preferred term was [redacted] (Table 36).

Table 36: TESAEs by primary system organ class and preferred term (Mini-COMET, PAP, safety population)

Preferred term, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
TEAEs (patients with at least 1)	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]
Upper RTI – viral	[redacted]	[redacted]	[redacted]	[redacted]
Lung infection pseudomonal	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid ptosis (drooping eyelids)	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]	[redacted]
Lung consolidation	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Joint dislocation	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; kg, kilogram; mg, milligram; PAP, primary analysis period; RTI, respiratory tract infection; TESAE, treatment-emergent serious adverse event; UTI, urinary tract infection.

Analysis of TESAEs during the ETP and overall avalglucosidase treatment period highlighted a consistent pattern of TESAEs primarily associated with intercurrent illness and not with administration of AVAL.

B.2.10.2.1.3 Adverse events of special interest

Adverse events of special interest (AESIs) are AEs (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. These included IARs, pregnancy, symptomatic overdose and particular clinical laboratory findings.

[redacted] Table

37 presents AESIs by primary system organ class and preferred term which occurred during the PAP.

Table 37: AESIs by primary system organ class and preferred term (Mini-COMET, PAP, safety population)

Parameter, n (%)	Cohort 1 AVAL 20 mg/kg N=6	Cohort 2 AVAL 40 mg/kg N=5	Cohort 3	
			AVAL 40 mg/kg N=5	ALGLU current dose N=6
Patients with at least 1 AESI	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; kg, kilogram; mg, milligram; PAP, primary analysis period.

B.2.10.2.2 *Extended treatment period*

Results during the ETP were comparable to those observed during the PAP, with no significant difference in occurrence of TESAEs between doses, no serious or severe TEAEs considered related to treatment with AVAL, and no deaths or TEAEs leading to treatment discontinuation (Table 38).

Table 38: Patients experiencing at least one TEAE when receiving AVAL (Mini-COMET, ETP, safety population)

Parameter, n (%)	AVAL 20 mg/kg initial planned dose N=6	AVAL 40 mg/kg initial planned dose N=10	ALGLU to AVAL N=6
TEAEs	6 (100)	10 (100)	6 (100)
TEAEs potentially related to study treatment	1 (16.7)	5 (50)	4 (66.7)
TESAEs†	5 (83.3)	3 (30)	3 (50)
TESAEs potentially related to study treatment	0	0	0
Severe TEAEs‡	3 (50)	1 (10.0)	2 (33.3)
Severe TEAEs potentially related to study treatment	0	0	0
TEAEs leading to permanent treatment discontinuation	0	0	0
TEAEs leading to death	0	0	0
TEAEs leading to death potentially related to study treatment	0	0	0
Adverse event of special interest	[redacted]	[redacted]	[redacted]
Protocol-defined IARs	1 (16.7)	4 (40)	3 (50)
Algorithm-defined IARs	1 (16.7)	5 (50)	3 (50)

Note: Includes data in ETP among patients who received AVAL in PAP and ETP (Cohort 1 patients with 20 mg/kg initial planned dose, and Cohort 2 and Cohort 3 AVAL patients with 40 mg/kg initial planned dose). Also includes patients who received ALGLU in PAP and received AVAL in ETP (Cohort 3, alglucosidase arm).
†A TESAE is any untoward medical occurrence that at any dose: results in death, or is life-threatening (not referring to an event which hypothetically might have caused death if it were more severe); ‡The term 'severe TEAE' describes the intensity or 'severity' of a specific medical occurrence; the event itself may be of relatively minor significance.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ETP, extended treatment period; IARs, infusion-associated reaction; kg, kilogram; mg, milligram; TEAE, treatment-emergent adverse event.

B.2.10.3 NEO1/NEO-EXT (up to data cut-off 27th February 2020)

In NEO1/NEO-EXT at the time of data cut-off (27th February 2020), there were a total of 2,685 infusions: 1,043 in Group 1 (ERT-naïve) and 1,642 in Group 2 (ERT-experienced), including qow IV infusions of 5, 10, or 20 mg/kg AVAL.

The median duration of exposure to AVAL was [redacted]

[redacted]

Up to the data cut-off (27th February 2020) 100% of patients initially receiving 5 mg/kg, 10 mg/kg and 20 mg/kg AVAL experienced an AE. [redacted] Only one patient permanently withdrew from treatment and no deaths were observed in any cohort. [redacted]

Table 39 presents an overview of the adverse event profile during NEO1/NEO-EXT.

Table 39: Overview of TEAEs in Group 1 (ERT-naïve) and Group 2 (ERT-experienced) treatment groups (NEO1/NEO-EXT, safety population, up to data cut-off 27th February 2020)

	5 mg/kg N=8		10 mg/kg N=7		20 mg/kg N=9		Combined N=24	
Parameter, n (%)	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24 (100.0)	[redacted]
TESAEs[ł]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9 (37.5)	[redacted]
Severe TEAEs[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	[redacted]
Adverse event of special interest	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol-defined IARs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6 (25.0)	[redacted]
Algorithm-defined IARs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to permanent treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 (4.2)	[redacted]
TEAEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	[redacted]

[ł]A TESAE is any untoward medical occurrence that at any dose: results in death, or is life-threatening (not referring to an event which hypothetically might have caused death if it were more severe); [†]The term 'severe TEAE' describes the intensity or 'severity' of a specific medical occurrence; the event itself may be of relatively minor significance.
Abbreviations: AE, adverse event; ERT, enzyme replacement therapy; IARs, infusion-associated reaction; kg, kilogram; mg, milligram; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

B.2.10.3.1 *Serious adverse events*

[redacted] Table 40 presents the prevalence of TESAEs by system organ class and preferred term.

Table 40: TESAEs by primary system organ class and preferred term, Group 1 (ERT-naïve) and Group 2 (ERT-experienced) combined (NEO1/NEO-EXT, safety population, up to data cut-off 27th February 2020)

	5 mg/kg N=8		10 mg/kg N=7		20 mg/kg N=9		Combined N=24	
Parameter, n (%)	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**
Any TESAEs	[redacted]							
Infections and Infestations								
Cystitis								
Diverticulitis								
Infection								
Neoplasms, benign, malignant and unspecified								
Basal cell carcinoma								
Lung carcinoma, stage IV								
Renal cell carcinoma								

	5 mg/kg N=8		10 mg/kg N=7		20 mg/kg N=9		Combined N=24	
Parameter, n (%)	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic inflammatory demyelinating polyradiculoneuropathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial ischaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aortic aneurysm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aortic dilatation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extravasation blood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral artery stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Volvulus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	5 mg/kg N=8		10 mg/kg N=7		20 mg/kg N=9		Combined N=24	
Parameter, n (%)	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Labour pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram Q wave abnormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fractured sacrum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lumbar vertebral fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-implantation syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERT, enzyme replacement therapy; kg, kilogram; mg, milligram; TESAEs, treatment emergent serious adverse events.

B.2.10.3.2 *Adverse events of special interest*

[redacted].

B.2.10.3.3 *Infusion-associated reactions*

[redacted] Table 41 presents the prevalence of IARs within the patient population of NEO1/NEO-EXT.

Table 41:Treatment-emergent protocol-defined or algorithm-defined IARs by primary system organ class and preferred term, Group 1 (ERT-naïve) and Group 2 (ERT-experienced) (NEO1/NEO-EXT, safety population, up to data cut-off 27th February 2020)

	5 mg/kg N=8		10 mg/kg N=7		20 mg/kg N=9		Combined N=24	
Parameter, n (%)	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**
Protocol-defined or algorithm defined IARs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ventricular extrasystoles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	5 mg/kg N=8		10 mg/kg N=7		20 mg/kg N=9		Combined N=24	
Parameter, n (%)	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**
Lip swelling								
Swollen tongue								
Gastrooesophageal reflux disease								
Nausea								
Skin and subcutaneous tissue disorders								
Erythema								
Palmar erythema								
Pruritus								
Rash								
Hyperhidrosis								
Musculoskeletal and connective tissue disorders								
Flank pain								
Myalgia								
Investigations								
Breath sounds abnormal								
Oxygen saturation decreased								
General disorders and administration site conditions								
Chills								

	5 mg/kg N=8		10 mg/kg N=7		20 mg/kg N=9		Combined N=24	
Parameter, n (%)	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**Events**
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion site pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERT, enzyme replacement therapy; IARs, infusion associated reactions; kg, kilogram; mg, milligram.

B.2.10.4 Overview of safety of AVAL

AVAL has a safety profile that is potentially improved compared with ALGLU, the current standard-of-care for the treatment of Pompe disease. Across the clinical trial programme, including COMET, Mini-COMET and NEO1/NEO-EXT, a total of 118 adults with LOPD and [redacted] paediatric patients ([redacted], 22 patients with IOPD) were treated with AVAL (Appendix C).

For patients with LOPD, the most common adverse events related to AVAL treatment (incidence ≥5%) were headache, fatigue, nausea, urticaria and pruritus, while in patients with IOPD, the most common adverse events related to treatment with AVAL were rash (60% of patients) and urticaria (40% of patients).

In the PAP of COMET, patients with LOPD who were treated with AVAL experienced fewer TESAEs than those treated with ALGLU, and no patients discontinued due to TEAEs (compared with four in the ALGLU arm). In NEO-1/NEO-EXT [redacted]

In patients with IOPD, those receiving 20 mg/kg AVAL experienced fewer TESAEs than those receiving AVAL 40 mg/kg or a stable dose of ALGLU, although TEAEs were predominantly of mild to moderate intensity. Furthermore, no permanent discontinuations of AVAL or deaths occurred during Mini-COMET

The SmPC reports the most frequently observed adverse drug reactions in a pooled safety analysis from all four clinical studies [redacted]

Across the clinical trials, [redacted] patients died; [redacted] one patient who received ALGLU (COMET, [redacted] were considered unrelated to treatment.

B.2.11 Ongoing studies

The randomised phase of COMET, and Stage 1 and Stage 2 of Mini-COMET have been completed; patients are currently enrolled in the long-term extension treatment periods of these trials, while the phase 2 trial NEO-EXT is also ongoing. In addition, a phase 3, open-label study, Baby-COMET (NCT04910776), will evaluate AVAL in IOPD patients who have not received prior ERT (137).

B.2.12 Innovation

B.2.12.1 Mode of action

Efficient delivery of ERT to lysosomes is critical for glycogen clearance in Pompe disease. One of the recognised limitations of ALGLU is its low muscle cell uptake activity, caused by a very low level of M6P – the glycan structure responsible for cellular binding and uptake of this enzyme. This is thought to be responsible for the sub-optimal efficacy of ALGLU in clearing glycogen.

AVAL has been innovatively designed through molecular glycoengineering to maintain the enzymatic activity of ALGLU, whilst increasing the uptake and lysosomal targeting. Compared with ALGLU, AVAL has a 15-fold increase in M6P levels, which enhance its receptor-mediated uptake (17, 18) and potency. Preclinical studies using *in vivo* Pompe models have demonstrated that, compared with ALGLU, AVAL has a 1000-fold higher binding affinity to M6P receptors (17, 18), leading to greater glycogen clearance from muscles at one-fifth of the dose of ALGLU (18).

B.2.12.2 Administration

[redacted] and free up staff capacity at treatment centres.

B.2.12.3 Access to innovation

An indirect impact of the technology may be to encourage other pharmaceutical companies developing improved rare/very-rare medications to seek reimbursement in the UK, to send a signal that the UK is a positive place for new rare medicines,

and to encourage further research into ways of improving recombinant therapeutic proteins currently available (e.g. novel delivery mechanisms to enhance efficacy).

B.2.13 Interpretation of clinical effectiveness and safety evidence

AVAL has been investigated in a robust clinical trial programme, comprising paediatric and adult patients across the spectrum of both IOPD and LOPD, including patients with LOPD who were treatment-naïve and ERT-experienced. The clinical evidence base for AVAL consists of a phase 1 study (NEO1) (105), with an extended, long-term phase 2 component (NEO-EXT), a phase 2 study with an extended treatment phase (Mini-COMET), and a phase 3, randomised controlled trial with an extended treatment phase (COMET). Across the four clinical trials 118 adults with LOPD and [redacted] paediatric ([redacted], 22 patients with IOPD) were treated with AVAL (Appendix C). This is a very comprehensive trial programme considering Pompe is an ultra-rare disease with low patient numbers.

In patients with LOPD, AVAL met the primary efficacy endpoint for non-inferiority over ALGLU in improving FVC% predicted in the upright position (COMET) (111). AVAL was non-inferior to ALGLU in patients with LOPD, and treatment with AVAL was associated with an improvement in outcomes measuring musculoskeletal heath and motor function (including 6MWT, QMWT, HHD, GMFM-88 and GSGC), as well as HRQoL (EQ-5D-5L, SF-12) and patient reported outcomes. During the ETP of COMET, the stabilisation and improvements observed during the PAP in patients treated with AVAL were maintained, with clinically meaningful stabilisation of the treatment effect observed during the PAP.

The stabilisation of clinical outcomes was maintained long-term (6 years) (110). Biomarkers associated with Pompe disease and muscle damage decreased in most patients and these decreases were also maintained long-term.

In patients with IOPD with clinical decline or suboptimal response to ERT, treatment with AVAL was associated with a trend for improvement or stabilisation across several clinical outcomes. Avalglucosidase alfa was well tolerated at 20 mg/kg and 40 mg/kg and had a safety profile comparable with ALGLU. Treatment with AVAL

decreased biomarkers associated with disease burden, and stabilised or improved clinical efficacy outcomes associated with motor function (GMFM-88, QMFT and Pompe-PEDI), and cardiovascular hypertrophy (LVM Z-score) (109). This compares favourably with the published data on outcomes such as Pompe-PEDI in patients treated with ALGLU (104).

[redacted]

C[redacted]

[redacted]

B.2.13.1 Strengths

The use of AVAL in patients with Pompe disease is supported by multiple clinical trials in a broad spectrum of patients followed up for up to six years (Section B.2).

In LOPD, the pivotal COMET trial was designed to provide robust evidence on the efficacy and safety of AVAL (Section B.2.3.1). The measures undertaken to ensure this and reduce bias included randomisation stratified by potential confounding factors, blinding of patients, clinicians and outcome assessors, the use of mITT analysis and ensuring close to complete follow-up, with 95 patients (95%) completing the PAP. Furthermore, beyond the randomised period of COMET, data are available from both the ongoing ETP, as well as from NEO-EXT which is currently collecting data in patients who have been treated with AVAL for up to six-years (Section B.2.3.4). Both trials are also collecting data on patients for whom AVAL was the first ERT, as well as for those switching from ALGLU.

In IOPD, the evidence is based on the phase 2 Mini-COMET trial, which included patients who declined or showed suboptimal response to treatment with the current standard-of-care, ALGLU (Section B.2.3.2). Patients who were previously treated with a range of ALGLU doses, frequently exceeding 40 mg/kg qow, have shown either improvement or stabilisation of their condition following treatment with AVAL. There is also data available for up to [redacted] of drug exposure from the ETP, further supporting the benefit of AVAL in these patients.

In both LOPD and IOPD, the clinical trials evaluated clinical endpoints used in Pompe disease (Section B.2.3.7). These included 6MWT, QMFT and FVC% predicted in the upright position, and QOL (SF-12, EQ-5D). In addition, to better capture the impact of the treatment on the patients, new tools were also developed (PDSS/PDIS).

The evidence base for AVAL can also be considered generalisable to the UK population. At an Advisory Board supporting UK HTA submissions for AVAL, three metabolic consultants and two clinical nurse specialists agreed that patients' baseline characteristics within COMET are generally comparable with those observed in UK clinical practice (Appendix M).

In addition, the clinical trial programme investigating AVAL in the treatment of IOPD and LOPD provides data on a wide range of patients of different ages, from paediatric (min: 1 year; Mini-COMET) to late adulthood (max: 78.3 years; NEO-EXT) (Section B.2.3.6).

Furthermore, as two publications studying UK-specific Pompe disease cohorts registered in England and Wales have found that all IOPD and virtually all LOPD patients were treated with ALGLU (only three untreated patients in a cohort of >60 patients) (16, 79), the use of ALGLU as a comparator in COMET and Mini-COMET ensures that AVAL is evaluated against current clinical practice.

In conclusion, the trials supporting the use of AVAL in Pompe disease provide a robust evidence base in a broad spectrum of patients. Most importantly, the benefit of treatment with AVAL is consistent across different clinical outcomes and is broadly maintained in the long-term.

B.2.13.2 Limitations

In rare conditions such as Pompe disease, the interpretation of trial results can be challenging, as reference standards often do not exist. In LOPD, the MCID has been investigated only for FVC % predicted in the upright position. One study reported the MCID to be between 1.6 and 4.8% (data on file), while an analysis of COMET data demonstrated an improvement of 1.7 units or greater in FVC% predicted to correspond to minimal patient relevant change (Section B.2.3.7.1). Therefore, the results of the COMET trial have shown an improvement on treatment with AVAL

which can be considered clinically meaningful. In addition, long-term experience with ALGLU shows a meaningful benefit in delaying the progression of the disease and reducing mortality (102). Therefore, it can be expected that the benefits of AVAL treatment seen in clinical trials and their extensions will translate to a prognosis that is similar to or better than that observed with ALGLU. This was confirmed during the advisory board, where the clinical trial data were viewed to be indicative that AVAL may lead to a greater delay in disease progression.

In LOPD, although the phase 3 COMET trial was close to attaining the threshold required to declare statistical superiority of AVAL over ALGLU (p=0.0626), such a simple interpretation may have limitations. The pre-defined primary statistical objective of the study was to demonstrate non-inferiority for % predicted FVC, as agreed with regulatory agencies, since recruiting a sufficient number of patients for superiority testing would be challenging due to the rarity of Pompe disease. It has been also pointed out in methodological literature that arbitrary p-value thresholds should not be used to accept or reject something as true (139). Rather, they should be interpreted as what they are: measures of uncertainty. In the context of rare disease, consistent trends across all clinical outcomes in the trials and a majority of subgroups are indicative of AVAL offering an improved treatment alternative compared with ALGLU.

In IOPD, the data supporting AVAL may be viewed as uncertain, given it is based on a relatively small phase 2, open-label trial (Mini-COMET). In addition, despite the inclusion of an ALGLU arm in Cohort 3 (n=11), valid comparisons between the two treatments cannot easily be made due to the small patient numbers and imbalances in baseline characteristics (Section B.2.3.6). Nevertheless, the stabilisation or improvement in patients who were previously declining or sub-optimally responding to ALGLU suggests a benefit of AVAL.

The uncertainty in both the IOPD and LOPD results can be largely attributed to the number of patients included in the trials. While this number may be viewed as small, the rare disease setting must be considered. Timely recruitment of patients into trials of rare conditions is often challenging and needs to be balanced against the avoidance of delays in bringing new treatments into routine care (140). For example, recruitment of patients to the COMET trial took approximately 2.5 years.

Furthermore, NICE has recently proposed in their Methods consultation (141) that there should be a greater acceptance of uncertainty for rare disease medicines.

In addition, the number of patients participating in the AVAL clinical programme is comparable to the total number of Pompe disease patients in the UK. These trial patients are also involved in long-term extension studies which have indicated treatment with AVAL provides a sustained benefit. Moreover, once AVAL is available in clinical practice, further long-term efficacy and safety data will be collected in the Pompe Registry.

To address the challenges associated with statistically powering a comparative trial in a rare disease, a pooled analysis which included patients from COMET and LOTS was performed (Section B.2.8). [redacted]

B.2.13.3 Factors which may influence external validity of study results to patients in routine clinical practice

The AVAL clinical trial programme provides evidence of the efficacy and safety of this ERT in a wide spectrum of patients which is generalisable to the UK population. Based on the selection criteria, only patients who would be treated with ERT in clinical practice in the UK were included in the studies. Across the trials, eight patients were from the UK, including five in COMET, two in Mini-COMET and one in NEO1/NEO-EXT.

At an advisory board, three metabolic consultants and two clinical nurse specialists who specialise in treating patients with Pompe disease agreed that the baseline characteristics in the COMET trial are generally comparable with patients observed in current clinical practice, except for FVC% predicted in the upright position (mean 62.1%) and 6MWD (mean 388.9 m). Both measurements were higher in the trial compared with those generally observed in clinical practice. This difference is likely due to the trial patients being naïve to ERT and therefore the most recently diagnosed. As such, the trial cohort were considered a good reflection of the patients who are currently newly referred to the LSD service in the UK for confirmatory diagnosis and commencement of treatment. Where patients have been living with

Pompe disease for several years and their disease has progressed, they do often have significantly worse measurements for these parameters.

For Mini-COMET, the clinicians at the advisory board highlighted that in clinical practice the number of older patients with IOPD is small, and that ambulatory device use is likely to be higher than seen in the trial. Patients in Cohort 3 treated with ALGLU were younger and likely to have a lower disease burden than the older patients treated with AVAL.

In COMET, patients received the anticipated licensed dose of AVAL for LOPD (20 mg/kg qow) and the licensed dose of ALGLU (20 mg/kg qow). NEO1 evaluated a range of AVAL doses, however once the dose to be taken forward in the phase 3 trial was established (20 mg/kg qow), all patients were switched to 20 mg/kg AVAL in NEO-EXT. In Mini-COMET some patients received a lower dose (20 mg/kg qow), while others received 40 mg/kg qow. In addition, the baseline stable doses of ALGLU in patients with IOPD were, in the majority of cases, above the licensed dose (20 mg/kg qow). It is important to note that this reflects the actual variation in clinical practice across the globe, where higher doses are frequently used due to the extremely low level or absence of endogenous GAA enzyme activity. In the UK, patients with IOPD may receive increased doses of ALGLU (20 mg/kg qw) for the first three months, or until their cardiomyopathy has resolved (Appendix M).

The external validity factors identified will not impact the selection of patients in clinical practice. The selection criteria currently used for initiating ALGLU treatment (Section B.1.3.7) will also apply to AVAL.

B.3 Cost effectiveness overview

AVAL offers an improved and cost-saving treatment option compared with the current standard-of-care for patients with LOPD and IOPD

- A conservative cost-comparison analysis was conducted to evaluate the cost-saving benefits of AVAL compared with ALGLU.
- AVAL was cost saving across all the scenarios considered.
- The clinical trial COMET demonstrated improvement across all outcomes with AVAL in patients with LOPD, while Mini-COMET has shown a trend for improvement or stabilisation across several clinical outcomes in patients with IOPD who were previously in clinical decline or had suboptimal response to ERT. However there remains uncertainty in the long-term extrapolations of efficacy for AVAL vs ALGLU and to simplify the economic case a conservative assumption of equivalent or better efficacy was made.
- A lifetime time horizon (60 years) was applied in the analysis for LOPD, while a 50-year time horizon was applied in the IOPD analysis.
- In the base-case analysis using the PAS price, AVAL was cost-saving compared with ALGLU, leading to a saving of [redacted] and [redacted] in LOPD and IOPD, respectively.
- Cost-savings were primarily driven by [redacted]
- An additional cost-effectiveness analysis has also shown AVAL to be a cost-saving and cost-effective treatment option compared with ALGLU (Appendix L).

B.3.1 Published cost-effectiveness studies

A cost-comparison analysis is presented in this document. Details of published cost-effectiveness studies are provided in Appendix L where a cost-effectiveness approach is presented.

B.3.2 Approach and populations modelled in the economic analyses

Two populations were modelled in the economic analyses:

- Patients with LOPD (Section B.4)
- Patients with IOPD (Section B.5).

This is consistent with the population considered in the COMET, NEO1 and NEO-EXT trials for LOPD, the Mini-COMET study for IOPD, and the draft scope issued by NICE (142). For both populations, a conservative cost-comparison approach was selected. The phase 3 trial COMET has shown that AVAL offers an improvement in the treatment of LOPD, with a trend for improved respiratory function (FVC% predicted) and mobility (6MWT) across 49 weeks compared with ALGLU.

Head-to-head data comparing AVAL with ALGLU in IOPD are limited, however Mini-COMET has shown a trend for improvement or stabilisation across several clinical outcomes in patients that previously were in clinical decline or had suboptimal response to ERT. While the majority of patients in Mini-COMET received a higher dose of AVAL than is stated in the licence for patients starting treatment (40 mg/kg qow vs 20 mg/kg qow), patients entering Cohort 3 of Mini-COMET had previously had a suboptimal response on the licensed or higher dose of ALGLU [redacted]

However, given the rarity of Pompe disease the company acknowledge that, as would be expected, there is uncertainty in the long-term extrapolations of any benefits. [redacted], and to simplify the economic case and expedite patient access, a cost-comparison approach was selected. Given the available evidence, the cost-comparison assumption of equivalent efficacy can be considered conservative. Cost-

effectiveness analyses have also been performed and results are presented in Appendix L; these show AVAL to be a cost-saving and cost-effective treatment option compared with ALGLU.

Two separate analyses were performed for LOPD and IOPD to account for differences in dosing regimens, patient characteristics, and survival between the two patient subgroups. Patients with IOPD present in the first year of life, thus the required dosing differs greatly between IOPD and LOPD. Additionally, patients with IOPD receive a double dose of ALGLU in the first 3 months of treatment. They also have poorer survival outcomes than patients with LOPD, meaning that the expected time on treatment is shorter.

The following section describes the methodology of the LOPD analysis. The IOPD methodology is provided in Section B.5.

B.4 Economic analysis in LOPD

B.4.1 Economic analysis

B.4.1.1 Model structure

The cost-comparison model was developed in Microsoft® Excel and adopted a Markov cohort approach to calculate the proportion of patients across three states over time: alive and on-treatment, alive and off-treatment or death. The primary outcome of the model was the total cost for each treatment option. Costs included in the model were those that may differ between therapies and includes drug acquisition costs and administration costs.

The model assumed a 1-year cycle length. A lifetime time horizon was applied, and costs were discounted at 3.5%. Costs were considered from the perspective of the NHS and Personal Social Services (PSS).

B.4.1.2 Features of the economic analysis

Key features of the LOPD economic model are outlined in Table 42.

Table 42: Features of the economic analysis

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime (60 years)	Sufficient to capture a lifetime horizon	NICE 2013 (20)
Discount rate for costs	3.5%	NICE reference case	
Perspective (NHS/PSS)	NHS	NICE reference case	

Abbreviations: NHS, National Health Service; PSS, Personal Social Services.

B.4.1.3 Intervention technology and comparators

The intervention considered is AVAL (20 mg/kg) and the comparator is ALGLU (20 mg/kg), both administered as an IV infusion every other week.

B.4.2 Clinical parameters and variables

B.4.2.1 Baseline characteristics

Baseline characteristics were taken from the mITT population in the COMET clinical trial (Table 43).

Table 43: Baseline characteristics

Characteristic	Mean (SD)
% male	52%
Baseline age (years)	48.1 (14.2)
Weight (kg)	78.5 (20.2)

Abbreviations: kg, kilogram; SD, standard deviation.

B.4.2.2 Overall survival

A parametric survival curve for patients with LOPD receiving no treatment, estimated from data presented by Gungor 2011 (143), was used to inform the baseline OS curve. Although these patients are unlikely to be representative of the current LOPD population, there was no current evidence identified with OS data that could be used for modelling. Weibull and Gompertz specifications were estimated, and the model allowed for selection of either. Measures of model fit (Akaike's Information Criteria [AIC] and Bayesian Information Criteria [BIC]) indicated the Weibull model provided a better fit to the data, but the Gompertz model was considered to provide more plausible extrapolations and was selected as the base case (Table 44).

Table 44: Parameters for the survival distributions for LOPD patients on no treatment

Fit	Scale	SE	Shape	SE	AIC	BIC
Weibull	3.4780	0.0672	0.5335	0.0477	814.919	822.055
Gompertz	4.9216	0.2322	0.0819	0.0135	817.395	824.532

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; LOPD, late-onset Pompe disease; SE, standard error.

Treatment with ERT was assumed to confer a survival advantage, independent of that implied by slowing disease progression. Gungor 2013 explored the impact of ERT on survival and demonstrated a benefit of ERT independent of disease severity, as measured by ventilation and ambulatory status (56). After adjustment for age, sex, country of residence, and disease severity, the HR for ERT was 0.41 (p=0.02) and this HR was applied in the model. It was conservatively assumed that the OS treatment effect was the same for both AVAL and ALGLU, as the observation period in COMET ETP and NEO-EXT did not allow sufficient data to be collected.

Mortality rates in the model were capped on general population mortality for England and Wales (144).

B.4.2.3 Discontinuation

In the base case, treatment discontinuation was modelled using all-cause discontinuation data from van Kooten 2020 (145), independent of treatment. A constant annual discontinuation rate of 0.76% was assumed.

B.4.2.4 Extrapolation of costs and clinical outcomes

The hazard ratio for mortality was assumed to apply while patients remain on treatment, with no waning effects applied.

B.4.2.5 Adverse events

While there was a trend of lower rates of adverse events (AEs) observed for AVAL and a potentially improved safety profile in COMET (Section B.2.10.1), AEs were generally consistent between two arms and thus a simplifying assumption to exclude AEs was made.B.2.10.1

B.4.3 Measurement and valuation of health effects

No HRQoL data were used in the model as a cost-comparison approach was applied.

Details of the measurement and valuation of health effects are provided in Appendix L where a cost-effectiveness approach is presented.

B.4.4 Cost and healthcare resource use identification, measurement and valuation

B.4.4.1 Costs and resource use for intervention and comparators

B.4.4.1.1 *List price for the technology*

The list price for AVAL is [redacted] per 100 mg vial. AVAL is a weight-based treatment, with a dose of 20 mg/kg. The price per kg at 20 mg/kg is [redacted].

B.4.4.1.2 *Acquisition and administration costs*

AVAL and ALGLU are administered (IV) every other week at a dose of 20 mg/kg. Acquisition costs for AVAL at PAS price and ALGLU are presented in Table 45.

Table 45: LOPD, acquisition cost

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; LOPD, late-onset Pompe disease.

Vial sharing was assumed to be in line with clinical advice; that doses are generally rounded to the whole vial to obtain the correct dose as an average of two infusions.

For both AVAL and ALGLU, treatment administration was assumed to occur in an outpatient hospital setting for the first three infusions and then at home thereafter. A scenario where AVAL is administered in a hospital setting for the first 4 doses is included, in line with EAMS. Home administration could occur with or without a nurse to reconstitute the drug (independent/semi-independent administration) or at home with a nurse for the duration of the reconstitution and infusion. The cost was applied as an ongoing, annual cost starting from treatment initiation. Administration costs used in the model were calculated as the weighted average of the proportion of patients receiving care in each setting and the cost of administration in that setting.

The cost of home administration with a nurse was calculated as the product of the hourly rate of the nurse (community nurse, sourced from the PSSRU (146)) and the nurse time required for [redacted] (91)(Appendix C). For patients who administer at home either independently or semi-independently the nurse time required for reconstitution was [redacted] (138). There is, however, likely to be some variability in the duration of the ERT administration. The day case administration unit cost was sourced from the 2021/22 National Tariff Payment System (147) and was assumed to be equal to the cost of delivering simple parenteral chemotherapy at first attendance (SB12Z).

An overview of the cost and distribution data applied to each treatment is presented in Table 46 and Table 47.

Table 46: LOPD, ERT administration costs for different settings

Category	Unit cost: AVAL	Unit cost: ALGLU	Source
At home: independent or semi-independent	[redacted]	[redacted]	Unit Costs of Health and Social Care, PSSRU (2020) (146) 2021/22 National Tariff Payment System (147)
At home: with nurse	[redacted]	[redacted]	
Outpatient	£165.00	£165.00	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; LOPD, late-onset Pompe disease; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 47: LOPD, ERT administration patient distribution across different settings

Category	% patients on AVAL	% patients on ALGLU	Source
At home: independent or semi-independent	[redacted]	[redacted]	Assumption
At home: with nurse	[redacted]	[redacted]	
Outpatient	[redacted]	[redacted]	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; LOPD, late-onset Pompe disease.

B.4.4.2 Health-state unit costs and resource use

Under the assumption of equivalent efficacy, no other costs were expected to differ between treatments and as such were excluded from this analysis.

B.4.5 Summary of base-case analysis inputs and assumptions

B.4.5.1 Summary of base-case analysis inputs

A summary of variables applied in the LOPD model is presented in Table 48.

Table 48: Summary of variables applied in the cost-comparison model

Variable	Value	Range or 95% CI	Source
Discount rate (costs)	0.035	Not varied	–
Time horizon	60 years	Not varied	
Age	48.1	Not varied	COMET baseline characteristics (111)
% male	52%	Not varied	COMET baseline characteristics (111)
Average weight (kg)	78.5	74.5 to 82.5	COMET baseline characteristics (111)
No treatment overall survival curve parameter, Weibull, intercept	3.48	3.35 to 3.61	Gungor 2011 (143)
No treatment overall survival curve parameter, Weibull, shape	0.53	0.44 to 0.63	
No treatment overall survival curve parameter, Gompertz, intercept (base case)	4.92	4.47 to 5.38	
No treatment overall survival curve parameter, Gompertz, Gamma (base case)	0.08	0.06 to 0.11	
Discontinuation rate, AVAL	0.76%	0.60% to 0.91%	van Kooten 2020 (145)
OS HR, AVAL vs no treatment	0.41	0.19 to 0.87	Assumed equal to ALGLU Schoser 2017 (15)
OS HR, ALGLU vs no treatment	0.41	0.19 to 0.87	Schoser 2017 (15)
Unit cost, ALGLU	356.06	356.06 to 356.06 (Not varied)	BNF (148)
Unit cost, AVAL	[redacted]	[redacted]	–
Unit strength, ALGLU	50	50 to 50 (Not varied)	BNF (148)
Unit strength, AVAL	100	100 to 100 (Not varied)	COMET trial CSR (111)

Variable	Value	Range or 95% CI	Source
Pack size, ALGLU	1	1 to 1 (Not varied)	BNF (148)
Pack size, AVAL	1	1 to 1 (Not varied)	–
Dose, ALGLU	20	20 to 20 (Not varied)	ALGLU SmPC (91)
Dose, AVAL	20	20 to 20 (Not varied)	COMET trial CSR (111)
Dose frequency per 4 weeks, ALGLU	2	2 to 2 (Not varied)	ALGLU SmPC (91)
Dose frequency per 4 weeks, AVAL	2	2 to 2 (Not varied)	COMET trial CSR (111)
Compliance, ALGLU	100	100 to 00 (Not varied)	Assumption based on clinical expert advice
Compliance, AVAL	100	100 to 00 (Not varied)	Assumption based on clinical expert advice
Cost of nurse time per hour	40	32 to 48	PSSRU 2020 (149)
Cost of administration, outpatient	165	132 to 198	2021/22 National Tariff Payments System
Proportion of patients, self-administration, adults, ALGLU	[redacted]	[redacted]	Sanofi data on file
Proportion of patients, self-administration, adults, AVAL	[redacted]	[redacted]	
Proportion of patients, at home with nurse administration, adults, ALGLU	[redacted]	[redacted]	
Proportion of patients, at home with nurse, adults, AVAL	[redacted]	[redacted]	
Proportion of patients, outpatient administration, adults, ALGLU	[redacted]	[redacted]	
Proportion of patients, outpatient, adults, AVAL	[redacted]	[redacted]	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CI, confidence interval; HR, hazard ratio; LOPD, late-onset Pompe disease; NA, not applicable; NHS, National Health Service; OS, overall survival; PSSRU, Personal Social Services Research Unit.

B.4.5.2 Assumptions

Assumptions applied in the LOPD model are presented in Table 49.

Table 49: LOPD model assumptions

Component of model	Assumption	Justification
Clinical efficacy	There is no difference in time on treatment or overall survival rates	The COMET clinical trial demonstrates the non-inferiority of AVAL compared with and shows a trend towards better

Component of model	Assumption	Justification
		outcomes. This assumption has been made to simplify the modelling approach and is considered conservative for AVAL.
	There is no difference in the discontinuation rates between AVAL and ALGLU	The most common reason for treatment discontinuation is IARs, which accounted for 40% of discontinuations in van Kooten 2020 (145). AVAL and ALGLU have comparable safety profiles and the rate of discontinuation due to IARs is not anticipated to differ between treatments. Two patients discontinued due to clinical deterioration, but under the assumption of equivalent efficacy this would not be expected to differ between treatments. Additional reasons for discontinuation were the burden of ERT, non-compliance with treatment and other life-threatening disease, none of which are expected to differ between treatments.
Infusion related costs	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy.

B.4.6 Base-case results

B.4.6.1 Base-case incremental cost-comparison analysis results

Table 50 presents the base case results of the cost-comparison analysis using the AVAL PAS price. These results show a cost-saving of [redacted] with AVAL, driven by reductions in administration costs due to [redacted]. [redacted]

Table 50: Base-case results, discounted – LOPD (PAS price)

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

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 51 present the results using the list price for AVAL.

Table 51: Base-case results, discounted – LOPD (list price)

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

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

B.4.7 Sensitivity analyses

The analysis addressed methodological uncertainty, parameter uncertainty and structural uncertainty. Discount rates of both costs and outcomes were varied from the base case value of 3.5%. The time horizon was varied in scenario analysis from the base case value of 60 years; time horizons of 15 and 30 years were examined. Additional scenarios considered alternative mortality distributions, a longer period of in hospital infusions for AVAL and [redacted] for AVAL and ALGLU.

One-way sensitivity analysis was conducted for parameters relating to patient characteristics, treatment discontinuation, mortality, and costs. Ranges were informed by 95% CIs derived from the parameter source, where available. In the absence of data to inform 95% CIs, parameters were varied by +/– 20%. The impact of parameter uncertainty on the incremental cost-effectiveness ratio (ICER) was reported using a Tornado plot.

B.4.7.1 Sensitivity analyses results

B.4.7.1.1 *Univariate sensitivity analysis results*

Figure 38 presents the results of the one-way sensitivity analysis for LOPD. The most influential parameters were the discontinuation rates for AVAL and ALGU, as these lead to differences in drug costs, however, while these parameters were varied independently here, in reality they would be correlated and therefore this analysis

may overstate the uncertainty. The remaining influential parameters are those associated with the cost of administration.

Figure 38: Tornado diagram - LOPD

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

B.4.7.1.2 *Scenario analyses*

Table 52 presents the results of the scenario analyses for LOPD. AVAL remains cost-saving in all scenarios.

Table 52: Scenario analysis results, LOPD

Scenario	Incremental cost	% change
Base case	[redacted]	–
Discount rates set to 0%	[redacted]	[redacted]
Discount rates set to 1.5%	[redacted]	[redacted]
Time horizon set to 15 years	[redacted]	[redacted]
Time horizon set to 30 years	[redacted]	[redacted]
Weibull curve used for mortality	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AVAL, avalglucosidase alfa.

B.4.8 Subgroup analysis

No subgroup analyses have been considered.

B.5 Economic analysis in IOPD

B.5.1 Economic analysis

B.5.1.1 Model structure

The cost-comparison model was developed in Microsoft® Excel and adopted a Markov cohort approach to calculate the proportion of patients across two states over time: alive and on-treatment or death. The model assumed that patients will remain on treatment until death. The primary outcome of the model was the total cost for each treatment option. Costs included in the model were those that may differ between therapies and included drug acquisition costs and administration costs.

The model assumed a 1-year cycle length. A 50-year time horizon was applied, and costs were discounted at 3.5%. Costs were considered from the perspective of the NHS and PSS.

B.5.1.2 Features of the economic analysis

The key features of the IOPD model not previously reported are presented in Table 53.

Table 53: IOPD, key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	50 years	IOPD is a severe life-limiting condition and patients treated with ERT are typically treated for the duration their lifetime. A time horizon of 50 years was selected to capture the long term cost implications of treatment. However, the long-term extrapolations of survival are uncertain as clinicians do not have experience treating patients with ERT beyond 20 years. Consequently, shorter time horizons were considered in sensitivity analysis.	NICE reference case (20)
Discount of 3.5% for costs	3.5%	This is in line with the reference case. A scenario using 1.5% was also considered (150)	
Perspective (NHS/PSS)	NHS and PSS	This is in line with the reference case.	

Abbreviations: IOPD, infantile-onset Pompe disease; NHS, National Health Service; PSS, Personal Social Services.

B.5.1.3 Intervention technology and comparators

B.5.1.3.1 *Intervention*

The intervention considered is AVAL (20 mg/kg) administered by IV infusion every other week. The comparator is ALGLU (20 mg/kg) administered by IV infusion every other week. According to clinical experts, in the first 12 weeks of treatment ALGLU is administered weekly rather than bi-weekly.

The anticipated license for AVAL states that patients may escalate their dose to 40 mg/kg every other week if there is not an adequate clinical response. Though this is not included in the license, clinical experts have stated that patients on ALGLU may also escalate their dose to 40 mg/kg if there is inadequate response to 20 mg/kg based on individual funding requests (151) and a higher dose is currently being considered by the CPAG (152). The rate of dose escalation with AVAL is unknown, however under the assumption of equivalent efficacy the number of patients requiring dose escalation is not anticipated to differ between arms. [redacted]

B.5.2 Clinical parameters and variables

The clinical data included in the model is limited to the OS data. As Mini-COMET does not provide adequate long-term data for modelling time-to-event outcomes directly, data on ALGLU were used. OS data was obtained from Broomfield 2015, a retrospective case-note review of 33 patients (16). Table 54 presents the baseline characteristics of the study, which have also been applied in the model. Given substantial differences in the diagnosis and treatment of IOPD between countries, the Broomfield 2015 study of UK routine care was considered the most relevant.

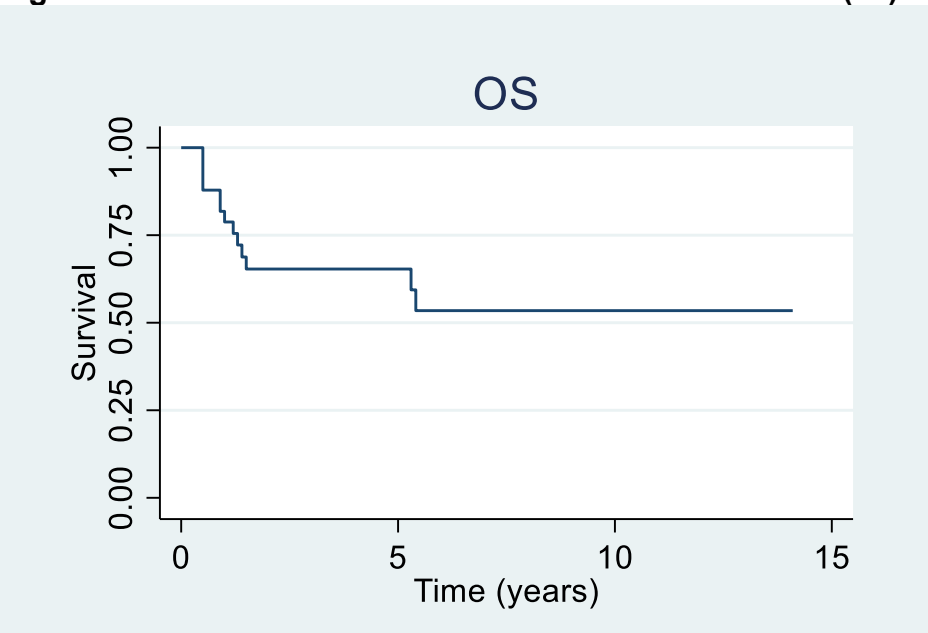
Table 54: Baseline characteristics of Broomfield 2015 (16)

Characteristic	
Male (%)	21 (64%)
Median age at initiation of ERT (IQR)	4.96 months (110 months)
Median follow-up (range)	37.5 months (6–165 months)
CRIM-positive	16/29 (55%)

Abbreviations: CRIM, cross-reactive immunological material positive; ERT, enzyme replacement therapy; IQR, interquartile range.

Figure 39 shows the Kaplan-Meier (KM) OS survival curve from Broomfield 2015 (16), which used age as the time reference for the survival curve.

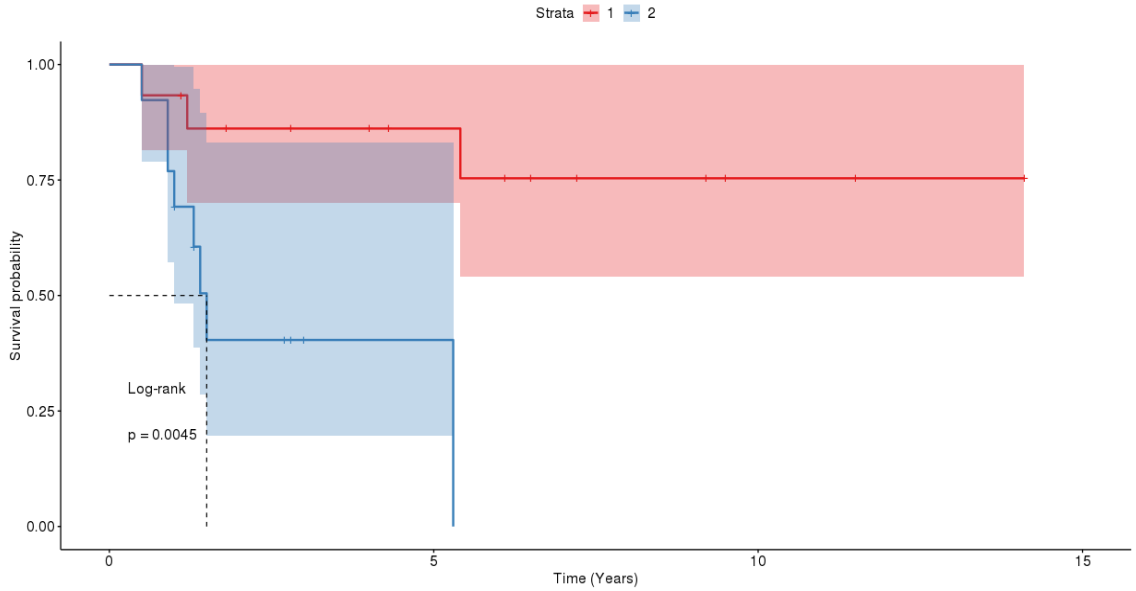
Figure 39: KM survival functions from Broomfield 2015 (16)



The time scale is age.
Abbreviations: OS, overall survival.

OS was modelled using parametric survival extrapolations of the ALGLU OS KM data presented in the Broomfield 2015 study (16). To estimate long-term survival, it was assumed that time to death KM data could be extrapolated over a patient's lifetime. However, there is large uncertainty to these extrapolations, as the data presented in Broomfield 2015 are immature. The stratified KM survival curve for OS with CRIM status as a stratum, and corresponding proportional hazards test results are presented in Figure 40 and Table 55, respectively. The proportional hazards assumption was not validated for OS, and therefore, subsets of CRIM-positive and CRIM-negative patients were analysed separately and considered as such for parametric analyses.

Figure 40: KM survival curve for OS with CRIM as a stratum (16)



Strata 1 is indicative of CRIM-positive, while strata 2 is CRIM-negative. The time scale is age.
Abbreviations: CRIM, cross-reactive immunological material; KM, Kaplan-Meier; OS, overall survival.

Table 55: CRIM status proportional hazards assumption, OS

Parameter	Chi sq.	DoF	p-value
CRIM-positive vs. CRIM-negative	2.59	1	0.11

Abbreviations: CRIM, cross-reactive immunological material; DoF, degrees of freedom; OS, overall survival.

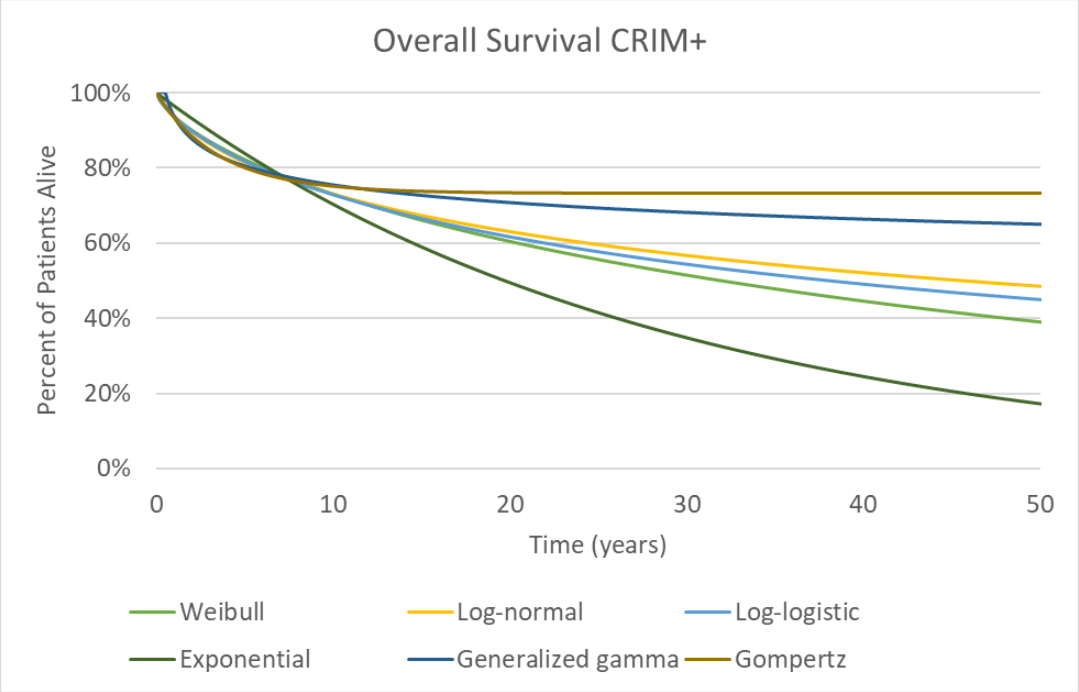
The Weibull, log-normal, and generalised gamma distributions each provided good fits to the observed data. However, the generalised gamma distribution produced a clinically implausible curve with high survival at 100 years in CRIM-positive patients, lacking face validity. The Weibull curve was chosen for the base case as the most conservative option following advice from clinical experts, though the curve for CRIM-negative patients showed a significant number of patients surviving to age 100 years. The survival model parameters for CRIM-positive and CRIM-negative patients are presented in Table 56 and Table 57, respectively. OS extrapolations for CRIM-positive and CRIM-negative patients are presented in Figure 41 and Figure 42, respectively.

Table 56: OS parameters, CRIM-positive patients

Distribution	Intercept	Scale	Shape	Akaike's information criterion	Bayesian information criterion
Weibull	0.6830	54.9040	–	29	31
Log-normal	3.8180	2.4670	–	29	30
Generalized Gamma	–0.6580	0.3780	–28.5000	29	31
Log-logistic	0.7410	37.9860	–	29	31
Exponential	0.0352	–	–	28	29
Gompertz	0.0778	–0.2507	–	29	30

Abbreviations: CRIM, cross-reactive immunological material; IVFS, invasive ventilation-free survival; SE, standard error.

Figure 41: OS extrapolations fitted to Broomfield 2015 data CRIM-positive patients (16)



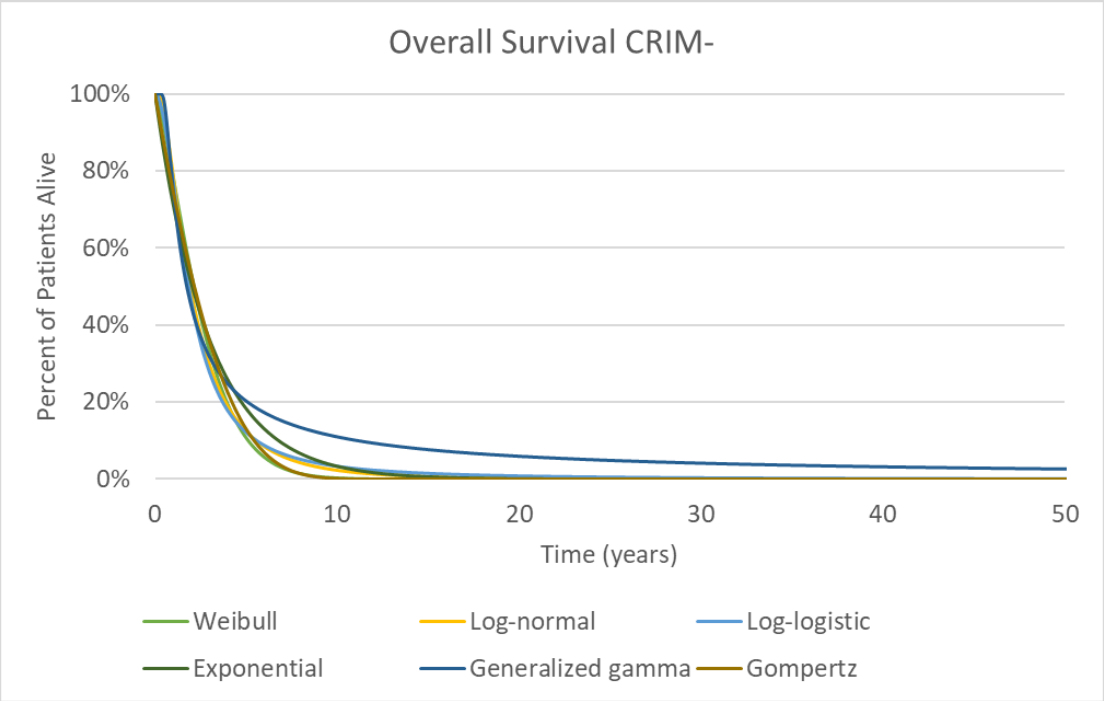
Abbreviations: CRIM, cross-reactive immunological material.

Table 57: OS parameters, CRIM-negative patients

Distribution	Intercept	Scale	Shape	Akaike's information criterion	Bayesian information criterion
Weibull	1.3720	2.7900	–	36	37
Log-normal	0.6580	0.8260	–	34	35
Generalized Gamma	0.0980	0.6990	–1.613	35	37
Log-logistic	1.9820	1.8480	–	35	36
Exponential	0.0352	–	–	35	36
Gompertz	0.0778	–0.2507	–	37	38

Abbreviations: CRIM, cross-reactive immunological material; IVFS, invasive ventilation-free survival; SE, standard error.

Figure 42: OS extrapolations fitted to Broomfield 2015 data CRIM-negative patients (16)



Abbreviations: CRIM, cross-reactive immunological material.

B.5.2.1 Extrapolation of costs and clinical outcomes

OS was extrapolated from KM curves for ALGLU from Broomfield 2015 (16) using standard survival analysis techniques in line with NICE Decision Support Unit Technical Support Document 14.

B.5.2.2 Adverse events

No serious treatment-related AEs were observed in the Mini-COMET trial. This is consistent with previous trials for ALGLU, with both Kishnani 2007 (153) and Nicolino 2009 (102) reporting that though the rate of infusion attributed reactions was high, events were managed by slowing or interrupting infusions and all patients recovered without sequalae and none led to treatment discontinuation. No other treatment related AEs were reported and therefore these were excluded from this analysis.

B.5.3 Measurement and valuation of health effects

B.5.3.1 Health-related quality of life data from clinical trials

HRQoL data from the clinical trials is described in Sections B.2.6.1.4 and B.2.6.2.4.

B.5.3.2 Health-related quality of life studies

See Section B.4.3.

B.5.3.3 Adverse reactions

Adverse reactions have not been included in the IOPD economic analysis.

B.5.3.4 HRQoL data used in the cost-effectiveness analysis

As a cost-comparison analysis was performed, no HRQoL data was used in the IOPD model.

B.5.4 Cost and healthcare resource use identification, measurement and valuation

B.5.4.1 Costs and resource use for intervention and comparators

B.5.4.1.1 *List price for the technology*

The list price for AVAL is [redacted] per 100 mg vial. AVAL is a weight-based treatment, with a dose of 20 mg/kg. The price per kg at 20 mg/kg is [redacted].

B.5.4.1.2 *Acquisition and administration costs*

AVAL and ALGLU are administered intravenously at a dose of 20 mg/kg qow. Acquisition costs and dosing information for AVAL and ALGLU are presented in Table 58. It was assumed that patients are 100% compliant with both treatments.

Table 58: IOPD, acquisition costs

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: after 3 months	£356.06	50 mg	1 vial	20 mg/kg	2	100%

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease.

In total, 26 administrations per year were modelled for AVAL. A total of 32 administrations were modelled in Year 1 for ALGLU to capture the additional doses in the first 12 weeks, followed by 26 doses in subsequent years.

As both AVAL and ALGLU use weight-based dosing, the model determined the patient's weight to calculate the total dose required for each administration. For patients <18 years, polynomial functions were fitted to weight-by-age data for girls and boys. Since the weight-by-age curves represent children in the general population at the 50th percentile, the weight for Pompe patients was adjusted using z-scores for boys and girls according to the following formula:

$$Weight_{Pompe}(age) = Weight_{50thPerc}(age) + (z - score) * SD$$

where $Weight_{Pompe}(age)$ is the Pompe patient's weight as a function of age, $Weight_{50thPerc}(age)$ is the 50th percentile weight as a function of age for the general population, and SD is the standard deviation. The SD was calculated for each age assuming a normal distribution by averaging the difference between the 15.9th percentile and the 50th percentile and the 84.1st percentile and the 50th percentile (one SD is approximately 34.1% from the mean). For patients ≥18 years, a weight equal to that of the general population was assumed and it remained constant until death. In line with clinical advice, the model did not consider vial wastage.

A cost of administration was applied to each dose of ALGLU and AVAL received by patients in the model. It was assumed that home-based nurse-led or semi-independent administrations incur the cost of one hour of nurse time for reconstitution of the drug. Based on the draft SmPC, treatment administration takes 4.0 hours. Administration costs for infusions administered with a nurse were calculated assuming the cost per hour of an at-home nurse or outpatient visit, multiplied by the infusion time.

The first 3 administrations were assumed to take place in a hospital outpatient setting at the initiation of treatment. A summary of administration costs and the proportion of patients receiving ERT in each setting is presented Table 59. Vial sharing was assumed to be in line with clinical advice that doses are generally rounded to the whole vial in order to obtain the correct dose as an average of two infusions.

For both AVAL and ALGLU, treatment administration was assumed to occur in an outpatient hospital setting for the first three infusions, and then at home thereafter. A

scenario where AVAL is administered in a hospital setting for the first 4 doses is included, in line with EAMS. Home administration could occur with or without a nurse to reconstitute the drug (independent/semi-independent administration), or at home with a nurse for the duration of the reconstitution and infusion. The cost was applied as an ongoing, annual cost starting from treatment initiation. Administration costs used in the model were calculated as the weighted average of the proportion of patients receiving care in each setting and the cost of administration in that setting.

The cost of home administration with a nurse was calculated as the product of the hourly rate of the nurse (community nurse, sourced from the PSSRU (146)), and the nurse time required for reconstitution and infusion was [redacted]. For patients that administer at home either independently or semi-independently the required nurse time for reconstitution was [redacted] (138). The day case administration unit cost was sourced from the 2021/22 National Tariff Payment System (147) and was assumed as equal to the cost of delivering simple parenteral chemotherapy at first attendance (SB12Z).

An overview of the cost and distribution data applied to each treatment is presented in Table 46 and Table 47.

Table 59: IOPD, ERT administration costs for different settings

Category	Unit cost: AVAL	Unit cost: ALGLU	Source
At home: independent or semi-independent	£40.00	£60.00	Unit Costs of Health and Social Care, PSSRU (2020) (146)
At home: with nurse	£188.00	£208.00	
Outpatient	£165.00	£165.00	2021/22 National Tariff Payment System (147)

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 60: IOPD, ERT administration patient distribution across different settings

Category	% patients on AVAL	% patients on ALGLU	Source
At home: independent or semi-independent	[redacted]	[redacted]	Assumption
At home: with nurse	[redacted]	[redacted]	
Outpatient	[redacted]	[redacted]	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease.

B.5.4.1.3 *Health state unit costs and resource use*

No further costs have been incorporated into the analysis, as no differences in resource use are expected.

B.5.5 Summary of base-case analysis inputs and assumptions

B.5.5.1 Summary of base-case analysis inputs

A summary of variables applied in the IOPD model is presented in Table 61.

Table 61: IOPD, summary of variables applied in the cost-comparison model

Variable	Value	Range	Source
Discount rate (costs)	0.035	Not varied	NICE 2013 (150)
Time horizon	50 years	Not varied	
Age at baseline (years)	0.41	Not varied	Broomfield 2015 (16)
% male	64%	Not varied	
% CRIM+	55%	37% to 73%	
OS, CRIM-positive, Weibull, shape parameter	0.683	0.15 to 1.22	Broomfield 2015 (16)
OS, CRIM-positive, Weibull, scale parameter	54.904	51.04 to 58.77	
OS, CRIM-negative, Weibull, shape parameter	1.372	1.23 to 1.51	
OS, CRIM-negative, Weibull, scale parameter	2.790	2.66 to 2.92	
ALGLU, unit cost	£356.06	Not varied	MIMS (154)
AVAL, unit cost	[redacted]		-
ALGLU, unit strength	50 mg	Not varied	MIMS (154)
AVAL, unit strength	100 mg	Not varied	Mini-COMET trial protocol (155)
ALGLU, doses per 4 weeks	2	Not varied	ALGLU SmPC (91)

Variable	Value	Range	Source
AVAL, doses per 4 weeks	2	Not varied	Mini-COMET trial protocol (155)
ALGLU, initial period dose	20 mg[†]	Not varied	ALGLU SmPC (91)
AVAL, initial period dose	20 mg	Not varied	Mini-COMET trial protocol (155)
ALGLU, subsequent period dose	20 mg	Not varied	ALGLU SmPC (91)
AVAL, subsequent period dose	20 mg	Not varied	Mini-COMET trial protocol (155)
ALGLU, compliance	100%	Not varied	Assumption
AVAL, compliance	100%	Not varied	Assumption
Nurse time (per hour)	£40	£30.40 to £45.60	PSSRU 2020 (146)
Nurse time, independent/semi-independent administration, AVAL (hours)	1	0.8 to 1.2	Assumption
Nurse time,independent/semi-independent administration, ALGLU (hours)	1.5	1.2 to 1.8	Assumption
Nurse time, with nurse administration, AVAL (hours)	4.7	3.76 to 5.64	Assumption
Nurse time, with nurse administration, ALGLU (hours)	5.2	4.16 to 6.24	Assumption
Cost, administration, outpatient, children	£165.00	£132 to £198	2021/22 National Tariff Payment System (147)
Proportion of patients, self-administration, ALGLU, infants	[redacted]	[redacted]	Sanofi Data on file
Proportion of patients, self-administration, AVAL, infants	[redacted]	[redacted]	
Proportion of patients, home administration with nurse, infants, ALGLU, infants	[redacted]	[redacted]	
Proportion of patients, home administration with nurse administration, infants, AVAL, infants	[redacted]	[redacted]	
Proportion of patients, outpatient administration, infants, ALGLU, infants	[redacted]	[redacted]	
Proportion of patients, outpatient administration, infants, AVAL, infants	[redacted]	[redacted]	

[†]dose is delivered weekly for first 12 weeks.

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CI, confidence interval, CRIM, cross-reactive immunological material; FVC, forced vital capacity; HR, hazard ratio; IOPD, infantile-onset Pompe disease; IVFS, invasive ventilation-free survival; MIMS, Monthly Index of Medical Specialties; NA, not applicable; NHS, National Health Service; ONS, Office for National Statistics; OS, overall survival; PSSRU, Personal Social Services Research Unit; RR, relative risk; VFS, ventilation-free survival.

B.5.5.2 Assumptions

Assumptions used in the IOPD model are presented in Table 62.

Table 62: IOPD model assumptions

Component of model	Assumption	Justification
Clinical efficacy	There is no difference in clinical efficacy between AVAL and ALGLU	The COMET clinical trial demonstrates the non-inferiority of AVAL compared with AGLU and shows a trend towards better outcomes. This assumption has been made to simplify the modelling approach and is considered conservative for AVAL
	No patients discontinue ERT	Clinical experts advised that patients with IOPD would not cease treatment
Dosing of ERT	Patients in the ALGLU arm would receive weekly dosing for the first 12 weeks	This is based on clinical advice that all patients on ALGLU received a double dose in the first 12 weeks
	No patients require dose escalation	This is a simplifying assumption in the model. While patients may require dose escalation, the proportion of patients escalating their dose is not expected to differ between arms
Infusion related costs	[redacted]	[redacted](138).

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERT, enzyme replacement therapy.

B.5.6 Base-case results

B.5.6.1 Base-case incremental cost-effectiveness analysis results

Table 63 presents the base-case results for IOPD using the AVAL PAS price. The results show a reduction in primary therapy costs, driven by the double dosing of ALGLU in the first 12 weeks, and a reduction in administration costs, driven by [redacted]. The overall cost saving was [redacted].

Table 63: Base-case results, IOPD, discounted (PAS price)

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

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 64 presents the results using the AVAL list price.

Table 64: Base-case results, IOPD, discounted (list price)

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

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

B.5.7 Sensitivity analyses

The analysis addressed methodological uncertainty, parameter uncertainty and structural uncertainty. Discount rates of both costs and outcomes were varied from the base-case value of 3.5%. The time horizon was varied in scenario analysis from the base-case value of 50 years; time horizons of 10 and 20 years were also examined. Additional scenarios considered alternative mortality distributions, a longer period of in hospital infusions for AVAL, [redacted], no double dosing for ALGLU and modelling only the CRIM-positive or CRM-negative patients.

A one-way sensitivity analysis was conducted for parameters relating to patient characteristics, treatment discontinuation, mortality, and costs. The parameters varied within the one-way sensitivity analysis are presented in Table 61. Ranges were informed by 95% CIs derived from the parameter source, where available. In the absence of data to inform 95% CIs, parameters were varied by +/– 20%. The impact of parameter uncertainty on the ICER was reported using a Tornado plot.

B.5.7.1 Sensitivity analyses results

B.5.7.1.1 *Univariate sensitivity analysis results*

Figure 38 presents the results of the one-way sensitivity analysis for IOPD. The most influential parameters were linked to the cost of administration, [redacted] These parameters were varied independently for AVAL and ALGLU, however in reality they would be correlated, and therefore, these estimates may overstate the uncertainty in the analysis. AVAL remained cost saving in all scenarios.

Figure 43: Tornado diagram, IOPD

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

B.5.7.1.2 *Scenario analyses*

Table 52 presents the results of the scenario analyses for IOPD. AVAL remains cost-saving in all scenarios.

Table 65: Scenario analysis results, IOPD

Scenario	Incremental cost	% change
Base case	[redacted]	[redacted]
Discount rates set to 0%	[redacted]	[redacted]
Discount rates set to 1.5%	[redacted]	[redacted]
Time horizon set to 10 years	[redacted]	[redacted]
Time horizon set to 20 years	[redacted]	[redacted]
Log-normal curve used for mortality	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
No double dosing for ALGLU	[redacted]	[redacted]
CRIM-positive only	[redacted]	[redacted]
CRIM-negative only	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CRIM, cross-reactive immunological material.

B.6 Validation

B.6.1 Validation of cost-effectiveness analysis

Both models were validated by researchers not involved in their development using standard procedures:

- Cell-by-cell checks of logic and consistency,
- Logical check of model outputs.

In addition to this, the inputs and assumptions used in the model were tested with clinicians at advisory boards, and models outputs have been discussed with clinical experts.

B.6.1.1 LOPD external validation

The outcomes for ALGLU produced by the LOPD model were compared with those reported by Kanters 2017 (156), when survival gains over standard treatment are extrapolated over a patient's lifetime. Kanters 2017 reported 21.84 discounted life years gained for a population of 49.1 years, compared with [redacted] in the present analysis (with discount rates set to 1.5% for comparability). This analysis predicts longer survival times, however this may be due to the more complex survival model in Kanters et al that also accounts for wheelchair and ventilation status. Cost outcomes cannot be directly compared, as the Kanters 2017 analysis takes a different perspective.

B.6.1.2 IOPD external validation

A single study considering the cost-effectiveness of ERT in IOPD from a UK perspective was identified. Castro-Jaramillo 2012 assumed a 5% discount rate for costs and outcomes and a 20-year time horizon, resulting in a total discounted cost of £1.34 million for ALGLU (157). Using the same discount rates and time horizon, the current analysis predicts a total discounted cost of [redacted] for ALGLU. The Castro-Jaramillo analysis includes more cost categories than this analysis and costs are driven by hospitalisation costs.

B.7 Interpretation and conclusions of economic evidence

B.7.1 Strengths and limitations

B.7.1.1 LOPD

The primary strength of this analysis is the availability of clinical data. The efficacy of AVAL in improving FVC% predicted and 6MWT distance in patients with LOPD have been shown in a phase 3, randomised, multicentre, double-blind, active-controlled study; the results of which are generalisable to UK practice as demonstrated by data from the Pompe Registry.

However, Pompe disease is a chronic, life-long disease, and as AVAL is a new therapeutic, a lack of data beyond six years is a limitation of this analysis. The data suggest that AVAL is an improved treatment option which may delay the disease progression and the onset of disability. Nevertheless, by conservatively assuming equivalent efficacy for AVAL and ALGLU, this analysis demonstrates that AVAL is a cost-saving treatment. This pragmatic approach was taken to facilitate rapid patient access to a new treatment whilst further data collection is being carried out in order to evaluate the impact of AVAL on long-term outcomes in the real-world setting.

B.7.1.2 IOPD

Although there is a lack of head-to-head evidence comparing AVAL and ALGLU in IOPD, treatment with AVAL is associated with a trend for improvement or stabilisation across several clinical outcomes in patients with IOPD with clinical decline or suboptimal response to ERT. Given the improvements observed with AVAL in LOPD, the assumption of equivalent efficacy in IOPD is likely to be a conservative assumption.

The clinical data used to inform the IOPD model were primarily taken from a retrospective case-note review from data collected between January 2000 and January 2014 (16). While this was considered the most appropriate data source, clinical practice has changed during this timeframe and therefore, not all the CRIM-negative patients will have been immunomodulated or received the same treatment regimen as that currently used in clinical practice. As such, the response to

treatment may be understated and the model may understate survival for these patients.

In both LOPD and IOPD, the results of this cost-comparison analysis are supported by the results of the cost-effectiveness analysis presented in Appendix L.

B.7.2 Conclusions

This analysis has demonstrated that compared with ALGLU, AVAL is an improved and cost-saving treatment option for both IOPD and LOPD. This result is consistent across the scenarios considered with AVAL remaining cost-saving in all scenarios under very conservative assumptions. AVAL is therefore a cost-saving therapy and a cost-effective use of NHS resources.

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Appendices

The following appendices are included with the submission as separate documents:

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Cost-effectiveness methods and results

Appendix M: UK advisory board report

Appendix N: Global advisory board report

Appendix O: COMET long-term follow-up results

Appendix L: Cost-effectiveness methods and results

Contents

L.1 Populations modelled in the economic analyses

Two populations were modelled in the economic analyses:

- Patients with LOPD (Section L.2)
- Patients with IOPD (Section L.4).

This is consistent with the population considered in the COMET, NEO1 and NEO-EXT trials for LOPD, the Mini-COMET study for IOPD, and the draft scope issued by NICE (1).

Two separate models were developed for LOPD and IOPD to account for differences in the natural history, the disease metrics typically used to measure progression and data availability.

In LOPD, the mean age of symptom onset is approximately 30 years (2, 3), with patients experiencing progressive muscle weakness and decline in respiratory function. The mean age of symptom onset in IOPD is around two months, the disease severity is greater (e.g. cardiac involvement is more severe), and disease progression is typically more rapid. Due to the rapid progression in IOPD, time-to-ventilation and OS can be measured over a shorter duration in studies. As patients with LOPD live a much longer life, extrapolation of OS and time-to-ventilation is needed based on FVC% predicted and other outcomes (e.g. loss of ambulation measured by 6MWT). Ambulation and 6MWT are more difficult to capture in IOPD, as patients are not ambulatory at baseline and many will not achieve ambulation. Additionally, it is often not possible to measure FVC in very young children and this is unreliable in paediatric patients (4).

There are also differences in the variability and level of data available for each population, as well as differences in the dosing schedules for AVAL in IOPD and LOPD (e.g. the anticipated dose for AVAL is 20 mg/kg for both LOPD and IOPD, however patients with IOPD would receive a double dose of ALGLU in the first 3 months of treatment) (Appendix C).

The following section describes the methodology of the LOPD model. The IOPD model methodology is provided in Section L.4.

L.2 Published cost-effectiveness studies

A systematic review was conducted to identify relevant cost-effectiveness studies. Appendix D contains the full details of the process and methods used.

Four studies were identified and these evaluated cost-effectiveness of ERT compared with no treatment. For efficacy of no treatment, these relied on making arbitrary assumptions (5), using expert opinion (6), or observational data from historical patients that is unlikely to reflect the current Pompe population (7, 8). None of the identified studies included AVAL as a comparator. A summary of the included studies is presented in Table 1.

Table 1: Summary list of published cost-effectiveness studies

Study name (reference), location	Summary of model	Patient population	Treatment arms	Costs	Outcomes	Incremental (active treatment vs. comparator)
LOPD studies						
Kanters 2017 (8) The Netherlands	• PLS • Societal perspective • 1.5% discount for outcomes; 4% for costs • Scenario 1: no extrapolation of survival gain due to ERT beyond observation period • Scenario 2: lifetime extrapolation of survival gain due to ERT	• LOPD • Mean age: 49.1 years	ALGLU 20 mg/kg qow and supportive therapy	Scenario 1: 6,795,495 EUR Scenario 2: 7,879,226 EUR	Scenario 1: 12.57 QALYs 18.21 LYs Scenario 2: 14.85 QALYs 1.84 LYs	Scenario 1: 3,167,914 EUR/QALY 3,417,713 EUR/LY Scenario 2: 1,774,390 EUR/QALY 1,389,925 EUR/LY
			Supportive therapy	Scenario 1: 329,105 EUR Scenario 2: 324,967 EUR	Scenario 1: 10.53 QALYs 16.33 LYs Scenario 2: 10.60 QALYs 16.42 LYs	–
IOPD studies						
Castro-Jaramillo 2012 (6) England and Colombia	• Markov model • Health system perspective • 5% discount for costs and outcomes	• IOPD • Mean age: NR	ERT 20 mg/kg qow	England: £1,337,118 Colombia: £607,329	5.23 QALYs	England: £234,308/QALY Colombia: £109,991/QALY
			No ERT	England: £149.178 Colombia: £49,676	0.16 QALYs	–
	• Decision tree and Markov model	• IOPD	ALGLU 20 mg/kg qow	381,852 USD	4.21 QALYs 6.01 LYs	96,809 USD/QALY 74,429 USD/LY

Study name (reference), location	Summary of model	Patient population	Treatment arms	Costs	Outcomes	Incremental (active treatment vs. comparator)
Hashempour 2020 (5) Iran	• Healthcare payer perspective • 0% discount for costs and outcomes • Lifetime horizon (22 years)	• Mean age: NR	Conventional therapy	15,075 USD	0.42 QALYs 1.09 LYs	–
Kanters 2014 (7) The Netherlands	• PLS • Societal perspective • 1.5% discount for outcomes; 4% for costs • Lifetime horizon	• IOPD • Mean age: 3.5 years	ALGLU 40 mg/kg weekly	7,032,899 EUR	7.00 QALYs	1,000,000 EUR/QALY
			Supportive therapy	32,871 EUR	0.24 QALYs	–

Abbreviations: ALGLU, alglucosidase alfa; CEA, cost-effectiveness analysis; ERT, enzyme replacement therapy; EUR, Euros; ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; LY, life year; NR, not reported; PLS, patient-level simulation; QALY, quality-adjusted life year; SD, standard deviation; USD, United States Dollar.

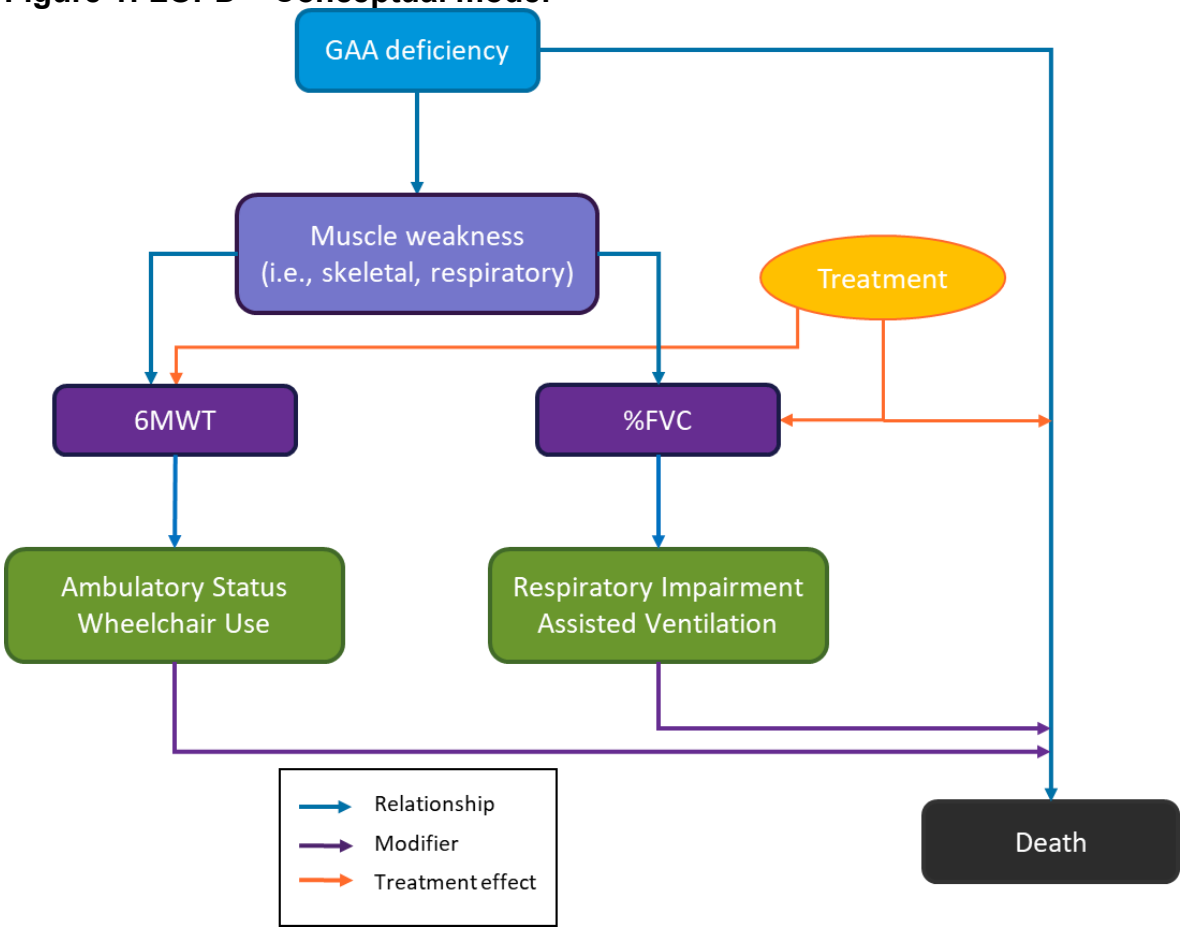
L.3 Cost-effectiveness in LOPD

L.3.1 Economic analysis

L.3.1.1 Model structure

Pompe disease affects multiple systems, including the cardiovascular, gastrointestinal, musculoskeletal and respiratory systems in which the normal functioning of muscle cells is essential (9). As the disease progresses, patients with LOPD can develop irreversible muscle damage which contributes to respiration insufficiency, vasculopathy and dysphagia (difficulty swallowing) (10-12). This irreversible functional loss and disability eventually leads to dependency on wheelchair use and mechanical ventilation. This reduces quality of life, increases associated management costs and eventually leads to premature death. A conceptual model for LOPD is presented in Figure 1 which captures the gradual worsening of the disease through ambulatory status and respiratory impairment.

Figure 1: LOPD – Conceptual model



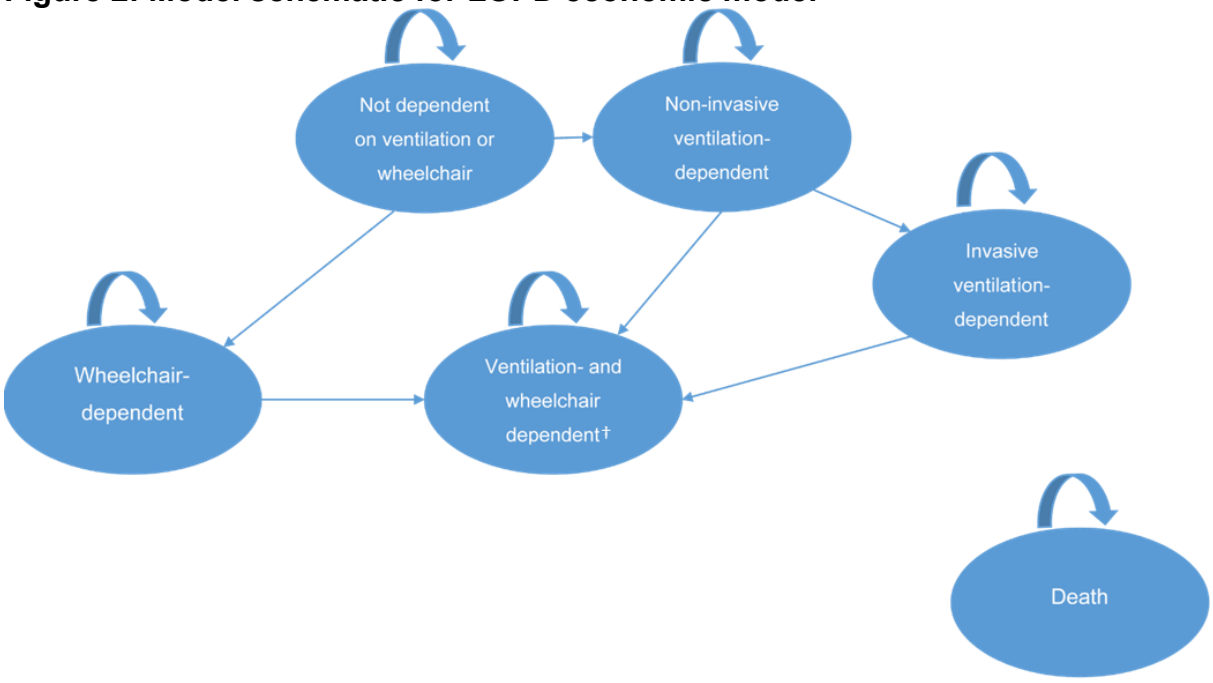
Abbreviations: %FVC, % predicted forced vital capacity; GAA, acid α-glucosidase; 6MWT, six-minute walk test.

To accurately capture the heterogeneity in patient characteristics, disease course and outcomes, a patient-level simulation was utilised. Patient profiles were generated using the patient data from the phase 3 trial, COMET. As such, these are predominantly early-stage symptomatic patients and are expected to be representative of those starting treatment. No patients require ventilation or wheelchair support at baseline. The same set of patients was separately simulated over a lifetime in the comparator (ALGLU) and the intervention (AVAL) arm. Outcomes were accumulated for each patient simulation and averaged over all simulated patients for each treatment.

Disease progression was modelled using FVC% predicted and 6MWT. As these decline to a particular level, patients reach disease milestones and move to a worse health state. With decline in FVC% predicted patients first start to use NIV and then IV. Decline in 6MWT distance results in wheelchair use in the model. The

introduction of wheelchair and ventilation support are both associated with significant changes in both costs and quality of life, as well as being predictors of mortality (13).

Figure 2: Model schematic for LOPD economic model



†Patients can be either invasive or non-invasive ventilator dependent
Note: Death is an absorbing health state whereby patients from each health state can move into.

Further discussion of the health state thresholds is provided in Section L.3.2.6.

As indicated above, an individual patient simulation model was deemed the most appropriate approach to reflect the heterogeneity of the patient population, with high variability of both disease severity, age at onset of LOPD and the point at which patients may require ventilation or a wheelchair. A simulation approach could account for individual patient-level characteristics and could represent the course of LOPD as a combination of evolving conditions (aspects that persist over time, such as age, disease activity, costs, utilities) and key events (treatment initiation, treatment discontinuation, time to requiring a wheelchair, time-to-ventilation, death).

FVC% predicted and the 6MWT are two measures commonly used in studies of LOPD to measure disease status and progression. FVC% predicted was the primary endpoint in COMET, while 6MWT was a secondary outcome. Both measures have previously been used to investigate the long-term efficacy of ERT (14, 15).

The model health states capture varying levels of severity of disease. These were validated in an advisory board including three metabolic consultants and two clinical nurse specialists (Appendix M).

L.3.1.2 Health states

The model used in the analysis incorporates six health states shown in Figure 2 intended to capture the progressive nature of the disease:

- Not dependent on wheelchair or ventilation
- Non-invasive ventilation-dependent
- Invasive ventilation-dependent
- Wheelchair-dependent
- Ventilation (either invasive or non-invasive) - and wheelchair-dependent
- Death.

As mentioned above, patients could progress to a worse health state as their FVC% predicted or 6MWT distance fell below a given milestone (based on the analysis of Pompe Registry data (16)). More details on the decline rates of patients are provided in Section L.3.2.6.

Once a patient reached a milestone, the costs and utilities associated with worsening disease were captured within the health state. At each milestone, the utility was adjusted by applying the corresponding disutility associated with the health state (i.e. ventilation/wheelchair support). The caregiver's disutility was also adjusted. The costs of managing the disease were updated and, if the societal perspective was specified, then the non-medical and indirect costs were also updated. The model health states also captured the increase in mortality risk on worsening of the disease by applying a hazard ratio to the all-cause mortality curve in each health state.

L.3.1.3 Features of the economic analysis

Key features of the LOPD economic model are outlined in Table 2.

Table 2: Features of the economic analysis

Factor	Chosen values	Justification	Reference
Time horizon of model	60 years	Sufficient to capture a lifetime horizon	NICE 2013 (17)
Discount rate for costs	3.5%	NICE reference case	
Discount rate for outcomes	3.5%	NICE reference case	
Perspective (NHS/PSS)	NHS	NICE reference case	

Abbreviations: NHS, National Health Service; PSS, Personal Social Services.

L.3.1.4 Intervention technology and comparators

The intervention considered is AVAL (20 mg/kg) and the comparator is ALGLU (20 mg/kg), both administered as an IV infusion every other week.

L.3.2 Clinical parameters and variables

The disease course was primarily captured through FVC% predicted and 6MWT. At the start of each model simulation, the baseline FVC% predicted and 6MWT of a patient was generated. Thereafter, FVC% predicted and 6MWT were discretely updated over time using progression equations which calculated CFB in FVC% predicted and 6MWT according to ERT treatment.

FVC% predicted and 6MWT were assumed to improve at one year following initiation of ERT; the size of the gain was treatment-specific and informed by the COMET trial. The model assumed this improvement was maintained for FVC% predicted and 6MWT (referred to as plateau) for durations specific to each treatment. These were determined based on published ALGLU data, clinical opinion, and data from NEO-EXT. At the end of the plateau period, FVC% predicted and 6MWT declined at the same rate for both ERTs, as no data was available for AVAL.

The rate of decline was derived from analysis of data in the Pompe Registry (16). A linear decline over time was assumed and the slope was estimated from mean values for FVC% predicted and 6MWT in the registry at two and nine years. While it is acknowledged that the decline in FVC% predicted and 6MWT may not be linear (14, 15), this has been made as a simplifying assumption. [redacted]

L.3.2.1 Patient profiles

The simulated population is summarised in Table 3 and is specified by a set of patient profiles that are selected to be representative of the patients studied in COMET. Each profile is passed through the model in turn and contains a set of characteristics that identify that profile:

- Baseline FVC% predicted and 6MWT
- Body weight
- Time since diagnosis
- Sex
- Age
- Baseline utility.

Table 3: Patient profiles

ID	Sex (Male=1)	Baseline Age (years)	Baseline FVC (%)	Time since diagnosis (years)	Baseline 6MWT (m)	Baseline weight (kg)	Baseline utility	Share
[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]	[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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Prior to each profile being passed through the model, baseline general population survival probability (based on age and sex) and baseline disease survival (based on time from diagnosis) were also calculated to ensure proper conditioning of the model survival calculations. Lastly, the weights for each profile (used to calculate the weighted average model results) were included.

The profiles for the simulation were designed to cover the population enrolled in COMET. The following steps were taken to generate the eight profiles used in the model:

Sample means and the sample covariance matrices were calculated based on the COMET individual patient data for males and females separately. These were then used to parameterise a multivariate normal (MVN) distribution. The following characteristics at baseline were included: age, time since diagnosis, weight, FVC% predicted in the upright position, 6MWT and UK EQ-5D-3L utility.

Since sampling from a MVN is best when all covariates are relatively symmetric in shape, time since diagnosis was log-square root-transformed to reduce the right-skewness of the observed distribution and was back-transformed after sampling.

A total of 2,000 simulated patients (pseudo patients) were generated by sampling from the MVN distribution. Two sampling methods were compared: 1) sampling and then filtering those that were out of the observed bounds of the COMET patient data, and 2) sampling from a truncated distribution. The two methods were compared by reviewing the observed vs. simulated covariate means, standard deviations, and graphical comparisons. Upon inspection, it was concluded that both sampling techniques produce pseudo patients that sufficiently represent the COMET population. As such, the truncated MVN distribution was used.

The 2,000 pseudo patients were then grouped into a certain number of strata to obtain representative profiles for use in the cost-effectiveness analyses.

In order to determine the minimum number of representative profiles required to accurately characterise the COMET population, the pseudo patients were first stratified into 48 groups by sex, age, weight, FVC% predicted and 6MWT. However,

it was determined that for some of the 48 groups, very few or no pseudo patients met the criteria for inclusion within some strata, while other strata had >100 patients meeting the criteria. For example, no pseudo patients were female, <48.5 years old, <76 kg, had an FVC% predicted between 52 and 70% or a 6MWT ≤206 m. On the other hand, 166 pseudo patients were male, <48.5 years old, <76 kg, had an FVC% predicted between 52 and 70% and had a 6MWT >206 m.

As such, the exercise was conducted again with eight groups, stratified by sex, age, and weight only, and again the pseudo patients were grouped into one of the eight strata. Compared with the 48 strata, a greater number of pseudo patients met the criteria for each group (the minimum number was 121). The characteristics of interest were then averaged across the pseudo patients in each group to obtain eight profiles, with a representative age, time since diagnosis, weight, FVC% predicted, 6MWT, UK EQ-5D-3L utility (mapped from the EQ-5D-5L), and Canada EQ-5D-5L utility.

Data from the Pompe Registry indicate that the average age at first treatment was 40.4 years and that the mean time from diagnosis to first treatment was 4.1 years. This indicates that the UK population may be slightly younger than that used here, with a longer time from diagnosis to treatment, however these patients are still expected to be reflective of the treatment naïve cohort in England and Wales. A subgroup analysis has been run using only patients below the median age to assess the impact of using a younger cohort.

L.3.2.2 ALGLU and AVAL treatment effects

The CFB for FVC% predicted and 6MWT values for patients in the COMET trial at Week 49 are reported in Table 4. The model assumed zero change in FVC% and 6MWT predicted in the first year of treatment. Thereafter, the change in FVC% and 6MWT predicted, according to treatment, was the value observed at Week 49. [redacted]. [redacted]. These durations were determined from analysis of the Pompe Registry (16) and clinical expert advice for ALGLU (Appendix M), and NEO-EXT for AVAL. Beyond the period of the treatment effect, FVC%

predicted and 6MWT declined linearly with time and progression is assumed to occur at the same rate from AVAL and ALGLU (Section L.3.2.6). The trajectory over 10 years for both therapies is plotted in Figure 3 and Figure 4.

The treatment effect of AVAL in terms of FVC% predicted and 6MWT was applied as a direct effect relative to ALGLU. The treatment benefit for both outcomes led to a delay in the modelled time to wheelchair and ventilation use. The model also assumed patients would move to receive no treatment once treatment was discontinued.

Table 4: LOPD – FVC% predicted and 6MWT estimates of CFB by visit, COMET

Time (Weeks)	AVAL	ALGLU	Difference
FVC% predicted			
Week 49	2.89	0.46	2.43
6MWT			
Week 49	32.21	2.19	30.01

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline, FVC, forced vital capacity; LOPD, late-onset Pompe disease; 6MWT, six-minute walk test.

Figure 3: FVC% predicted trajectory over time

Abbreviations: FVC, forced vital capacity.

Figure 4: 6MWT trajectory over time

Abbreviations: 6MWT, 6-minute walk test.

In addition to improvement in FVC% predicted and 6MWT, AVAL and ALGLU were associated with a [redacted] and [redacted] improvement in utility after one year, respectively. These are the median values observed in COMET. The utility benefit was assumed to persist for the same period of time as the 6MWT benefit.

Table 5 summarises the efficacy inputs used in the model.

Table 5: Efficacy Inputs

Item	No treatment	ALGLU	AVAL	Source
Short-term				
FVC change (1 year)	–	0.46	2.43	COMET CSR (18) Table 12
FVC effect persistence (years)	–	[redacted]	[redacted]	Assumption based on clinical advice/Visual Inspection of Pompe Registry data
6MWT change (1 year)	–	2.19	30.01	COMET CSR (18) Table 16
6MWT effect persistence (years)	–	[redacted]	[redacted]	Assumption based on clinical advice/Visual Inspection of Pompe Registry data
Utility gain	0.000	[redacted]	[redacted]	COMET, analysis on file

Item	No treatment	ALGLU	AVAL	Source
Long-term				
FVC decline (% points/year)	–1.040	[redacted]	[redacted]	No treatment: van der Beek 2012 (19) ERT: Pompe Registry
6MWT decline (m/year)	[redacted]	[redacted]	[redacted]	No treatment: Assumption ERT: Pompe Registry
HR mortality	1.0	0.410	0.410	Gungor 2013 (20)
Treatment discontinuation (rate)	–	0.0076	0.0076	Kooten 2019 (21)
Apply discontinuation risk over (yrs)	–	60	60	Assumption, 60 years represents a lifetime time horizon and patients are assumed to be at constant risk of discontinuation.

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CSR, Clinical Study Report; ERT, enzyme replacement therapy; FVC, forced vital capacity; HR, hazard ratio; 6MWT, six-minute walk test.

L.3.2.3 No treatment

A steeper annual decline in FVC% predicted of 1.04 points was assumed for patients who cease ERT and receive no treatment (informed by van der Beek 2012 (19)). As no data on the decline in 6MWT for patients on no treatment were identified, it was conservatively assumed to be the same as that for patients on ERT. A scenario with a faster rate of decline for patients on no treatment was also explored.

L.3.2.4 Overall survival

A parametric survival curve for LOPD patients on no treatment, estimated from data presented in Gungor 2011 (22), was used to inform the baseline OS curve. Weibull and Gompertz specifications were estimated, and the model allowed for selection of either. These models were used as they can be specified on the proportional hazards scale. Measures of model fit (Akaike's Information Criteria [AIC] and Bayesian Information Criteria [BIC]) indicated the Weibull model was associated with a better fit to the observed data, but the Gompertz model was considered to provide more plausible extrapolations and was selected as the base case. The cost-effectiveness model also included Weibull and Gompertz models of all-cause mortality, estimated from UK lifetable data for 2016–2018 (23). Patient longevity is always the lesser of values generated from the disease-specific survival curve (after

adjustment for treatment and functional status) and the survival curve for the general population according to age and sex.

Given that patients do not begin the simulation at diagnosis, the selection of a time to disease-related death is adjusted to reflect the time since diagnosis by conditioning the random number used in the quartile equation. For example, if the patient begins treatment two years after diagnosis, then the expected survival up to that point (*S(t)*) is computed and used to adjust the random number (*r*) drawn: adjusted *r* = *r* x *S(t)*.

This kind of adjustment ("spent luck" approach) is also applied when selecting a time to all-cause death, since the life table begins at birth and not at the patient's starting age: adjusted *r* = *r* x *S(age)*.

Treatment with ERT was assumed to confer a survival advantage, independent of that implied by slowing disease progression. Gungor 2013 explores the impact of ERT on survival and demonstrates a benefit of ERT independent of disease severity as measured by ventilation and ambulatory status (20). After adjustment for age, sex, country of residence, and disease severity, the HR for ERT was 0.41 (p=0.02) and this HR has been applied in the model. As insufficient mortality data were available for AVAL, it was conservatively assumed that the OS treatment effect was the same for both AVAL and ALGLU. It is likely that since ALVAL is an improved treatment compared with ALGLU, it will provide benefit in terms of OS. Survival was assumed to be negatively impacted by progression to ventilation and wheelchair milestones.

Further HRs were calculated based on an analysis of the Pompe Registry (16) and were applied to the OS curve for the following disability statuses:

- Wheelchair-dependent
- Non-invasive ventilation-dependent
- Invasive ventilation-dependent.

HRs applied in the model are presented in Table 6. The baseline hazard was adjusted by applying a HR according to treatment and disease progression. The

relevant HR was calculated by exponentiating the sum of the natural logarithms of the HRs for each applicable condition. Hence, for patients on treatment and dependent on non-invasive ventilation and a wheelchair, mortality was adjusted by applying the HR for each of the three conditions. This approach assumes each has a proportional impact on the baseline hazard.

Table 6: LOPD – OS HR vs. no treatment

Time (months)	HR	Source
ALGLU	0.41	Gungor 2013 (20)
AVAL	0.41	
Non-invasive ventilator dependent	[redacted]	Pompe registry analysis (16)
Invasive ventilator dependent	[redacted]	
Wheelchair-dependent	[redacted]	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; HR, hazard ratio; LOPD, late-onset Pompe disease; OS, overall survival.

L.3.2.5 Discontinuation

In the base case, treatment discontinuation was modelled using all-cause discontinuation data from van Kooten 2020 (21), independent of treatment. A constant annual discontinuation rate of 0.76% was assumed.

Further to all-cause discontinuation, a patient could discontinue treatment if the FVC% predicted dropped to the threshold for invasive ventilation use.

L.3.2.6 Extrapolation of costs and clinical outcomes

The improvement for FVC% predicted and 6MWT at one-year following treatment initiation on ERT was assumed to be maintained (referred to as plateau) for durations specific to each treatment (Section L.3.2). Beyond this period, FVC % predicted and 6MWT declined on ERT and if treatment was discontinued, the rate of decline increased.

The on-treatment FVC% predicted decline rate was derived from an analysis of the Pompe Registry data (16). The mean FVC% predicted at two years and nine years from ERT initiation were used to calculate the annual decline rate. Similarly, the variation in FVC% predicted at these timepoints were used to estimate the standard error of the decline rate for use in the sensitivity analyses. The values from the

Pompe Registry and the calculated annual decline are presented in Table 7. The formulas for the calculated values are as follows:

$$SD(FVC_{Ti}) = sqrt(Ti_N) * (\mathrm{Ti}_{SE})$$

$$Var(FVC_{Ti}) = SD(FVC_{Ti})\text{^}2$$

$$Decline\ Rate = (FVC\_T2 - FVC\_T1)/(T2 - T1)$$

$$Var(Decline\ Rate) = \frac{Var(FVC_{T1}) + Var(FVC_{T2}) - 2 * corr * SD(FVC_{T1}) * SD(FVC_{T2})}{(T2 - T1)^2},$$

$$SD(Decline\ Rate) = sqrt(Var(Decline\ Rate))$$

$$SE(Decline\ Rate) = \frac{SD(Decline\ Rate)}{sqrt(T1_N)}, use\ the\ smaller\ of\ the\ 2\ Ns$$

Here Ti represents measurements at timepoints 1 and 2 and correlation (corr) is assumed to be 0.5.

Table 7: FVC% predicted decline rate derivation from the Pompe Registry data

Item	FVC% predicted at 2 years	FVC% predicted at 9 years	FVC% predicted Annual Decline Rate
Mean	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Var	[redacted]	[redacted]	[redacted]

Source: Pompe Registry (16)
Abbreviations: ERT, enzyme replacement therapy; FVC, predicted forced vital capacity; N, number; SD, standard deviation; SE, standard error.

The 6MWT on-treatment decline rate was derived in an analogous manner to FVC % predicted from an analysis of the Pompe Registry data (16). The mean 6MWT at four years and nine years from ERT initiation were used to calculate the annual decline rate. The values from the Pompe Registry and the calculated annual decline are presented in Table 8.

Table 8: 6MWT predicted decline rate derivation from the Pompe Registry data

Item	6MWT at Timepoint 1	6MWT at Timepoint 2	6MWT Annual Decline Rate
Years from ERT initiation	[redacted]	[redacted]	[redacted]
Mean (m)	[redacted]	[redacted]	[redacted]

Item	6MWT at Timepoint 1	6MWT at Timepoint 2	6MWT Annual Decline Rate
SE	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Var	[redacted]	[redacted]	[redacted]

Source: Pompe Registry (16)
Abbreviations: ERT, enzyme replacement therapy; N, number; SD, standard deviation; SE, standard error; 6MWT, six-minute walk test.

ERT therapy was assumed to provide a survival benefit whilst patients are on treatment. This was captured by applying a hazard ratio to the mortality rate estimated for patients receiving no treatment from Gungor 2013 (20). It was assumed that ALGLU and AVAL provide the same survival benefit, and this benefit persists for the duration of treatment.

Following discontinuation of ERT the rate of decline in FVC% predicted increased. Patients receive the same rate of annual decline in FVC% predicted of 1.04 points as no treatment (from van der Beek 2012 (19); Section B.2.2.3).

Costs and utilities were extrapolated over the lifetime of the patient assuming that both ERT therapies provided a direct reduction in mortality, and an indirect reduction through the slowing of progression of the disease as measured by FVC% predicted and 6MWT.

The model simulated initiation of ventilation and wheelchair use based on thresholds for FVC% predicted and 6MWT. The model included three thresholds: for non-invasive ventilation use, invasive ventilation use, and wheelchair use (Section L.3.2.5).

In clinical practice, the point at which patients commence ventilation or wheelchair use varies and no single value is used. To reflect this, lognormal functions were fitted to FVC% predicted and 6MWT from the Pompe Registry corresponding to the initiation of non-invasive ventilation and wheelchair use, respectively. Figure 5 presents the cumulative distribution of milestone levels across the population.

Figure 5: Cumulative distribution of values of FVC% predicted at which NIV use started (panel A) and values of 6MWT at which a wheelchair was first used (Panel B)

Abbreviations: CDF, cumulative distribution function; FVC, forced vital capacity; WC, wheelchair. Points reflect actual values and lines display the fitted distributions; 6MWT, six-minute walk test.

The parameters of the fitted distributions (of the logarithms of values) are presented in Table 9.

Table 9: Parameters of fitted log normal distributions levels at which patients required support

Users	FVC% predicted	6MWT
Parameter	**Non-invasive ventilation**	**Wheelchair**
mean (ln)	[redacted]	[redacted]
standard deviation (ln)	[redacted]	[redacted]
Derived quartiles		
lower quartile	[redacted]	[redacted]
median	[redacted]	[redacted]
upper quartile	[redacted]	[redacted]

Abbreviations: FVC, forced vital capacity; ln, log normal; 6MWT, six-minute walk test.

For invasive ventilation use, the distribution of FVC% predicted was concentrated over a very narrow range of values, with a tail of lower values. 75% of patients who initiated invasive ventilation with an FVC% predicted between 32% and 38%, while the remaining 25% did so between 32% and 16%. Consequently, a uniform distribution was fitted to the upper three quarters of FVC% predicted values, and a lognormal distribution with mean of 3.119 (SD: 0.149) was fitted to the remaining lower quarter.

At commencement of a simulation run, values were sampled from the respective FVC% predicted and 6MWT distributions to generate the thresholds at which non-invasive and invasive ventilation use, and wheelchair use was initiated. The

sampling was constrained according to the patient's FVC% predicted and 6MWT at initiation of treatment to ensure thresholds were not implausibly high.

L.3.2.7 Adverse events

Adverse events were not explicitly modelled. The risk of discontinuation due to adverse events or other causes was modelled (see L.3.2.5).

L.3.3 Measurement and valuation of health effects

L.3.3.1 Health-related quality-of-life data from clinical trials

In accordance with NICE guidance (136), EQ-5D-5L values from the COMET trial were mapped to the EQ-5D-3L values set using the van Hout mapping function (137).

Utility data from the trial were used to inform the initial gain in QoL, up to the end of 6MWT plateau. Beyond this timepoint, health state utility values (HSUVs) were informed by an analysis of the Pompe Registry data. Analysis of the Pompe Registry was deemed more appropriate, as it contains more observations of patients in the more severe health states.

The Pompe Registry is a global, multicentre, international, longitudinal, observational, and voluntary program for patients with Pompe disease, designed to track the disease's natural history and outcomes in patients. The registry has enrolled 2,000 patients, both treatment-naïve or ERT-experienced (24). The registry includes patients irrespective of treatment and data has been collected both prospectively and retrospectively (25).

SF-36 data collected from the Registry were mapped to the EQ-5D (details in Section L.3.3.2) and used to inform the economic model.

In order to obtain a sufficient sample size, the analysis population included patients with LOPD from any country with a known treatment status (treated or untreated) and with 2011/2012 informed consent encompassing data used to obtain reimbursement. Patients with LOPD were defined as age of symptom onset >12 months or ≤12 months without cardiac enlargement/myopathy. To be included in the analysis, patients were required to have completed at least one SF-36

assessment at age 14 years or older. Patients with missing age at SF-36 and those with missing data for any of the eight component scores were excluded.

For patients with sufficient data, Registry records were retrieved for FVC% predicted and 6MWT measured within a +/- six-month window around the date of the SF-36 assessment, and disability status (non-invasive ventilation use, invasive ventilation use, wheelchair use) at the time of the SF-36 assessment. Table 10 presents the baseline characteristics of the population included in the analysis and Table 11 presents mapped EQ-5D scores by disability status, accounting for wheelchair and respiratory support use.

Table 10: Baseline characteristics of the Pompe Registry utility analysis population

Parameter	Statistic	Value
Total patients with at least one SF-36 assessment	n	708
SF-36 assessments per patient	Mean (SD)	5.7 (4.87)
	Median (25th percentile, 75th percentile)	[redacted]
	Min, Max	[redacted]
Mapped EQ-5D score	n	4036
	Mean (SD)	0.616 (0.2043)
	Median (25th, 75th)	[redacted]
	Min, Max	[redacted]
Gender		[redacted]
Male	n (%)	341 (48.2)
Female	n (%)	367 (51.8)
Age at symptom onset (years)	n	664
	Mean (SD)	32.5 (16.61)
	Median (25th, 75th)	[redacted]
	Min, Max	[redacted]
Age at Pompe diagnosis (years)	n	703
	Mean (SD)	40.2 (16.72)
	Median (25th, 75th)	[redacted]
	Min, Max	[redacted]
Treatment		[redacted]
Never treated	n (%)	41 (5.8)
Ever treated	n (%)	667 (94.2)
Age at first treatment (years)	n	665
	Mean (SD)	44.6 (15.87)
	Median (25th, 75th)	[redacted]

Parameter	Statistic	Value
	Min, Max	[redacted]
Age at last follow-up (years)	n	708
	Mean (SD)	52.6 (15.69)
	Median (25th, 75th)	[redacted]
	Min, Max	[redacted]
Deceased	n (%)	[redacted]
Age at death (years)	n	[redacted]
	Mean (SD)	[redacted]
	Median (25th, 75th)	[redacted]
	Min, Max	[redacted]

Source: Malottki 2021 (26)
Abbreviations: max, maximum; min, minimum; n. number of patients; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

Table 11: Mapped EQ-5D scores from the Pompe Registry by disability status

Disability status	N	Mean (SD)	CI
No wheelchair use, no respiratory support	[redacted]	[redacted]	[redacted]
No wheelchair use, non-invasive respiratory support	[redacted]	[redacted]	[redacted]
No wheelchair use, invasive respiratory support	[redacted]	[redacted]	[redacted]
Wheelchair use, no respiratory support	[redacted]	[redacted]	[redacted]
Wheelchair use, non-invasive respiratory support	[redacted]	[redacted]	[redacted]
Wheelchair use, invasive respiratory support	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; N, number of observations; SD standard deviation.

Data from the registry demonstrate a clear reduction in HRQoL as disease progresses. EQ-5D was generally lower for wheelchair users compared to patients not using a wheelchair except for patients receiving invasive ventilation. This result is counterintuitive and may be a function of the small sample size of this subgroup. In addition, it is unlikely that these patients would be ambulatory, but rather bed bound and thus not recorded as using a wheelchair. There is some uncertainty around how well wheelchair and ventilator use has been recorded in the registry as it relies on voluntary data entry.

It should also be noted that previous analyses have found that neither the EQ-5D nor the SF-6D perform particularly well in Pompe disease (27) and the analysis may not capture all important aspects of HRQoL in Pompe disease.

L.3.3.2 Mapping

The Health Economic Research Centre database of mapping studies was searched to identify the most appropriate algorithm for mapping the SF-36 to EQ-5D. Six papers were identified in total (28-33), however Rowen 2009 (28) was considered the most appropriate based on population size, indications considered, and the reported statistical fit.

Rowen 2009 (28) considered 33,248 hospital inpatients and outpatients with any condition. The algorithm providing the most accurate prediction of EQ-5D was based on the generalised least squares model, which utilised all eight dimensions of the SF-36 in the form of single, squared, and interaction terms. Table 12 presents the coefficients of each variable, however, standard errors were not reported in the paper. A limitation of the model was the overestimation of the utility score for more severe health states, implying that the utility value for the ventilation-free health state might be more accurately estimated than for the ventilation- and wheelchair-dependent health states, with utility scores for more severe health states biased towards higher values. Model fit was assessed by comparing mean errors, mean absolute errors and mean squared errors in predicted values, both across the full range of EQ-5D values and for subsets. Models were also compared with predicted values from two external algorithms.

Table 12: Mapping algorithm coefficients, Rowen 2009

Variable	Coefficient
Intercept	–0.256
Physical functioning	0.559
Social functioning	0.293
Role physical	–0.146
Role emotional	0.067
Mental health	0.483
Vitality	0.017
Bodily pain	0.715
General health	0.407
Physical functioning^2	–0.227
Role physical^2	0.001
Social functioning^2	–0.163
Mental health^2	–0.242

Variable	Coefficient
Bodily pain^2	–0.330
General health^2	0.032
Vitality^2	–0.012
Role emotional^2	0.034
Physical functioning*Role physical	0.022
Physical functioning*bodily pain	–0.032
Physical functioning*general health	0.073
Physical functioning*vitality	–0.132
Physical functioning*social functioning	–0.023
Physical functioning*role emotional	0.047
Physical functioning*mental health	–0.014
Role physical*bodily pain	0.019
Role physical*general health	0.068
Role physical*vitality	0.050
Role physical*social functioning	0.067
Role physical*role emotional	–0.012
Role physical*mental health	0.022
Bodily pain*general health	–0.217
Bodily pain*vitality	–0.002
Bodily pain*social functioning	0.055
Bodily pain*role emotional	–0.038
Bodily pain*mental health	0.131
General health*vitality	–0.066
General health*social functioning	–0.157
General health*role emotional	–0.033
General health*mental health	–0.084
Vitality*social functioning	0.143
Vitality*role emotional	–0.020
Vitality*mental health	0.023
Social functioning*role emotional	–0.023
Social functioning*mental health	–0.065
Role emotional*mental health	–0.048

Source: Rowen 2009 (28)

L.3.3.3 Health-related quality-of-life studies

A systematic review was undertaken to identify studies reporting clinical, HRQoL and economic outcomes in patients with Pompe disease (Appendix D). Studies reporting key outcomes of interest (EQ-5D, SF-36 or PDSS/PDIS) are summarised in Table 13 and Table 14.

Table 13: Studies reporting utility values identified in the systematic review

Study (reference), type, population, country (setting), follow-up time, sample size	Intervention (follow-up time)	Elicitation method	Response rate (%)	Mean (SD) baseline utility value[†]	Mean (95% CI)[†] change from baseline [timepoint]
Wyatt 2012 (34) Prospective cohort LOPD England (hospital – multicentre) Follow-up (NR) N=NR	ALGLU 20 mg/kg qow	EQ-5D	NR	NA	–0.19 (–0.36, –0.01) [<12 months]
					–0.2 (-0.35, –0.04) [12–36 months]
					–0.25 (–0.43, –0.07) [>36 months]
Kanters 2015 (27) Prospective cohort LOPD Netherlands (hospital – single) Follow-up: 0.5–6.3 years N=80	NA	EQ-5D	73%	All patients: 0.670 (0.201)	NA
				Wheelchair-dependent: 0.533 (NR)	
				Not wheelchair-dependent: 0.729 (NR)	
				Ventilation-dependent: 0.593 (NR)	
				Not ventilation-dependent: 0.693 (NR)	
		SF-36		All patients: 0.699 (0.092)	NA
				Wheelchair-dependent: 0.666 (NR)	
				Not wheelchair-dependent: 0.713 (NR)	
				Ventilation-dependent: 0.688 (NR)	
				Not ventilation-dependent: 0.704 (NR)	
Kanters 2013 (35) Prospective cohort IOPD and LOPD Netherlands (hospital – single) Follow-up: NR N=67	NA	EQ-5D	76%	All patients: 0.70 (NR)	NA

Study (reference), type, population, country (setting), follow-up time, sample size	Intervention (follow-up time)	Elicitation method	Response rate (%)	Mean (SD) baseline utility value†	Mean (95% CI)† change from baseline [timepoint]
Simon 2019 (36) HQoL/PROs/Utility study IOPD and LOPD USA (community) Follow-up: NA N=see column 5	ERT	Stated-preference survey using a time trade-off approach (PDSS/PDIS)	40%	**Health state utilities:** Early Infantile Onset, Severe Symptoms (6 months) (N=170): 0.399 (95% CI 0.341–0.457) Childhood Onset, Mild Symptoms (8 yr) (N=171): 0.799 (95% CI 0.750–0.844) Childhood Onset, Moderate Symptoms (8 yr) (N=169): 0.414 (95% CI 0.355–0.475) Childhood Onset, Severe Symptoms (8 yr) (N=169): 0.466 (95% CI 0.407–0.525) ERT Treatment, 8 yr (N=170): 0.475 (95% CI 0.417–0.534) Adult Onset, Mild Symptoms (≥18 yr) (N=170): 0.853 (95% CI 0.811–0.892) Adult Onset, Moderate Symptoms (≥18 yr) (N=170): 0.683 (95% CI 0.634–0.729) Adult Onset, Severe Symptoms (≥18 yr) (N=171): 0.536 (95% CI 0.480–0.594) ERT Treatment, ≥18 yr (N=169): 0.673 (95% CI 0.621–0.723) **Health state disutilities:** Early Infantile Onset, Severe Symptoms (6 months) (N=170): 0.180 (95% CI 0.129–0.230) Childhood Onset, Mild Symptoms (8 yr) (N=171): 0.072 (95% CI 0.042–0.103) Childhood Onset, Moderate Symptoms	NA

Study (reference), type, population, country (setting), follow-up time, sample size	Intervention (follow-up time)	Elicitation method	Response rate (%)	Mean (SD) baseline utility value†	Mean (95% CI)† change from baseline [timepoint]
				(8 yr) (N=169): 0.162 (95% CI 0.116–0.208) Childhood Onset, Severe Symptoms (8 yr) (N=171): 0.131 (95% CI 0.090–0.173) ERT Treatment, 8 yr (N=169): 0.155 (95% CI 0.110–0.200)	

†Unless otherwise stated.
Abbreviations: CI, confidence interval; EQ-5D, EuroQol-5 Dimensions; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; NA, not applicable; NR, not reported; PDIS, Pompe disease impact scale; PDSS, Pompe disease symptom scale; qow, every other week; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

Table 14: Studies reporting SF-36 scores identified in the systematic review

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
Wyatt 2012 (34) Prospective cohort/ open-label LOPD England (hospital – multicentre) Follow-up: NR N=NR	ALGLU 20 mg/kg qow	PCS	NR	29.8 (8.73)	NR
		MCS		50.07 (12.5)	
Stepien 2016 (37) Retrospective cohort LOPD NR (hospital – single centre) Follow-up: 5 years N=22	ALGLU 20 mg/kg qow	PCS	NR	Median (range): 35 (16–54)	p-value [5 years]: 0.8627
		MCS		Mean (95% CI): 46.5 (28.5–64.5)	p-value [5 years]: 0.8571

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
Hagemans 2004 (13) Prospective cohort/open-label LOPD Australia, Germany, Netherlands, US, UK (NR) Follow-up: NR N=420 (20 in the UK)	NA	Physical functioning‡	58%‡	17.5 (NR)	NR
		Physical role‡		32 (NR)	
		Bodily pain‡		62.9 (NR)	
		General health‡		51.3 (NR)	
		Vitality‡		37.2 (NR)	
		Social role‡		63.2 (NR)	
		Emotional role‡		68.4 (NR)	
		Mental health‡		66.8 (NR)	
Güngör 2016 (38) Prospective cohort/open-label LOPD Netherlands, US, UK, Germany, Australia, other unspecified countries (NR) Follow-up: 7 years N=174	ERT	PCS	NR	NR	Mean change in score per year pre-ERT: –0.73 (–1.07, –0.39) Mean change in score per year following initiation of ERT: 1.49 (0.76, 2.21) [0–2 years] –0.15 (–0.43, 0.13) [>2 years]
		MCS			Mean change in score per year pre-ERT: 0.16 (–0.25, 0.57) Mean change in score per year following initiation of ERT: 1.03 (–0.07, 2.13) [0–2 years] 0.02 (–0.41, 0.46) [>2 years]
Sechi 2020 (39) RCT LOPD	ERT + exercise	Vitality	NR	Median: 40	Median: 0
		Physical functioning		Median: 25	Median: 0

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
Italy (multicentre) Follow-up: 26 weeks N=21		Bodily pain		Median: 52	Median: 0
		General health		Median: 45	Median: –5
		Physical role		Median: 50	Median: 0
		Emotional role		Median: 100	Median: 0
		Social role		Median: 75	Median: 12.5
		Mental health		Median: 72	Median: 4
		PCS		Median: 34.25	Median: 0.26
		MCS		Median: 53.92	Median: 3.06
	ERT + exercise + diet	Vitality	NR	Median: 40	Median: 10
		Physical functioning		Median: 45	Median: 5
		Bodily pain		Median: 52	Median: 0
		General health		Median: 30	Median: 5
		Physical role		Median: 25	Median: 0
		Emotional role		Median: 66.67	Median: 0
		Social role		Median: 50	Median: 0
		Mental health		Median: 56	Median: 12
		PCS		Median: 33.61	Median: 1.83
		MCS		Median: 41.15	Median: 4.29
Strothotte 2010 (40) Prospective cohort/ open-label LOPD Germany (hospital – multicentre) Follow-up: 12 months N=44	ALGLU 20 mg/kg qow	NA	NR	48.5 (NR)	NR

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
van der Ploeg 2010 (41) RCT (LOTS study) LOPD Netherlands, France, US (hospital – multicentre) Follow-up: 78 weeks N=90	ALGLU 20 mg/kg qow	PCS	100%	34.3 (8.9)	0.8 (–1.22, 2.82) [78 weeks]
	Placebo			34.9 (7.3)	1.16 (–1.64, 3.97) [78 weeks]
Fernández-Simón 2019 (42) Prospective cohort/open-label LOPD Spain (hospital – single) Follow-up: 4 years N=49	ALGLU 20 mg/kg qow	PCS		All patients: Median (IQR): 50 (23 to 65)	All patients: Median (IQR): 4.3 (–3.1 to 11.4) [1 year]
		MCS	NR	Patients who did not develop antibodies: Median (IQR): 45 (18.5 to 61.4)	Patients who did not develop antibodies: Median (IQR): 9.7 (–0.9 to 33.4) [1 year]
				Patients who developed antibodies: Median (IQR) 50 (26.2 to 65.6)	Patients who developed antibodies: Median (IQR) 3.7 (–4 to 8.7) [1 year]
				All patients: Median (IQR): 66 (50 to 73)	All patients: Median (IQR): 2.7 (–11.8 to 13.7) [1 year]
				Patients who did not develop antibodies: Median (IQR): 69 (65.9 to 73.6)	Patients who did not develop antibodies: Median (IQR): 8.5 (–9.8 to 16.5) [1 year]

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
				Patients who developed antibodies: Median (IQR): 62.6 (47.5 to 76.1)	Patients who developed antibodies: Median (IQR): 1 (–12.4 to 13.2) [1 year]
Boentert 2015 (43) Cross-sectional LOPD Germany (hospital – multicentre) Follow-up: NR N=130	ERT	PCS	95.4%	All patients: 32.1 (9.9) Home ventilation: 28.9 (9) No home ventilation: 36.1 (9.1)	NA
		MCS		All patients: 49.6 (9.2) Home ventilation: 49.1 (9.9) No home ventilation: 50.2 (8.5)	
Favejee 2015 (44) Prospective cohort/open-label LOPD Netherlands (hospital – single) Follow-up: 24 weeks N=23	Exercise training	PCS	NR	Baseline median: 40 (range: 24–53) 12-weeks median: 42 (range: 21–51)	NR

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
		MCS	NR	Baseline median: 56 (range: 25–69) 12-weeks median: 59 (range: 34–69)	
Güngör 2013 (45) Cross-sectional LOPD Germany, Netherlands (NR) Follow-up: NR N=86	ERT	PCS	NR	Patients reporting pain in the last 24 hours Median: 30 (range 11–45) Patients not reporting pain in the last 24 hours Median: 35 (range 17–58)	NA
		MCS		Patients reporting pain in the last 24 hours Median: 54 (range 29–74) Patients not reporting pain in the last 24 hours Median: 58 (range 29–71)	

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
Boentert 2016 (46) Prospective cohort/open-label LOPD Germany (hospital – single) Follow-up: 40 months N=22	NIV (all patients) ERT 20 mg/kg qow (14/22 patients)	PCS	NR	All patients: 33.3 (8.6) Sleep-disordered breathing absent: 38.8 (11.6) Sleep-disordered breathing present: 30.8 (5.6)	Not assessed
		MCS		All patients: 47.6 (7.5) Sleep-disordered breathing absent: 55.2 (3.1) Sleep-disordered breathing present: 44.0 (6.1)	

Study reference, type, population, country (setting), follow-up time, sample size	Intervention	SF-36 domain	Response rate (%)	Mean (SD) baseline value†	Mean (95% CI)† change from baseline [timepoint]
Yuan 2020 (47) Cross-sectional LOPD Netherlands (hospital – single) Follow-up: NR N=121	NA	PCS	NR	Median: 33 (range 17–63)	NA
		MCS		Median: 48 (range 19–72)	

†Unless otherwise stated; ‡UK-specific. PCS/MCS were not presented.

Abbreviations: CI, confidence interval; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; IQR, interquartile range; LOPD, late-onset Pompe disease; MCS, mental component score; NA, not applicable; NIV, non-invasive ventilation; NA, not applicable; NR, not reported; PCS, physical component score; qow, every other week; RCT, randomised controlled trial; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

L.3.3.4 Adverse reactions

In the COMET trial, there was a small trend towards fewer TEAEs and TESAEs in patients treated with AVAL compared with those treated with ALGLU. However, due to the uncertainty around this estimate, it was conservatively assumed that the AE profiles of the two treatments are the same.

In trials in patients with LOPD, the most common potentially treatment-related TEAEs were mild-to-moderate in intensity, generally easily treatable and patients recovered once ERT was withdrawn. Therefore, it is unlikely that any treatment-related AEs would have a lasting impact on HRQoL or costs.

L.3.3.5 Health-related quality-of-life data used in the cost-effectiveness analysis

EQ-5D-based utilities were used for the cost-effectiveness analysis in line with the NICE reference case. In spite of the fact that EQ-5D does not reflect the entire effect of Pompe disease on HRQoL (48), it captured significant differences between health states.

Health state utility values

For each patient profile, a utility at the start is assigned based on the mean baseline EQ-5D-5L value observed for that profile in COMET. This value is updated during simulation based on the treatment and at milestones, as described in Section B.2.1.1. The initial utility gain due to treatment was based on analyses of COMET data at the end of the 49-week randomised period and applied at one year.

The impact of reaching a milestone (NIV, INV, WC) was obtained from utility analyses of the Pompe Registry data (16). Specifically, disutilities were derived from the difference between the utility value for patients requiring a ventilator or wheelchair and the utility of patients without a ventilator or a wheelchair. It was assumed that the disutility for patients using both a ventilator and wheelchair was equivalent to the sum of the disutilities applied for each disability.

Registry data were used beyond the plateau period as they cover a broader spectrum of disease severity than the COMET trial. The utility values reported from

the Registry analysis and the calculated disutilities used in the model are shown in Table 15. For patients that are both ventilator- and wheelchair-dependent the individual disutilities for both states have been applied. While results for ventilator- and wheelchair-dependent patients were available from the registry analysis, given the small sample size and counterintuitive results this was deemed the most plausible approach.

Table 15: 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: Pompe Registry (16)

Other sources for utility values were considered, including values from Simon 2019 (36) which were discussed at the UK advisory board. Clinicians stated that the values from Simon 2019 underestimated the impact of disability, stating that the proposed utility values for wheelchair and ventilator dependency in the model are higher than what is observed in clinical practice. The company were advised to explore other options, including using data from diseases such as Duchenne muscular dystrophy (DMD), however differences in the natural history of the diseases made this difficult.

Based on this feedback, the registry values were considered the most suitable source. A scenario using data from prior analyses in DMD was applied. Landfeldt 2017 present 3 model frameworks for use in DMD which are accompanied by health state utility values for patients and caregivers (49). Utilities were estimated from a cross-sectional observational study and were assessed using the Health Utilities Index questionnaire (HUI) for patients and the EQ-5D-3L for caregivers. Model II is based on ambulatory status and model III is based on ventilatory status, and these have been used to calculate disutilities for the current model. The disutility for wheelchair use was assumed to be the difference between the late ambulatory and

early non-ambulatory health states in model II. The disutility for non-invasive ventilator use was assumed to be the difference between the no ventilator use and night-time ventilator use in model III. The disutility for invasive ventilator use was assumed to be the difference between no ventilator use and day and night-time ventilator use in model III. Table 16 summarises the disutilities used in this scenario.

Table 16: Summary of disutilities calculated from the DMD models

Health state	Disutility (patients)	Disutility (caregivers)
Wheelchair-dependent	–0.383	–0.055
Non-invasive ventilator	–0.389	–0.062
Invasive ventilator-dependent	–0.467	–0.063

Abbreviations: DMD, Duchenne muscular dystrophy.

As the baseline utilities, even upon treatment, are well below comparable age and sex general population utilities, no adjustment was made, in accordance with NICE guidance (50).

Caregiver disutilities

Caregiver disutilities (Table 17) were obtained from Simon 2019, a US study which used the time trade-off method in a community sample of 862 individuals (36). Participants received descriptions of three health states, defined in consultation with patients and clinical experts: severe (requiring both a ventilator and a wheelchair), as well as mild and moderate Pompe disease (no requirement for ventilation or wheelchair. The caregiver disutilities reported for the mild and moderate states (0.062 and 0.172, respectively) were averaged (0.117) for use in the model for patients not dependent on ventilator or wheelchair.

These values were discussed at the UK advisory board (Appendix M); clinicians stated that carer quality of life is significantly impacted by ventilator and wheelchair dependency, and that disutilities are likely to be lower than those currently available from the literature.

A limitation of the Simon 2019 data is that it does not differentiate values by disability status, only by disease severity, with the severe state covering all patients requiring ventilatory and wheelchair support. Due to lack of other data, the severe health state disutility (0.131) was applied to all of the other disease states in the model. Patients

are assumed to have a single caregiver in each state. A scenario analysis excluding caregiver disutilities was also explored.

Table 17: Caregiver disutilities by disease state

Health state	Disutility	Source
Not dependent on ventilator or wheelchair	0.117	Simon 2019 (36)
Non-invasive ventilator	0.131	
Wheelchair-dependent	0.131	
Invasive ventilator-dependent	0.131	
Ventilator & wheelchair	0.131	

L.3.4 Cost and healthcare resource use identification, measurement and valuation

L.3.4.1 Costs and resource use for intervention and comparators

List price for the technology

The list price for AVAL is [redacted] per 100 mg vial. AVAL is a weight-based treatment, with a dose of 20 mg/kg. The price per kg at 20 mg/kg is [redacted].

Acquisition and administration costs

AVAL and ALGLU are administered via IV every other week at a dose of 20 mg/kg. Acquisition costs for AVAL at PAS price and ALGLU are presented in Table 18.

Table 18: LOPD – Acquisition cost

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; LOPD, late-onset Pompe disease.

The acquisition cost of AVAL and ALGLU was calculated using a weight-based approach, based on the baseline weight of individual patients. Vial sharing was assumed in line with clinical advice that doses are generally rounded to the whole vial to obtain the correct dose as an average of two infusions.

For both ERTs treatment administration was assumed to occur in an outpatient hospital setting for the first three infusions and then at home thereafter. Home administration could occur with or without a nurse to reconstitute the drug (independent/semi-independent administration) or at home with a nurse for the duration of the reconstitution and infusion. The cost was applied as an ongoing, annual cost starting from treatment initiation. Administration costs used in the model were calculated as the weighted average of the proportion of patients receiving care in each setting and the cost of administration in that setting.

The cost of home administration with a nurse was calculated as the product of the hourly rate of the nurse (community nurse, sourced from the PSSRU (51)) and the nurse time required for reconstitution and infusion: 4.7 hours for AVAL and 5.2 hours for ALGLU. For patients that administer at home either independently or semi-independently the nurse time was that needed for reconstitution: 45–60 minutes for AVAL and 75–90 minutes for ALGLU (52).

The day case administration unit cost was sourced from the National Schedule of NHS Costs: Year 2019–20 (53, 54).

An overview of the cost and distribution data applied to each treatment is presented in Table 19 and Table 20.

Table 19: LOPD – ERT administration costs for different settings

Category	Unit cost: AVAL	Unit cost: ALGLU	Source
At home: independent or semi-independent	£40.00	£60.00	Unit Costs of Health and Social Care, PSSRU (2020) (51)
At home: with nurse	£188.00	£208.00	
Outpatient	£165.00	£165.00	National schedule of NHS costs (2019/20) (53)

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; LOPD, late-onset Pompe disease; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 20: LOPD – ERT administration patient distribution across different settings

Category	% patients on AVAL	% patients on ALGLU	Source
At home: independent or semi-independent	[redacted]	[redacted]	Assumption
At home: with nurse	[redacted]	[redacted]	
Outpatient	[redacted]	[redacted]	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; LOPD, late-onset Pompe disease.

Monitoring costs

Treatment-related monitoring costs were included for each arm. A unit cost of £7.40 was applied and informed by the NHS reference costs (2019/20), code DAPS06. Table 21 summarises the monitoring costs applied.

Table 21: Monitoring costs for AVAL and ALGLU

Category	Unit cost	Annual frequency in years 1 and 2	Long term annual frequency (years 3+)	Source
IgG antibody monitoring	£7.40	4	2	NHS reference costs 2019/20 (53)

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IgG, immunoglobulin G; NHS, National Health Service.

L.3.4.2 Health-state unit costs and resource use

Ventilation-related costs

When a patient reached a ventilation-related milestone, a one-off cost was discretely accumulated (including ventilator assessment and purchase), which was followed by the accumulation of annual ventilation costs. Cost data were divided into ventilation and ventilation-related categories, and the former was further divided into non-invasive ventilation and invasive ventilation costs (Table 22). Cost data were inflated to 2020 values where necessary.

Table 22: LOPD – Ventilation-related costs

Description	One-off cost	Annual cost	Reference
Ventilator			
Non-invasive ventilation, home, adults	£4,286.16	£654.83	Dretzke 2015 (55)
Invasive ventilation, home	£129,295	£149,025.09	Noyes 2006 (56), Cooke 2010 (57)
Ventilation-related costs			
Outpatient assessment, adults	£389.63	–	NHS reference costs (2019/20) (53)

Abbreviations: LOPD, late-onset Pompe disease.

The one-off cost associated with invasive ventilation represents a protracted inpatient stay for patients going on to invasive ventilation. These estimates are based on data and expertise from IOPD, as invasive ventilation is rarely used in LOPD. Clinical experts estimated that patients would require a 4–6-month inpatient stay. The one-off cost associated with invasive ventilation therefore assumes that patients spend four months in a high-dependency unit at a cost of £800 per day (56). This cost has been inflated from 2006 GBP using the PSSRU pay and prices index.

Wheelchair-related costs

When a patient reached a wheelchair-related milestone, a one-off cost was incurred, which was followed by an annual maintenance cost. Patients were assumed to require a new wheelchair every 5 years. Cost data were sourced from the 2019/20 NHS reference costs (53) (Table 23). One-off costs for home adjustments and a hoist were also accounted for.

Table 23: LOPD – Wheelchair costs

Description	One-off cost	Annual cost	Reference
Wheelchair (powered)	£1,306.48	£164.00	NHS reference costs (2019/20), WC08 and WC10 (53)
Wheelchair-related cost			
Home adjustments	£30,000.00	–	Maximum disability facilities grant in England (2020) (58)
Hoist	£669.99	–	NRS Healthcare, Oxford midi mobile hoist

Abbreviations: NHS, national healthcare service; NRS, Nottingham rehab limited.

Disease-related monitoring and management

Costs of the relevant assessments were obtained from the 2019/20 NHS reference costs and are shown in Table 24. The frequency of monitoring tests was assumed to be independent of health state and was informed by EPOC guidelines (59), which state that patients receiving ERT require monitoring at least once per year.

Table 24: LOPD – Annual monitoring costs

Description	Unit cost	Frequency (per year)	Reference
Pulmonary function	£146.44	1	NHS reference costs 2019/20, DZ52Z, DZ46Z, DZ32Z, DZ50Z (53)
Respiratory muscle strength	£146.40	1	
Muscle strength	£194.05	1	
Sleep study	£173.52	1	

In addition to monitoring costs, the annual cost of disease management due to hospitalisations and general practitioner (GP) visits was also included. An analysis of the Clinical Practice Research Datalink (CPRD) was performed, investigating the resource use in patients with LOPD (60). Costs were collected for all LOPD patients. Costs were assumed to be equal for patients regardless of wheelchair and ventilator status.

Secondary care costs were calculated by mapping the activity to the 2019/20 Payment Grouper HRGs and allocating the 2019 base tariffs. The reason for this was to place all of the activity on an equal footing (inpatient, outpatient, Accident & Emergency). Critical care activity costs were based on this tariff cost as the actual critical care costs were not available. Primary care costs were obtained from PSSRU 2019 (51).

General practitioner prescribing costs were estimated by linking the data to NHS Digital GP prescribing data using the BNF pack code / description, a unit cost was calculated. This unit cost was then multiplied by the quantity (tablets / doses / grams / bottles) in order to provide a total cost for each prescription line. Annual disease-related costs are summarised in Table 25.

Table 25: Disease-related costs per patient year by category

Cost category	Cost	Reference
Elective and day-case	£330.99	CPRD analysis (60)

Cost category	Cost	Reference
Non-elective	£434.93	
ITU	£117.82	
Outpatient	£210.96	
A&E	£49.13	
Primary care consultations	£255.22	
GP prescribing	£491.99	
Total	**£1,891**	**–**

†No ITU costs were available for ventilated patients, so costs were assumed to be equal to those for patients with no dependence.
Abbreviations: A&E, accident and emergency; CPRD, Clinical Practice Research Datalink; GP, general practitioner; ITU, intensive treatment unit.

L.3.4.3 Adverse event costs

AEs were not explicitly considered in the model. Costs of AEs were assumed not to differ between treatments and to be captured within the cost data derived from CPRD (see L.3.4.2).

L.3.4.4 Indirect costs

No quantifiable data on the escalation of indirect costs with disease progression was identified in the literature, however there can be significant costs to both the patient and society that will increase as the disease progresses. Document B Section B.2 summarises the outputs of interviews seeking to document the patient experience (48).

These describe how, as symptoms progress, patients gradually adapt to cope with their individual limitations. Initial mobility problems faced by patients are steps and an inability to get up easily if they bend, crouch, or sit down, so patients start to rely more on their arms and upper body, changing the way that they approach everyday tasks. In time they may gradually make adaptions to their home so that, for example, ovens are at chest height, there is a stool near the washing machine. In addition, the disease limits their world so for example certain tube stations are avoided because of steps, they cross the road in certain places, work from home more, reduce time outside the house, or avoid leaving the house alone.

Fatigue and pain lead to gradual shortening of work hours, choosing to work from home more, having to change their job or reduce the amount of time out of the house

alone and spending increasing amounts of time asleep, shortening their day. As a consequence, there is an increasing dependence on loved ones to help.

While indirect costs have not been incorporated into the model, there is a significant burden of disease associated with home adaptations and reduction in time working that increases for both the patients and their carers as the disease progresses.

L.3.5 Summary of base-case analysis inputs and assumptions

L.3.5.1 Summary of base-case analysis inputs

A summary of variables applied in the LOPD model is presented in Table 26.

Table 26: Summary of variables applied in the cost-effectiveness model

Variable	Value	Range or 95% CI (distribution)	Source
Discount rate (outcomes)	0.035	Not varied	NA
Discount rate (costs)	0.035	Not varied	
Time horizon	60	Not varied	
Age	[redacted]	Not varied	COMET baseline characteristics (18)
% female	[redacted]	Not varied	COMET baseline characteristics (18)
Baseline FVC	[redacted]	Not varied	COMET baseline characteristics
Baseline 6MWT	[redacted]	Not varied	COMET baseline characteristics
Baseline utility	[redacted]	Not varied	COMET trial

Variable	Value	Range or 95% CI (distribution)	Source
FVC% predicted, rate of annual decline rate, ERT post plateau	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
6MWT, rate of annual decline rate, ERT post plateau	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
FVC% predicted, rate of annual decline rate, no treatment	1.04	3.23 to 0.33 (Lognormal)	Van der beek 2012 (19)
6MWT, rate of annual decline rate, no treatment	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
Relative FVC% predicted change from baseline, ALGLU during plateau	0.46	to 2.31 (truncated Normal)	COMET trial (18)
Relative FVC% predicted CFB, AVAL during plateau	2.43	0 to 4.99 (truncated Normal)	
Relative 6MWT CFB, ALGLU during plateau	2.19	0 to 22.86 (truncated Normal)	
Relative 6MWT CFB, AVAL during plateau	30.01	1.33 to 58.69 (truncated Normal)	
Duration of plateau period for 6MWT, ALGLU	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
Duration of plateau period for 6MWT, AVAL	[redacted]	[redacted]	Analysis of NEO-EXT (61)
Duration of plateau period for FVC% predicted, ALGLU	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
Duration of plateau period for FVC% predicted, AVAL	[redacted]	[redacted]	Analysis of NEO-EXT (61)
Utility gain during plateau period, ALGLU	[redacted]	[redacted]	COMET (18)
Utility gain during plateau period, AVAL	[redacted]	[redacted]	COMET (18)
AVAL discontinuation rate, per year	0.0076	0.006 to 0.009 (Beta)	van Kooten 2020 (21)
ALGLU discontinuation rate, per year	0.0076	0.006 to 0.009 (Beta)	
Non-invasive ventilation use, ln(FVC% predicted)	[redacted]	[redacted]	

Variable	Value	Range or 95% CI (distribution)	Source
Invasive ventilation use, threshold, ln(FVC% predicted)	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
Wheelchair use, ln(6MWT)	[redacted]	[redacted]	
Treatment discontinuation rate per year, ALGLU	0.0076	0.00608 to 0.00912 (Beta distribution)	van Kooten 2020 (21)
Treatment discontinuation rate per year, AVAL	0.0076	0.00608 to 0.00912 (Beta distribution)	
Adverse event leading to treatment discontinuation, ALGLU	0.0052	0.004 to 0.006 (Beta distribution)	
Adverse event leading to treatment discontinuation, AVAL	0.0052	0.004 to 0.006 (Beta distribution)	
No treatment overall survival curve parameter, Weibull, intercept	3.48	3.35 to 3.61 (Multivariate normal)	Gungor 2011 (22)
No treatment overall survival curve parameter, Weibull, shape	0.53	0.44 to 0.63 (Multivariate normal)	
No treatment overall survival curve parameter, Gompertz, intercept	4.92	4.47 to 5.38 (Multivariate normal)	
No treatment overall survival curve parameter, Gompertz, Gamma	0.08	0.06 to 0.11 (Multivariate normal)	
OS HR, AVAL vs. No treatment	0.41	0.19 to 0.87 (Log-normal)	Assumed equal to ALGLU Schoser 2017 (14)
OS HR, ALGLU vs. No treatment	0.41	0.19 to 0.87 (Log-normal)	Schoser 2017 (14)
OS HR, non-invasive ventilation-dependent	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
OS HR, wheelchair-dependent	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
OS HR, invasive ventilation-dependent	[redacted]	[redacted]	
General population mortality, female, Gompertz – intercept	6.95×10^{-6}	Not varied	UK, national life tables (62)

Variable	Value	Range or 95% CI (distribution)	Source
General population mortality, female, Gompertz – Gamma	0.1087	Not varied	
General population mortality, female, Weibull – intercept	88.67	Not varied	
General population mortality, female, Weibull – shape	9.14	Not varied	
General population mortality, male, Gompertz – intercept	2.28×10^{-5}	Not varied	
General population mortality, male, Gompertz – Gamma	0.10	Not varied	
General population mortality,male, Weibull – intercept	85.53	Not varied	
General population mortality, male, Weibull – shape	7.87	Not varied	
Unit cost – ALGLU	356.06	356.06 to 356.06 (Not varied)	BNF (63)
Unit cost – AVAL	[redacted]	[redacted]	–
Unit strength – ALGLU	50	50 to 50 (Not varied)	BNF (63)
Unit strength – AVAL	100	100 to 100 (Not varied)	Appendix C
Pack size – ALGLU	1	1 to 1 (Not varied)	BNF (63)
Pack size – AVAL	1	1 to 1 (Not varied)	Appendix C
Dose – ALGLU	20	20 to 20 (Not varied)	ALGLU SmPC (64)
Dose– AVAL	20	20 to 20 (Not varied)	COMET trial CSR (18)
Dose frequency per 4 weeks – ALGLU	2	2 to 2 (Not varied)	ALGLU SmPC (64)
Dose frequency per 4 weeks – AVAL	2	2 to 2 (Not varied)	COMET trial CSR (18)

Variable	Value	Range or 95% CI (distribution)	Source
Compliance – ALGLU	100	100 to 00 (Not varied)	Assumption based on clinical expert advice
Compliance – AVAL	100	100 to 00 (Not varied)	Assumption based on clinical expert advice
Cost of nurse time per hour	40.00	40.00 to 40.00 (Not varied)	PSSRU 2020 (51)
Cost of administration – outpatient	165	165 to 165 (Not varied)	NHS reference costs 2019/20 (53) Cost of simple parenteral chemotherapy (SB12Z)
Proportion of patients – self administration, adults – ALGLU	[redacted]	[redacted]	Assumption
Proportion of patients – self administration, adults – AVAL	[redacted]	[redacted]	
Proportion of patients – at home with nurse administration, adults – ALGLU	[redacted]	[redacted]	
Proportion of patients – at home with nurse, adults – AVAL	[redacted]	[redacted]	
Proportion of patients – outpatient administration, adults – ALGLU	[redacted]	[redacted]	
Proportion of patients – outpatient, adults – AVAL	[redacted]	[redacted]	
Disutility, non-invasive ventilation-dependent health state	[redacted]	[redacted]	Analysis of the Pompe Registry (16)
Disutility, invasive ventilation-dependent health state	[redacted]	[redacted]	
Disutility, wheelchair dependent health state	[redacted]	[redacted]	
Disutility, non-invasive ventilation- and wheelchair-dependent health state	[redacted]	[redacted]	
Disutility, invasive ventilation- and	[redacted]	[redacted]	

Variable	Value	Range or 95% CI (distribution)	Source
wheelchair-dependent health state			
Number of caregivers, age 0–17	1.78	1.42 to 2.14 (Gamma)	Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutation (65)
Disutility, caregiver, no wheelchair or ventilation dependence state	0.117	Not varied	Simon 2019 (36)
Disutility, caregiver, non-invasive ventilation-dependent health state	0.131		
Disutility, caregiver, invasive ventilation-dependent health state	0.131		
Disutility, caregiver, wheelchair-dependent health state	0.131		
Disutility, caregiver, ventilator and wheelchair-dependent health state	0.131		

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; CI, confidence interval, FVC, forced vital capacity; HR, hazard ratio; LOPD, late-onset Pompe disease; NA, not applicable; NHS, National Health Service; OS, overall survival; PSSRU, Personal Social Services Research Unit; 6MWT, six-minute walk test.

L.3.5.2 Assumptions

Assumptions applied in the LOPD model are presented in Table 27.

Table 27: LOPD model assumptions

Component of model	Assumption	Justification
Model structure	The model assumed that mortality is independently impacted by treatment and disability status. The impacts of both are modelled as a HR applied to the baseline hazard of death 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.
	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.

Component of model	Assumption	Justification
Clinical Data	Patients were assumed to experience a linear decline in FVC% predicted.	This is a simplifying assumption, applied based on data from the literature. Analysis of disease progression by Van der Beek 2012 suggested adults experience a steady linear decline in FVC% predicted (19).
	Treatment effects of AVAL and ALGLU were applied 1 year after treatment initiation.	This corresponds to the timing of the COMET trial primary endpoint.
	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 5 years [redacted]. This was based on registry analysis (16) and clinical feedback (Appendix M).
	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.
	The decline in 6MWT for patients on No treatment was assumed equal to those on ERT.	There is little data available on the progression of 6MWT on No treatment. This represents the most conservative assumption.
	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.
HRQoL	The impacts of ventilator- and wheelchair-dependence on utility values can be applied additively.	While data were available for combined health states, these were based on small patient numbers and gave counterintuitive results. This approach seems the most plausible given the available data.
	The caregiver disutility for all ventilator- and wheelchair dependent states is equal.	There is a lack of data on caregiver impact and the values come from a study that reports values for severe disease, which incorporated all these states. This assumption is

Component of model	Assumption	Justification
		assumed to be conservative as it understates the value of slowing disease progression.
Cost data	The base case assumed an adult will require a wheelchair replacement once every 5 years and a child will require a replacement every 2 years.	The NHS wheelchair service provides wheelchair vouchers that last up to 5 years (66). The wheelchair replacement time for children was set to 2 years to account for patient growth.
	The costs associated with invasive ventilation were not stratified by paediatric and adult patients, and as such were assumed to be the same for both.	This assumption was necessary due to the paucity of data available to inform the model.

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CFB, change from baseline; ERT, enzyme replacement therapy; FVC, forced vital capacity; HR, hazard ratio; IPD, individual patient data; 6MWT, six-minute walk test.

L.3.6 Base-case results

L.3.6.1 Base-case incremental cost-effectiveness analysis results

Table 28 presents the base-case results for the LOPD population. [redacted]

Table 29, Table 30 and Table 31 present clinical outcomes from the model. AVAL leads to a reduction in the proportion of patients reaching each milestone and a longer period of time free from ventilation and wheelchair support, leading to a gain in QALYs. Table 32 presents disaggregated cost outputs from the model. [redacted]

Table 28: Base-case results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; LYG, life years gained; QALY, quality-adjusted life year.

Table 29: Disaggregated QALYs (discounted)

	ALGLU	AVAL	Difference
Patient Life years	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Patient QALYs	[redacted]	[redacted]	[redacted]
Caregiver disutility	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALY, quality-adjusted life year.

Table 30: Proportion of patients reaching each milestone (not mutually exclusive)

	ALGLU	AVAL	Difference
Non-invasive ventilator	[redacted]	[redacted]	[redacted]
Invasive ventilator	[redacted]	[redacted]	[redacted]
Wheelchair	[redacted]	[redacted]	[redacted]
Ventilator and wheelchair	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 31: Time on treatment and to reaching milestones

	ALGLU	AVAL	Difference
On treatment	[redacted]	[redacted]	[redacted]
To non-invasive ventilator*	[redacted]	[redacted]	[redacted]
To invasive ventilator*	[redacted]	[redacted]	[redacted]

	ALGLU	AVAL	Difference
To wheelchair*	[redacted]	[redacted]	[redacted]

*Among patients that reached these endpoints.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 32: Disaggregated costs (discounted)

	ALGLU	AVAL	Difference
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Drug initiation	[redacted]	[redacted]	[redacted]
Ventilator	[redacted]	[redacted]	[redacted]
One-off costs	[redacted]	[redacted]	[redacted]
Annual costs	[redacted]	[redacted]	[redacted]
Wheelchair	[redacted]	[redacted]	[redacted]
One-off costs	[redacted]	[redacted]	[redacted]
Annual costs	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
Treatment-related monitoring	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

L.3.7 Sensitivity analyses

The analysis addressed methodological uncertainty, parameter uncertainty and structural uncertainty. Discount rates of both costs and outcomes were varied from the base case value of 3.5%. The time horizon was varied in scenario analysis from the base case value of 60 years (representing the lifetime of the cohort); time horizons of 15 and 30 years were also examined. The assumption that treatment ceases once a patient requires invasive ventilation was relaxed in a sensitivity analysis. Scenario analyses were conducted to address the impact of simultaneously varying assumptions on the duration of the plateau period for both FVC% predicted and 6MWT with AVAL. Parameter uncertainty was addressed in both one-way and probabilistic analysis.

L.3.7.1 Univariate sensitivity analysis

One-way sensitivity analysis was conducted for parameters relating to treatment effectiveness, treatment discontinuation, health state disutilities and mortality. The parameters varied within the one-way sensitivity analysis are presented in Table 33. Ranges were informed by 95% CIs derived from the parameter source, where available. Where ranges for short-term treatment effects were derived from COMET data, the lower bound was capped at zero to avoid negative values considered clinically implausible. In the absence of data to inform 95% CIs, parameters were varied by +/- 20%. The impact of parameter uncertainty on the ICER was reported using a Tornado plot.

Table 33: Variables used in the univariate sensitivity analysis

Variable	Base case value	Range of values
FVC% predicted change, ALGLU	[redacted]	[redacted]
FVC% predicted change, AVAL	[redacted]	[redacted]
6MWT change, ALGLU	[redacted]	[redacted]
6MWT change, AVAL	[redacted]	[redacted]
FVC% predicted plateau period, ALGLU	[redacted]	[redacted]
FVC% predicted plateau period, AVAL	[redacted]	[redacted]
6MWT plateau period, ALGLU	[redacted]	[redacted]
6MWT plateau period, AVAL	[redacted]	[redacted]

Variable	Base case value	Range of values
Utility gain (%) ALGLU	[redacted]	[redacted]
Utility gain (%), AVAL	[redacted]	[redacted]
Treatment discontinuation rate, ALGLU	[redacted]	[redacted]
Treatment discontinuation rate, AVAL	[redacted]	[redacted]
Adverse event rate, ALGLU	[redacted]	[redacted]
Adverse event rate, AVAL	[redacted]	[redacted]
Mortality HR on ERT	0.41	0.19 to 0.87
Mortality HR, wheelchair use	1.30	0.74 to 2.29
Mortality HR, non-invasive ventilation use	0.98	0.51 to 1.90
Mortality HR, invasive ventilation use	3.72	1.63 to 8.49
Disutility, wheelchair use	[redacted]	[redacted]
Disutility, non-invasive ventilation use	[redacted]	[redacted]
Disutility, invasive ventilation use	[redacted]	[redacted]

[t] Parameter lower bound capped for plausibility reasons.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC, forced vital capacity; HR, hazard ratio; 6MWT, six-minute walk test.

L.3.7.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted, which included all parameters varied in one-way sensitivity analysis. Table 34 lists the parameters included in the PSA along with the distribution and the standard error used to inform the variance of the distribution. Standard errors were obtained from published data or estimated at 10% of the point estimate when published data were unavailable. 1000 Monte Carlo simulations were recorded, with each simulation consisting of 10 replications of the eight patient profiles. Results were plotted on the cost-effectiveness plane and a cost-effectiveness acceptability curve was generated.

Table 34: Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution
FVC% predicted change, ALGLU	[redacted]	[redacted]
FVC% predicted change, AVAL	[redacted]	[redacted]
6MWT change, ALGLU	[redacted]	[redacted]
6MWT change, AVAL	[redacted]	[redacted]
FVC% predicted plateau period, ALGLU	[redacted]	[redacted]

Variable	Base-case value	Distribution
FVC% predicted plateau period, AVAL	[redacted]	[redacted]
6MWT plateau period, ALGLU	[redacted]	[redacted]
6MWT plateau period, AVAL	[redacted]	[redacted]
Utility gain (%) ALGLU	[redacted]	[redacted]
Utility gain (%), AVAL	[redacted]	[redacted]
Treatment discontinuation rate, ALGLU	[redacted]	[redacted]
Treatment discontinuation rate, AVAL	[redacted]	[redacted]
Adverse event rate, ALGLU	[redacted]	[redacted]
Adverse event rate, AVAL	[redacted]	[redacted]
Mortality HR on ERT	0.41	Lognormal (SD: 0.713)
Mortality HR, wheelchair use	1.30	Lognormal (SD: 0.395)
Mortality HR, non-invasive ventilation use	0.98	Lognormal (SD: 0.355)
Mortality HR, invasive ventilation use	3.72	Lognormal (SD: 1.750)
Disutility, wheelchair use	[redacted]	[redacted]
Disutility, non-invasive ventilation use	[redacted]	[redacted]
Disutility, invasive ventilation use	[redacted]	[redacted]
FVC decline (%/year) after plateau, ALGLU	[redacted]	[redacted]
FVC decline (%/year) after plateau, AVAL	[redacted]	[redacted]
FVC decline (%/year) after plateau, no treatment	1.04	Lognormal (SD: 0.561)
6MWT decline (m/year) after plateau, ALGLU	[redacted]	[redacted]
6MWT decline (m/year) after plateau, AVAL	[redacted]	[redacted]
6MWT decline (m/year) after plateau, no treatment	[redacted]	[redacted]
Mortality, Gompertz shape parameter	0.0819	Multivariate Normal
Mortality, Gompertz scale parameter	4.9216	Multivariate Normal
Wheelchair purchase	1306.48	Gamma (SE: 52.143)
Wheelchair annual	164.00	Gamma (SE: 21.032)
Wheelchair-related one-off cost 1	30000.00	Gamma (SE: 3000)
Wheelchair-related one-off cost 2	669.99	Gamma (SE: 94.454)
Outpatient ventilator assessment	389.63	Gamma (SE: 38.963)
Non-invasive ventilator purchase	4286.16	Gamma (SE: 428.616)

Variable	Base-case value	Distribution
Non-invasive ventilator annual	654.83	Gamma (SE: 65.483)
Invasive ventilator purchase	129295.00	Gamma (SE: 0.1)
Invasive ventilator annual	149025.09	Gamma (SE: 14902.509)

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; FVC, forced vital capacity; HR, hazard ratio; SD, standard deviation; 6MWT, six-minute walk test.

Parameters capturing direct medical and non-medical costs were not varied in sensitivity analysis, as these costs were considered not to be subject to sampling uncertainty.

L.3.7.3 Scenario analyses

A scenario analysis was used to test uncertainty in the duration of the plateau period and progression rates for %FVC and 6MWT. Additional scenarios include varying the time horizon and discount rates, using alternate survival distributions, only considering younger patients, and excluding caregiver disutilities.

L.3.7.4 Sensitivity analyses results

Univariate sensitivity analysis results

Figure 6 presents the results of the one-way sensitivity analysis for LOPD. The majority of the most influential parameters are treatment specific parameters that have been varied independently in this analysis, though this may not be the case in clinical practice. There are 8 parameters that lead to AVAL being more costly than ALGLU, including the rates of treatment discontinuation, mortality HRs for wheelchair use, non-invasive ventilation and ALGLU and the utility gain for ALGLU. These are primarily factors which influence the difference in time on treatment with AVAL compared with ALGLU. If patients die faster in later states or discontinue at different rates, the time on treatment changes, which leads to significant differences in drug costs.

Figure 6: Tornado diagram - LOPD

Abbreviations: AE, adverse event; Alg, alglucosidase alfa; Ava, avalglucosidase alfa; HR, hazard ratio; 6MWT, six-minute walk test.

Scenario analyses

Table 35 presents the results of the scenario analyses for LOPD. AVAL remains dominant in the majority of scenarios and in those where AVAL is both more expensive and more effective, meaning that ALGLU ICERs remain within normally accepted thresholds. When considering the younger age group the total costs increase as patients are spending longer on treatment.

Table 35: Scenario analysis results - LOPD

Scenario	Incremental cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	Dominant
Effect persistence for AVAL equal to ALGLU	[redacted]	[redacted]	Dominant
Effect persistence for AVAL set to 6 years	[redacted]	[redacted]	Dominant
Effect persistence for AVAL set to 4 years	[redacted]	[redacted]	Dominant
Discount rates set to 0%	[redacted]	[redacted]	£16,382
Discount rates set to 1.5%	[redacted]	[redacted]	£5,465
Time horizon set to 15 years	[redacted]	[redacted]	Dominant
Time horizon set to 30 years	[redacted]	[redacted]	Dominant
FVC decline no treatment - 0.832% per year	[redacted]	[redacted]	Dominant
FVC decline no treatment - 1.248% per year	[redacted]	[redacted]	Dominant

Scenario	Incremental cost	Incremental QALYs	ICER
6MWT decline no treatment - 9.528m per year	[redacted]	[redacted]	Dominant
Weibull curve used for mortality	[redacted]	[redacted]	Dominant
Patients below the median age only	[redacted]	[redacted]	£18,062
No caregiver disutility	[redacted]	[redacted]	Dominant
[redacted]	[redacted]	[redacted]	Dominant
Alternative disutilities from DMD	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; QALYS, quality-adjusted life year; 6MWT, six-minute walk test.

Probabilistic sensitivity analysis results

Table 36: LOPD – Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 7: LOPD - cost-effectiveness plane

Abbreviations: LOPD, late-onset Pompe disease; QALYs, quality-adjusted life years.

Figure 8: LOPD - CEAC

Abbreviations: CEAC, cost-effectiveness acceptability curve; LOPD, late-onset Pompe disease.

L.3.8 Subgroup analysis

No subgroup analyses have been considered.

L.4 Cost-effectiveness in IOPD

L.4.1 Economic analysis

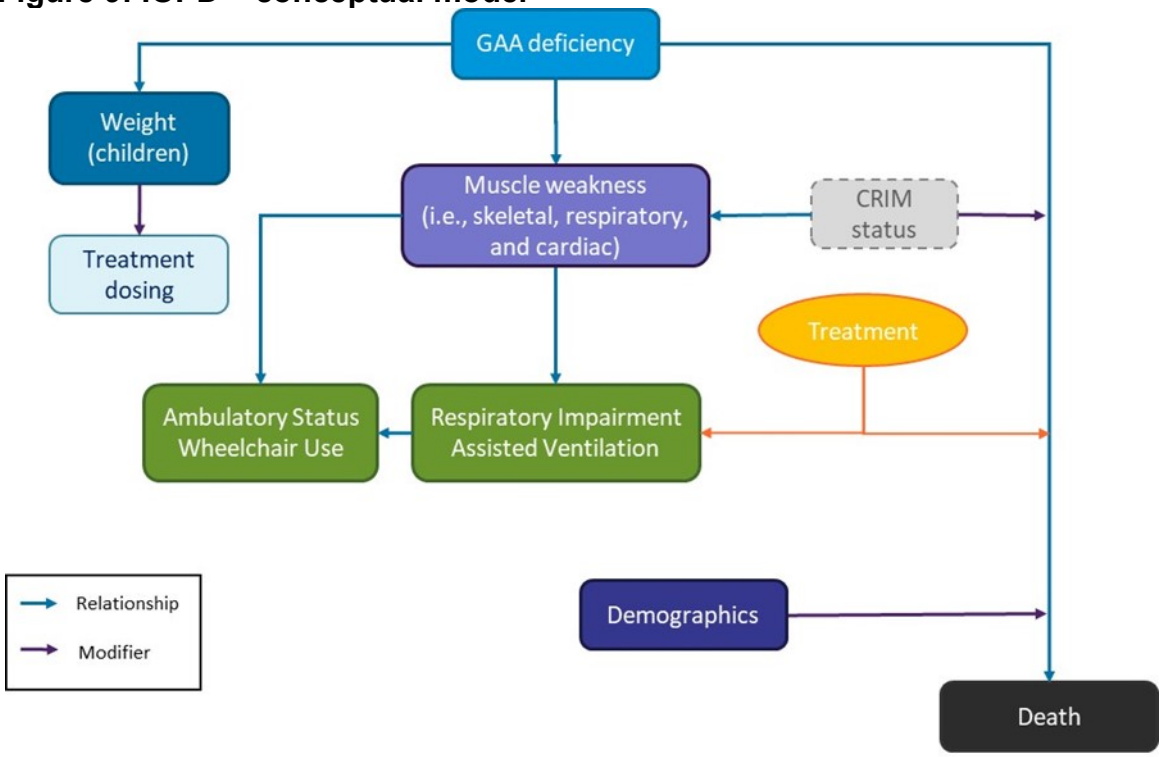
L.4.1.1 Model structure

A conceptual model for IOPD is presented in Figure 9.

IOPD typically manifests during the first weeks of life, with the most common symptoms in untreated patients being cardiomegaly, hypotonia, hypertrophic cardiomyopathy, respiratory distress, and rapidly progressive muscle weakness (particularly of the upper and lower limbs) (9, 67, 68). As the disease progresses, muscle weakness becomes more severe, affecting a patient's ability to breathe, walk and sit unaided (for untreated patients the effect on the heart muscle can severely compromise the patient, or prove fatal). This means that developmental milestones are not met, and patients can experience loss of those already achieved, thus impacting quality of life and increasing management costs. Treatment with ERT aims to resolve the cardiomyopathy, slow down and stall the progression of the disease, improve quality of life and extend ventilation-free survival.

Due to the progressive nature of IOPD, patients will eventually require ventilation and/or a wheelchair, with those requiring ventilation more likely to also require a wheelchair (69). As knowledge and understanding of the disease increases, improvements in treatment administration are prolonging the time to ventilator and wheelchair use (4). Patients who are CRIM-negative have worse clinical outcomes on ERT than patients who are CRIM-positive, experiencing faster disease progression and higher mortality (69-71). Refinement of immunotolerance regimens is improving outcomes, but differences are still observed (72).

Figure 9: IOPD – conceptual model

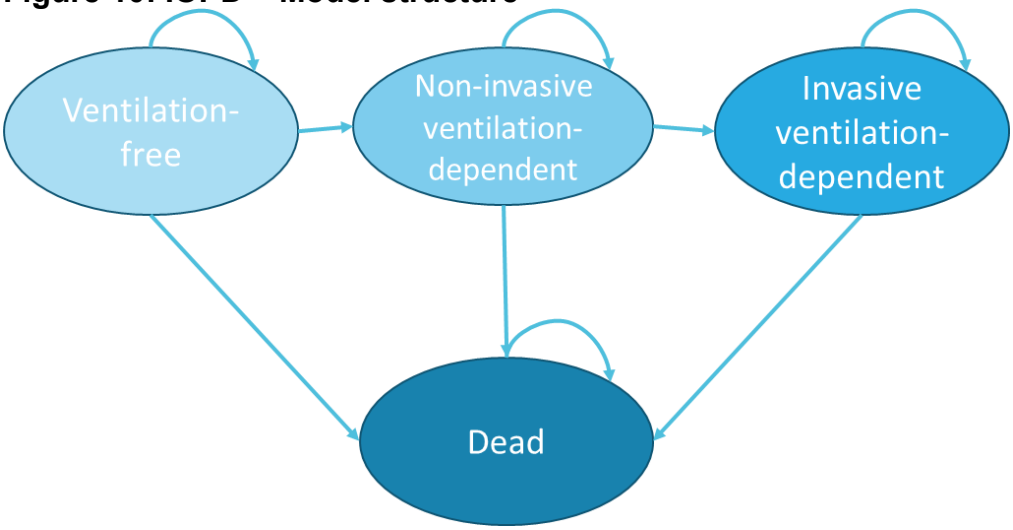


Abbreviations: CRIM, cross-reactive immunological material; GAA, acid α-glucosidase; IOPD, infantile-onset Pompe disease.

The IOPD model is structured as a partitioned survival model with four health states (Figure 10):

- Ventilation-free
- Non-invasive ventilation-dependent
- Invasive ventilation-dependent
- Death.

Figure 10: IOPD – Model structure



Abbreviations: IOPD, infantile-onset Pompe disease.

All patients enter the model in the 'Ventilation-free' health state and receive either ALGLU or AVAL. Over time, they can either progress to a more severe health state or directly to death. Patients remain in this health state until death. Due to the progressive nature of IOPD, individuals are unable to transition to a less severe health state within the model.

Disease progression is defined by OS and ventilation-free survival curves (Section L.4.2.1). The OS curve is used to define patients who progress to the 'Dead' health state over time. The ventilation-free survival (VFS) curve is used to inform the number of patients in the 'Non-invasive ventilation-dependent' health state over time. The invasive ventilation-free survival (IVFS) curve is used to inform the number of patients in the 'Invasive ventilation-dependent' health state over time.

As CRIM-positive and CRIM-negative patients experience disease progression at different rates, separate survival curves are calculated for each group by applying a relative risk (RR) calculated from Broomfield 2015 (69) to the baseline curves (Section L.4.2.1).

In the survival extrapolations, the non-invasive ventilation-free and invasive ventilation-free survival curves are not permitted to exceed the OS curve. Further details of the approach applied are provided in Section L.4.2.1.

Progression-based cohort models are commonly used in health economic analyses to model progressive disease, as they can reflect the nature of the disease by capturing costs and health outcomes as they change between health states. In the case of IOPD, a

progression-based cohort model defined by “the health states described makes the best use of the available data and directly uses VFS, IVFS and OS curves reported in the Kishnani 2009 (73) and Broomfield 2015 (69); these were validated at an advisory board (Appendix M). As membership in each health state is modelled using survival curves, OS is independent of ventilator and wheelchair status.

Unlike LOPD (in which a patient-level model is required; Section L.3.1.1), due to the increased speed of disease progression for patients with IOPD, time-to-ventilation and death can be modelled directly.

L.4.1.2 Health states

The IOPD model has four health states:

- Ventilation-free
- Non-invasive ventilation-dependent
- Invasive ventilation-dependent
- Death.

The modelled health states are intended to capture the progressive nature of IOPD by estimating the costs and outcomes accrued across the health states. Each consecutive health state represents an increased loss of lung function, greater dependence on caregivers and equipment (wheelchair and ventilation use) as the disease progresses, leading to increased costs and reduced QoL. In particular, patients experience a dramatic increase in costs associated with care and decrease in QoL once they become ventilator-dependent.

L.4.1.3 Features of the economic analysis

The key features of the IOPD model not previously reported are presented in Table 37.

Table 37: IOPD – Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	50 years	IOPD is a severe life-limiting condition. Treatment with AVAL is expected to continue for a patient’s life time. Consequently, a time horizon of 50 years was examined in the base case. This time horizon was	NICE reference case (74)

Factor	Chosen values	Justification	Reference
		considered appropriate to balance the desire to capture long term costs and outcomes with the uncertainty of extrapolating outcome data over very long time periods. A scenario was considered which limits the model time horizon to 20 years to account for uncertainty in the long-term extrapolations of outcome	
Discount of 3.5% for costs	3.5%	This is in line with the reference case. A scenario using 1.5% was also considered (17)	
Discount of 3.5% for outcomes	3.5%	This is in line with the reference case. A scenario using 1.5% was also considered	
Perspective (NHS/PSS)	NHS and PSS	This is in line with the reference case.	
Cycle length	Monthly	A cycle length of one month was sufficient to capture meaningful changes in patient utility over the course of the disease	

Abbreviations: IOPD, infantile-onset Pompe disease; NHS, National Health Service; PSS, Personal Social Services.

L.4.1.4 Intervention technology and comparators

The intervention considered is AVAL (20 mg/kg) and the comparator is ALGLU (20 mg/kg), both administered as an IV infusion every other week. [redacted]

The anticipated license for AVAL states that patients may escalate their dose to 40 mg/kg every other week if there is not an adequate clinical response. Though this is not included in the license, patients on ALGLU may also escalate their dose to 40 mg/kg if there is inadequate response to 20 mg/kg based on individual funding requests. The rate of dose escalation with AVAL is unknown, however under the assumption of equivalent efficacy the number of patients requiring dose escalation is not anticipated to differ between arms. Given that there is no difference in anticipated drug acquisition costs, dose escalation is not expected to affect results and has been excluded from the model.

L.4.2 Clinical parameters and variables

Although Mini-COMET showed a benefit of AVAL in IOPD patients, it did not provide adequate long-term data for modelling time-to-event outcomes directly. Therefore, data

were taken from studies of ALGLU and it was conservatively assumed that the benefits of AVAL are the same in this population. Baseline VFS, IVFS and OS data were taken from Broomfield 2015; a retrospective case-note review. Additional data were taken from Kishnani 2009, a long-term extension study to a the 52-week trial of ALGLU. A summary of each study is presented in Table 38.

Table 38: Summary of Broomfield 2015 and Kishnani 2009

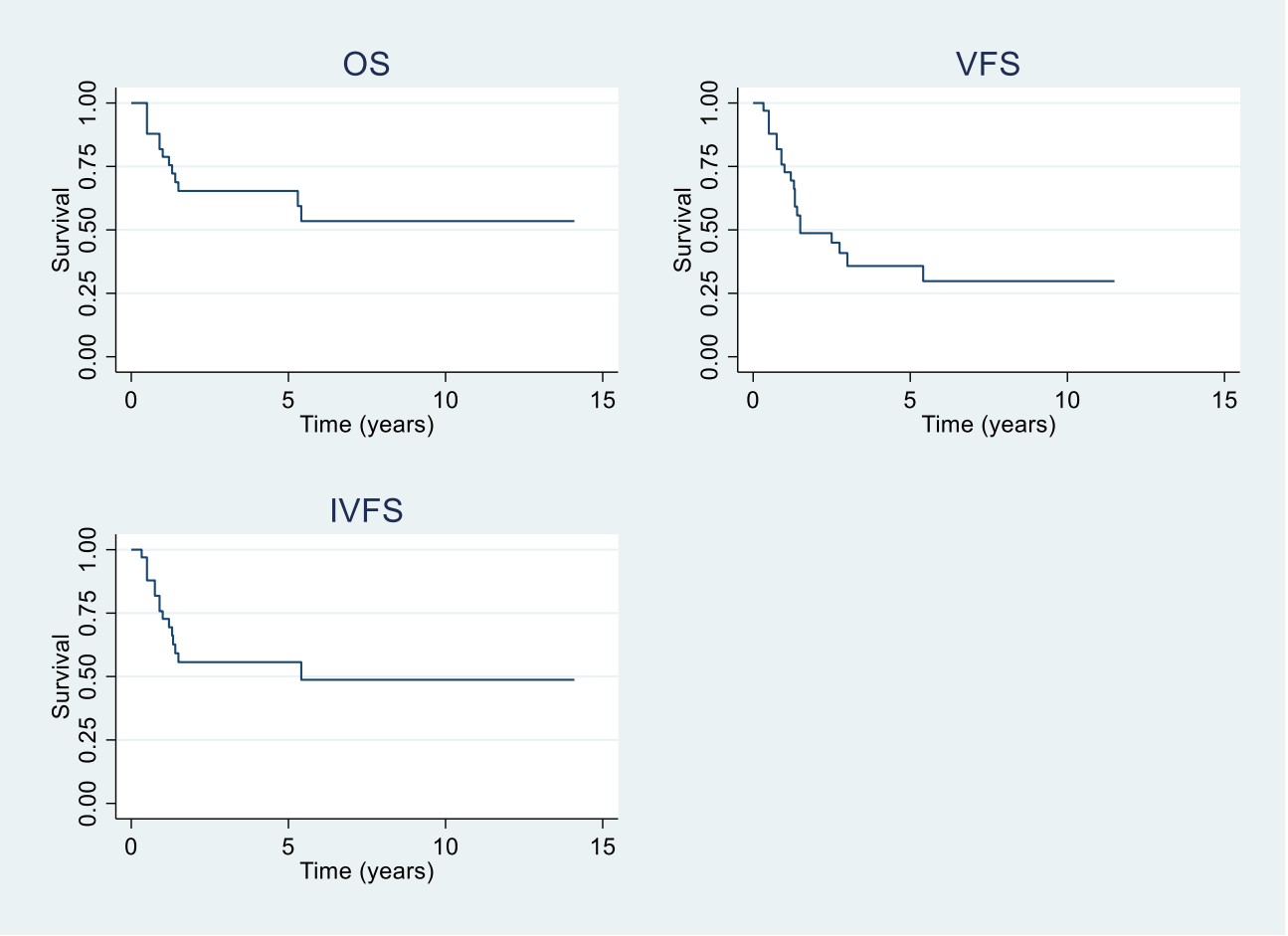
Value	Broomfield 2015 (n=33) (69)	Kishnani 2009 (n=16) (73)
Male %	64%	62%
Median age at ERT initiation, months	4.96 (IQR; 110 months)	5.3 (range; 1.2–6.1)
Median follow-up, months	37.5 (range: 6–165)	–

Abbreviations: ERT, enzyme replacement therapy; IQR, inter-quartile range.

Given substantial differences in the diagnosis and treatment of IOPD between countries, the Broomfield 2015 study of UK routine care was considered the most relevant and therefore used as the base case data source. Furthermore, Broomfield 2015 provides more recent data, a larger sample size and longer follow-up than Kishnani 2009. The latter was utilised in scenario analyses.

Figure 11 shows the Kaplan-Meier (KM) survival curves for VFS, IVFS, and OS from Broomfield 2015 (69).

Figure 11: KM survival functions from Broomfield 2015 (69)



Abbreviations: IVFS, invasive ventilation-free survival; OS, overall survival; VFS, ventilation-free survival.

Time to non-invasive and invasive ventilation use was estimated from parametric fits to KM curves for both VFS and IVFS. Ventilator status did not impact OS, only costs and QALYs. The time reference for the survival curve was age.

To estimate long-term disease progression, it was assumed that time-to-ventilation KM data can be extrapolated over a patient's lifetime. This approach may have some limitations, as data are not mature for all patient subgroups.

To avoid the crossing of survival curves, the model assumed that VFS was the minimum of time to death, time to non-invasive and invasive ventilation. Similarly, the model assumed that IVFS is the minimum of time to death and time to invasive ventilation. Non-invasive VFS was computed as the difference between IVFS and VFS.

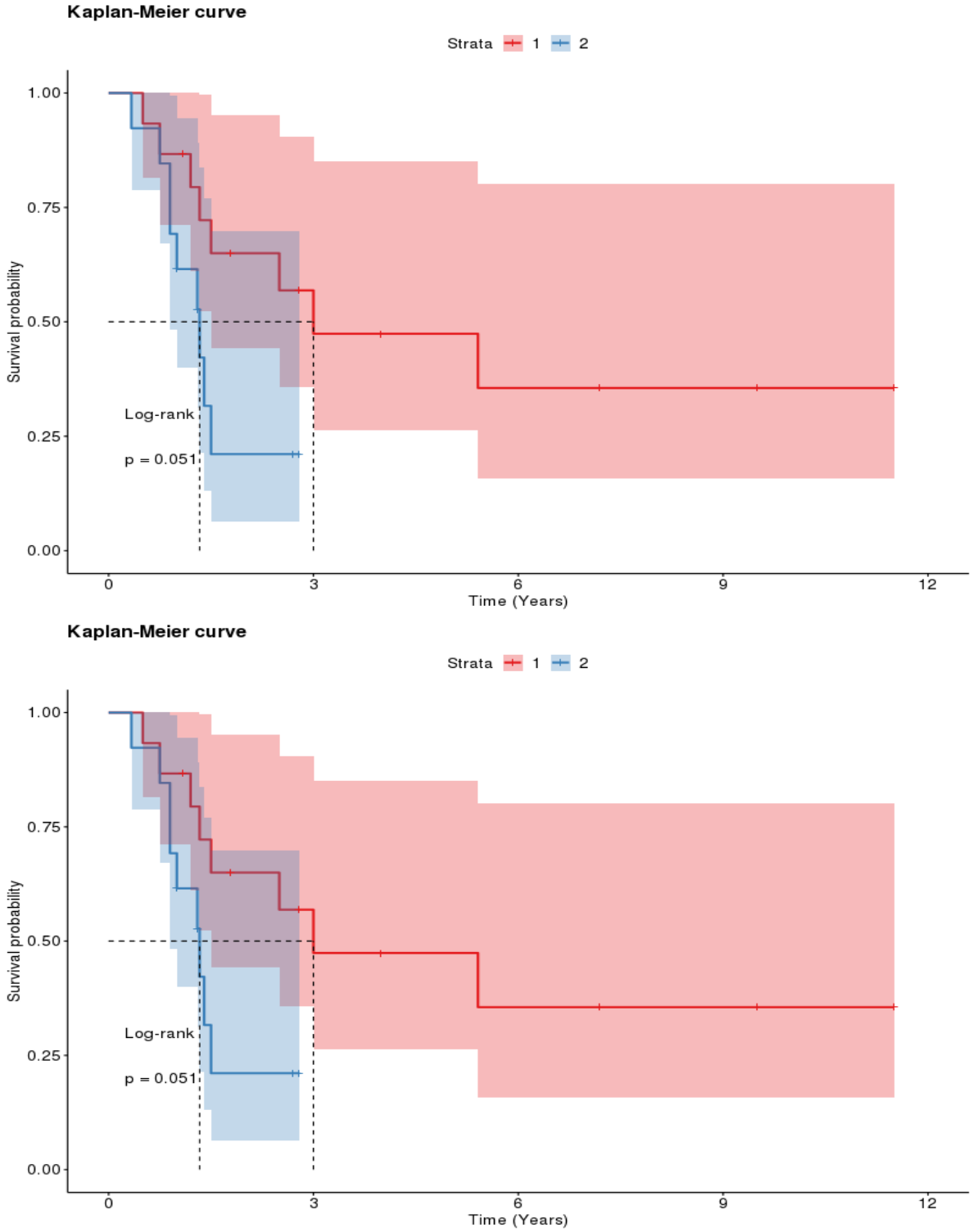
L.4.2.1 CRIM status and assessment of proportional hazards

In the base case, outcomes were modelled separately by CRIM status to account for the significant differences in outcomes observed in each patient group. The proportional hazards assumption was tested with the Schoenfeld test (75), considering only the subset of 28 patients with reported CRIM status. If the proportional hazards assumption appeared reasonable, a common model with CRIM status as a stratum was considered. Otherwise, a separate KM curve was built for each CRIM status-related subset.

Ventilation-free survival

The stratified KM survival curve for VFS with CRIM as a stratum is presented in Figure 12.

Figure 12: KM survival curve for VFS with CRIM as a stratum



NOTE: Stratum 1 is indicative of CRIM-positive, while stratum 2 is CRIM-negative.

The Schoenfeld residual test indicates no violation of the proportional hazards assumption (p=0.85), therefore VFS by CRIM status was modelled using a RR applied to the VFS curve for the IOPD population combined.

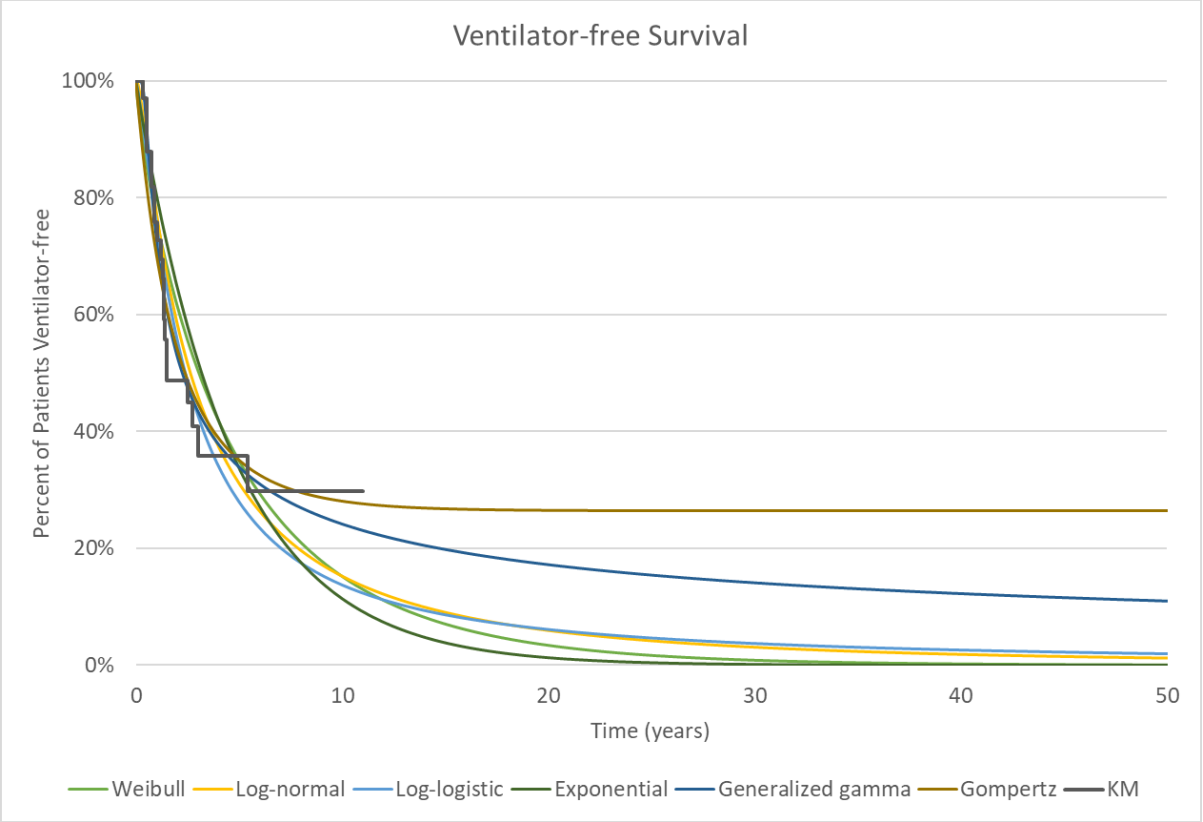
Parametric survival curves of VFS in patients receiving ALGLU were estimated from the patient-level data presented in Broomfield 2015. The Weibull, log-normal, and generalised gamma all provided reasonably good fits to the observed data. While the generalised gamma had the best fit by AIC and BIC (Table 39), the extrapolation for this curve predicts a heavy tail, with many patients surviving without ventilation past the age of 60 years (Figure 13). Thus, this curve lacks face validity, and the improved AIC and BIC were not deemed to be meaningful. The Weibull curve was chosen for the base-case as the most conservative and realistic option (as confirmed by clinical opinion).

Table 39: VFS model parameters

Distribution	Intercept (SE)	Scale (SE)	Shape (SE)	AIC	BIC
Weibull	0.8430	4.7220	–	104	107
Log-normal	0.9720	1.2940	–	97	100
Generalised gamma	–0.1120	0.9110	–2.2400	92	96
Log-logistic	1.2860	2.3990	–	98	101
Exponential	0.2170		–	103	105
Gompertz	0.4108	–0.3087	–	98	101

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; SE, standard error; VFS, ventilation-free survival.

Figure 13: VFS extrapolations



Abbreviations: KM, Kaplan Meier; VFS, ventilation-free survival.

The hazard ratio of an event (starting ventilation or death) due to having a CRIM-positive status or CRIM-negative status were calculated using the following formula:

$$HR_{CRIM+} = \frac{1}{(\%\ CRIM\ positive\ + \%\ CRIM\ negative * HR_{CRIM-\ vs\ CRIM+})}$$

Where $\boldsymbol{HR}_{\boldsymbol{CRIM-\ vs\ CRIM+}}$ is the HR of CRIM-negative vs. CRIM-positive patients calculated from the Cox regression model of CRIM status from data presented in Broomfield 2015 (69) (Table 40). This provides HRs for VFS and being either CRIM-positive or CRIM-negative, which are then applied to the baseline curve, which was fitted to the combined data. Five patients did not have a known CRIM status and were therefore not included in the calculations. The hazard ratios are presented in Table 40.

Table 40: HR calculated from Cox regression, VFS

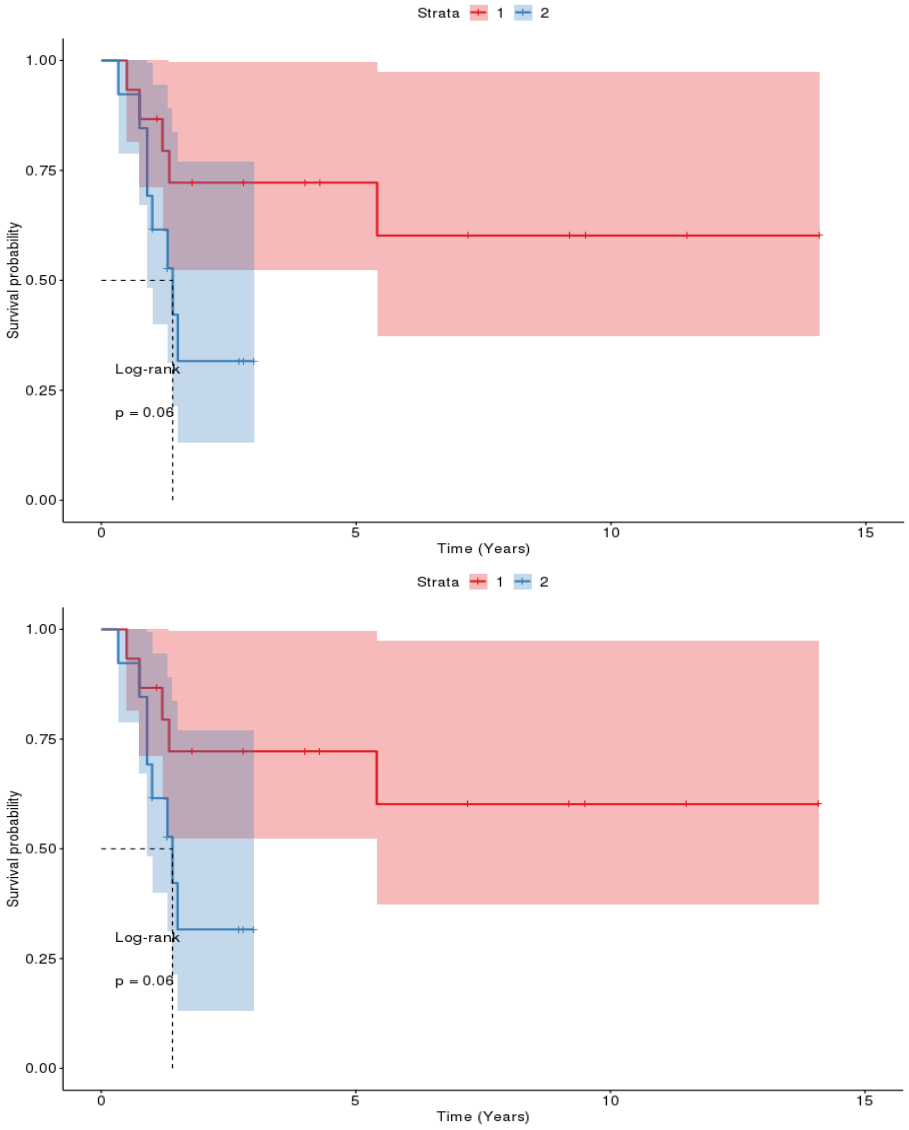
	HR for CRIM status	% of patients	HR used in the model	Reference
CRIM-positive	2.7777	15 (54%)	0.55	Broomfield 2015 (69)
CRIM-negative	0.3636	13 (46%)	1.52	Broomfield 2015 (69)

Abbreviations: CRIM, cross-reactive immunological material; VFS, ventilation-free survival; HR, hazard ratio.

Invasive ventilation-free survival

The stratified KM survival curve and proportional hazards assumption for IVFS with CRIM as a stratum are presented in Figure 14 and Figure 15.

Figure 14: KM survival curve for IVFS with CRIM as a stratum



NOTE: Stratum 1 is indicative of CRIM-positive, while stratum 2 is CRIM-negative.

The Schoenfeld residual test indicates no violation of the proportional hazards assumption (p=0.41), therefore IVFS by CRIM status was modelled using a HR applied to the IVFS curve for the IOPD population combined.

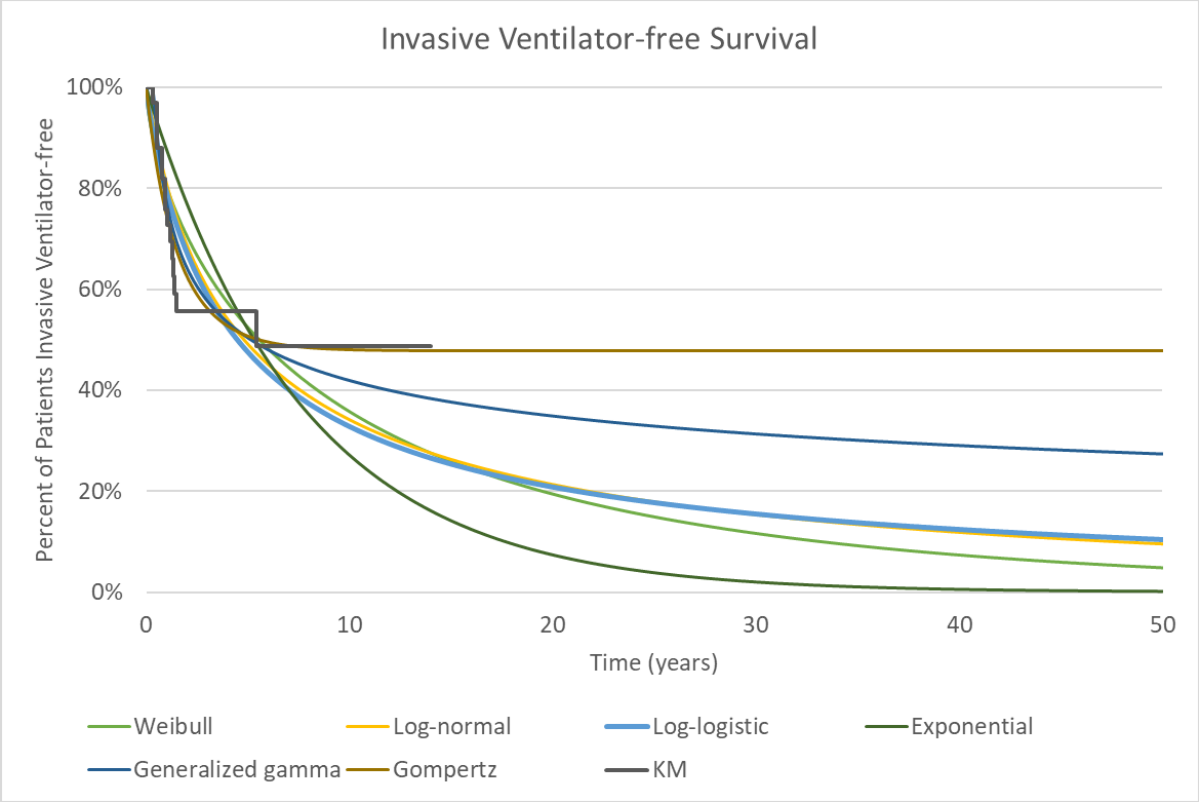
Parametric survival curves of IVFS were estimated based on the patient-level data presented in Broomfield 2015 (69). As in the case of VFS, the Weibull, log-normal, and generalised gamma all provided reasonably good fits to the observed data. Again, as observed for VFS, while the generalised gamma distribution had the best fit by AIC and BIC (Table 41), the extrapolation for this curve predicts a heavy tail, with many patients surviving past the age of 60 years without invasive ventilation (Figure 15). Thus, this curve lacks face validity, and the improved AIC and BIC were not deemed to be meaningful. The Weibull curve was chosen for the base-case analysis as the most conservative and realistic option (as confirmed by clinical opinion), despite having slightly higher AIC and BIC values than the other distributions fitted to the data.

Table 41: IVFS Parameters

Distribution	Intercept (SE)	Scale (SE)	Shape (SE)	AIC	BIC
Weibull	0.6730	9.6050	–	91	94
Log-normal	1.5750	1.7940	–	86	89
Generalised gamma	–0.5240	0.8230	–4.578	77	82
Log-logistic	0.8940	4.4880	–	88	91
Exponential	0.1303	–	–	93	95
Gompertz	0.3710	–0.5040	–	82	85

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; IVFS, invasive ventilation-free survival; SE, standard error.

Figure 15: IVFS curve



Abbreviations: IVFS, invasive ventilation-free survival; KM, Kaplan Meier.

HRs by CRIM status for IVFS was calculated using the same method as for VFS. The hazard ratios are presented in Table 42.

Table 42: HR calculated from Cox regression, IVFS

	HR for CRIM status	% of patients	HR used in the model	Reference
CRIM-positive	0.33	15 (54%)	0.51	Broomfield 2015 (69)
CRIM-negative	3.03	13 (46%)	1.56	Broomfield 2015 (69)

Abbreviations: CRIM, cross-reactive immunological material; VFS, ventilation-free survival; HR, hazard ratio.

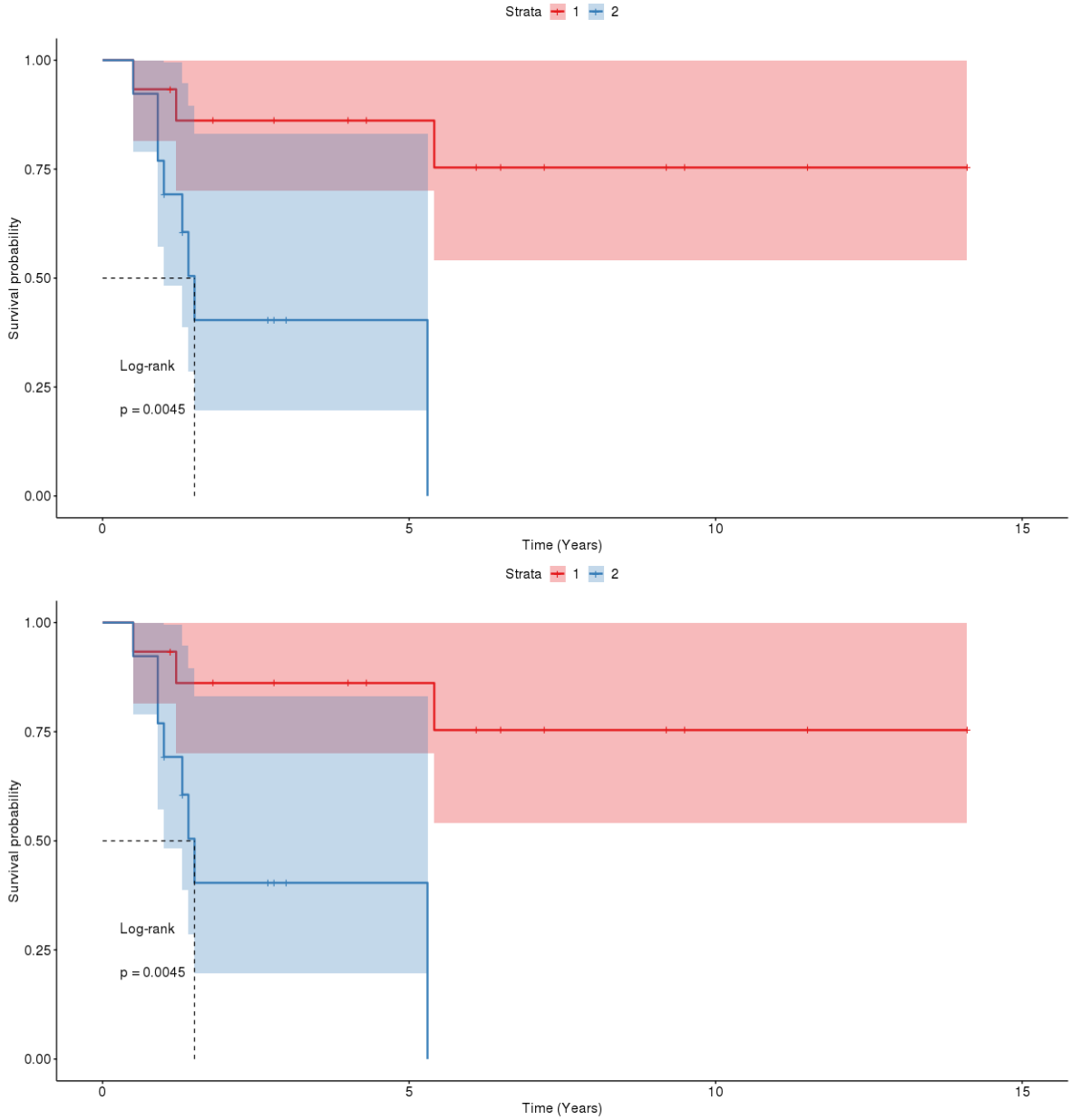
Mortality

Overall survival was modelled using parametric survival extrapolations of the ALGLU OS KM data presented in the Broomfield 2015 study (69). While data from the study does allow differentiation between ventilation and death events, no deaths were observed in ventilated patients and mortality rates by ventilation status cannot be obtained. Overall survival was modelled separately to VFS, IVSF and therefore, it was assumed that OS was independent of ventilation status. The time reference for the survival curve is age. To estimate long-term

survival, it was assumed that time to death KM data can be extrapolated over a patient's lifetime. However, data presented in Broomfield 2015 are immature and therefore the long-term extrapolations used in the model are uncertain.

The stratified KM survival curve for OS with CRIM as a stratum and corresponding proportional hazards test results are presented in Figure 16 and Figure 17, respectively. The Schoenfeld test indicated the proportional hazards assumption may not hold for OS, and therefore, subsets of CRIM-positive and CRIM-negative patients were analysed separately and considered as such for parametric analyses.

Figure 16: KM survival curve for OS with CRIM as a stratum



NOTE: Stratum 1 is indicative of CRIM-positive, while stratum 2 is CRIM-negative.

CRIM status

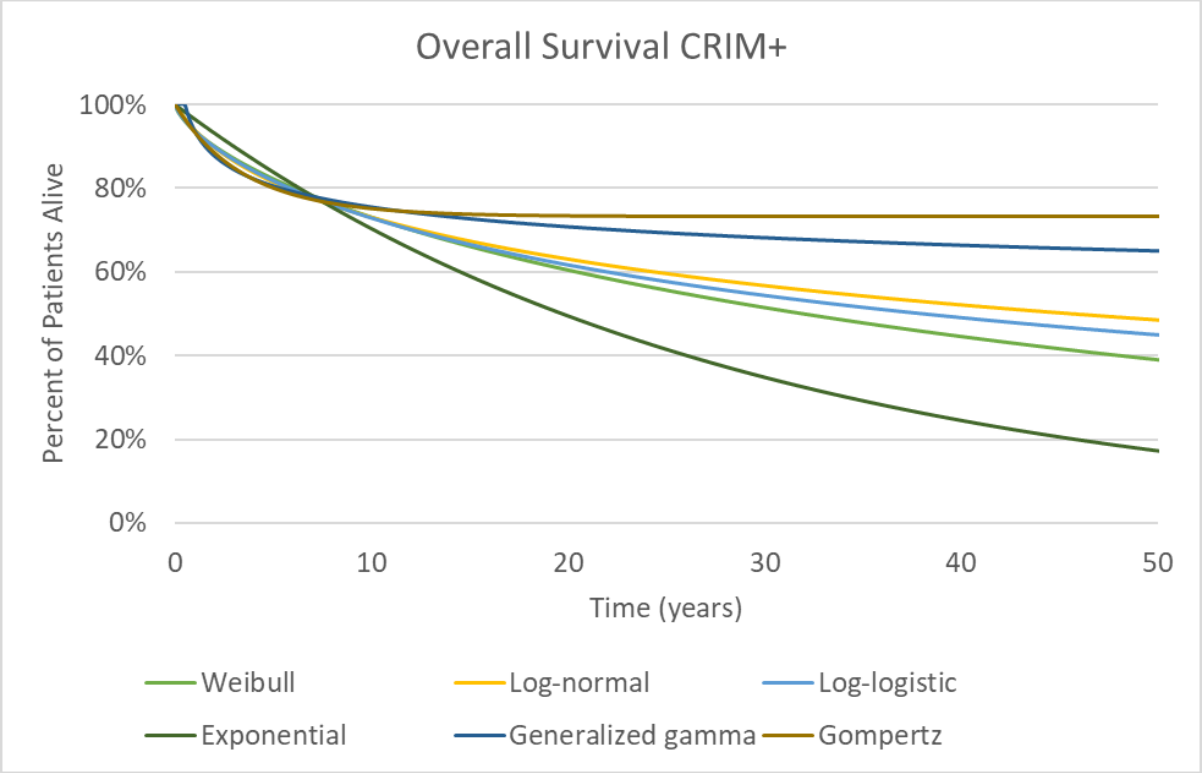
The Weibull, log-normal, and generalised gamma all provided good fits to the observed data. However, for both CRIM-positive and CRIM-negative populations the generalised gamma produces a clinically implausible curve with high survival at 100 years in CRIM-positive patients, lacking face validity. The Weibull curve was chosen for the base-case as the most conservative option for both populations, though the curve for CRIM-positive patients shows a significant number of patients surviving to age 100 years. Discussions with clinicians indicated that there was a lack of experience treating patients beyond 25 years and that the long-term outcomes for these patients were being explored. The survival model parameters for CRIM-positive and CRIM-negative patients are presented in Table 43 and Table 44, respectively. Overall survival extrapolations for CRIM-positive and CRIM-negative patients are presented in Figure 17 and Figure 18, respectively.

Table 43: OS parameters for distributions fitted to data from Broomfield 2015 (69), CRIM-positive patients

Distribution	Intercept (SE)	Scale (SE)	Shape (SE)	AIC	BIC
Weibull	0.6830	54.9040	–	29	31
Log-normal	3.8180	2.4670	–	29	30
Generalized Gamma	–0.6580	0.3780	–28.5000	29	31
Log-logistic	0.7410	37.9860	–	29	31
Exponential	0.0352	–	–	28	29
Gompertz	0.0778	–0.2507	–	29	30

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CRIM, cross-reactive immunological material; IVFS, invasive ventilation-free survival; SE, standard error.

Figure 17: OS extrapolations fitted to Broomfield 2015 data CRIM-positive patients



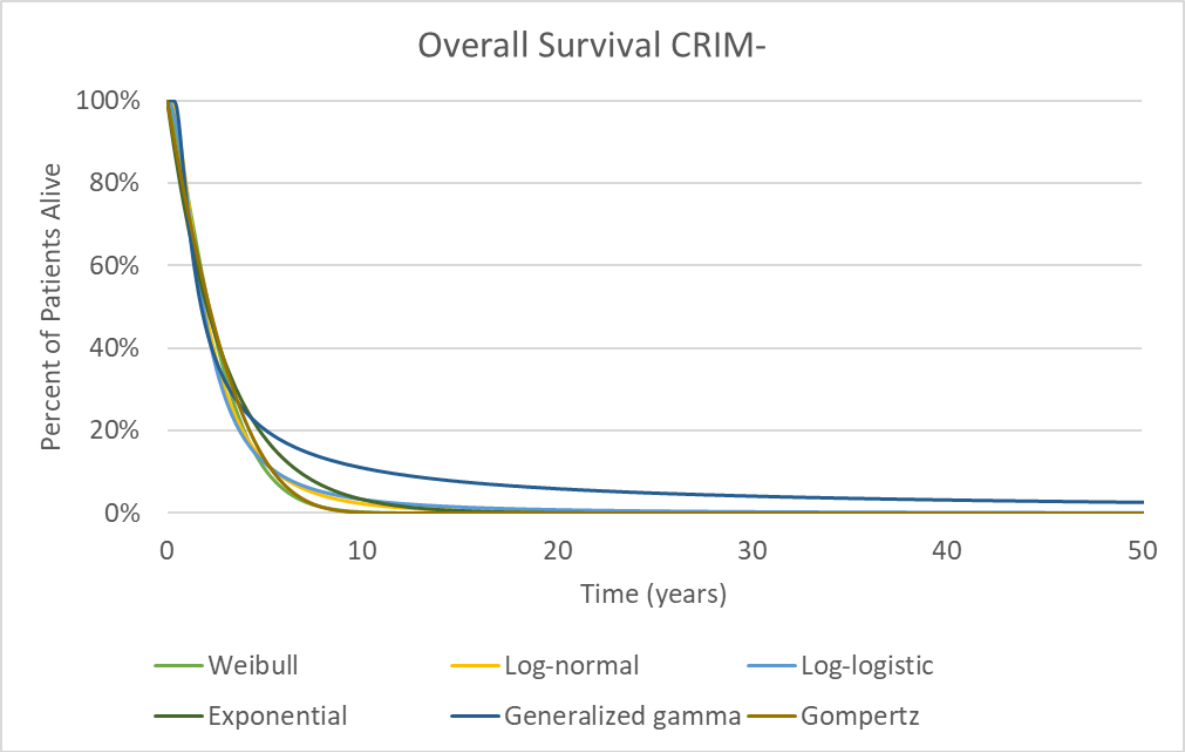
Abbreviations: CRIM, cross-reactive immunological material.

Table 44: OS parameters, CRIM-negative patients (69)

Distribution	Intercept (SE)	Scale (SE)	Shape (SE)	AIC	BIC
Weibull	1.3720	2.7900	–	36	37
Log-normal	0.6580	0.8260	–	34	35
Generalized Gamma	0.0980	0.6990	–1.613	35	37
Log-logistic	1.9820	1.8480	–	35	36
Exponential	0.0352	–	–	35	36
Gompertz	0.0778	–0.2507	–	37	38

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CRIM, cross-reactive immunological material; IVFS, invasive ventilation-free survival; SE, standard error.

Figure 18: OS extrapolations fitted to Broomfield 2015 data CRIM-negative patients (69)



Abbreviations: CRIM, cross-reactive immunological material.

L.4.2.2 Wheelchair use

Wheelchair use was modelled using the percentage of patients who were not ambulatory in Broomfield 2015 (69). This variable was stratified by age and ventilation status as shown in Table 45. Ambulatory infants were assumed to become ambulatory at 18 months of age, based on the mean age of onset of ambulation observed in the Broomfield 2015 study (69). Wheelchair use in the model was associated with an impact on both costs and QALYs.

In Broomfield 2015 no IVF dependent patients were ambulatory and one non-invasive ventilation-dependent patient who was initially ambulatory subsequently lost the ability to walk. Therefore, the model assumed that:

- For those who are not ventilation-dependent, 30% were able to walk and maintain ambulation. It also assumed that for those who were non-invasive ventilation-dependent, 30% were ambulatory as infants, falling to 27% in children and adults.
- None of the invasive ventilation-dependent patients were ambulatory and the model assumes all invasive ventilation-dependent patients are non-ambulatory.

Clinical opinion gathered at the global advisory board (Appendix N) confirmed that approximately half of young patients who do not require ventilatory support require ambulatory assistance, and that it was appropriate to assume that invasively ventilated patients would not be ambulatory.

Table 45: Proportion of patients who achieve ambulation by health state based on Broomfield 2015 (69)

Health state	Infants (0-2 years old)	Children (2-16 years old)	Adults (16+ years old)
Not ventilation-dependent	30.0%	27.0%	27.0%
Non-invasive ventilation-dependent	30.0%	27.0%	27.0%
Invasive ventilation-dependent	0.0%	0.0%	0.0%

To allow the calculation of costs and QALYs related to the use of a wheelchair, the model assumed that non-ambulatory status is equivalent to wheelchair-dependence. Thus, the model estimated the proportion of the cohort in each of the health states. If the cohort was younger than the minimum age to become ambulatory, these proportions were set to zero.

The proportion of incident wheelchair-dependent patients was also used to calculate one-off costs related to wheelchair equipment.

L.4.2.3 Extrapolation of costs and clinical outcomes

Ventilation-free survival, IVFS and OS were extrapolated from KM curves for ALGLU from Broomfield 2015 (69) using standard survival analysis techniques in line with NICE Decision Support Unit Technical Support Document 14. Further details of each extrapolation are described in Sections L.4.2.1 and L.4.2.2.

L.4.2.4 Adverse events

No serious treatment-related adverse events were observed in the Mini-COMET trial. This is consistent with previous trials for ALGLU, with both Kishnani 2007 (76) and Nicolino 2009 (77) reporting that though the rate of infusion attributed reactions was high, events were managed by slowing or interrupting infusions and all patients recovered without sequalae and none led to treatment discontinuation. No other treatment related AEs were reported and therefore these were excluded from this analysis.

L.4.3 Measurement and valuation of health effects

L.4.3.1 Health-related quality of life data from clinical trials

Registry data were not available to inform the IOPD model, as the SF-36 was only collected in adults.

It was concluded that the PedsQL and pain VAS scales from Mini-COMET cannot be used to produce utility values suitable for use in the economic model. While the PedsQL can be mapped to the EQ-5D, given the small patient numbers in the clinical trial and lack of coverage across health states, it was considered more suitable to use utility values from the literature (18, 133).

L.4.3.2 Health-related quality-of-life studies

See Section L.3.3.3.

L.4.3.3 Adverse reactions

Adverse reactions have not been included in the IOPD cost-effectiveness model.

L.4.3.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Patients are assigned a utility value based on their age and current disability status related to ventilation-dependence. Health state utility values are derived from Simon 2019 (36). Simon 2019 estimated health state utility values for three rare diseases, including Pompe, in a stated-preference survey using a time trade-off approach. The survey describes health states associated with Pompe disease, without distinguishing explicitly between LOPD or IOPD. Health state utilities were elicited for Pompe disease for mild, moderate and severe onset of symptoms in infancy (6 months old), childhood (8 years old) and adulthood (≥18 years old). Study participants were a representative sample of US adults.

It has been assumed that the mild, moderate and severe symptoms health states in the paper can be mapped to the not ventilation-dependent, non-invasive ventilation dependent and invasive ventilation-dependent health states in the model. Similarly, it is assumed values for 6-month-olds are representative of infants, 8 year olds of children and ≥ 18 years olds adults in the model.

As no data were available on infants with mild disease in Simon 2019, the utility value for infants in the “not ventilation-dependent” health state was calculated applying the multiplier between not ventilation-dependent and invasive ventilation-dependent as children (1.71) to generate a value of 0.684. The utility value for children (8 years old) with mild symptoms was below that for children with severe symptoms and thus this value was discarded, and the average of the mild and severe states was used in its place.

Health state utility values used in the model are presented in Table 46.

Table 46: Summary of IOPD utility values used in the cost-effectiveness analysis

State	Utility value	Confidence interval	Source	Justification
Not ventilation-dependent: Infant (0-2 years)	0.684	NR	Simon 2019 (36)	No trial or registry data were available for IOPD. The values presented here were deemed the most suitable values obtained from the literature.
Non-invasive ventilation-dependent: Infant (0-2 years)	0.542	NR		
Invasive ventilation-dependent: Infant (0-2 years)	0.399	0.341, 0.457		
Not ventilation-dependent: Child (2-16 years)	0.799	0.750, 0.844		
Non-invasive ventilation-dependent: Child (2-16 years)	0.633	NR		
Invasive ventilation-dependent: Child (2-16 years)	0.466	0.407, 0.525		
Not ventilation-dependent: Adult (≥16 years)	0.853	0.811, 0.892		
Non-invasive ventilation-dependent: Adult (≥16 years)	0.683	0.634, 0.729		
Invasive ventilation-dependent: Adult (≥16 years)	0.536	0.480, 0.594		

Abbreviations: NR, not reported.

The caregiver disutilities applied in the model were also taken from Simon 2019 (36). The paper reports disutilities for caregivers of infants with severe symptoms and children with mild, moderate and severe symptoms. The reported disutility for moderate symptoms was greater than that for severe symptoms and was excluded from the analysis. For children, it

was assumed not ventilation-dependent was equivalent to mild symptoms and invasive ventilation-dependent was equivalent to moderate symptoms, with the non-invasive ventilation dependent state being the midpoint of these values. For infants, the severe symptoms value was applied to the invasive ventilation state, and disutilities for the other states were calculated by assuming the same relative impact as was seen in children. No caregiver disutility was included for adults. All patients were assumed to have 1.72 caregivers.

Table 47: Summary of caregiver disutilities in the IOPD model

Health state	Infants (0-2 years old)	Children (2-16 years old)	Adults (16+ years old)
Not ventilation-dependent	–0.099	–0.072	0.000
Non-invasive ventilation-dependent	–0.139	–0.102	0.000
Invasive ventilation-dependent	–0.180	–0.131	0.000

L.4.4 Cost and healthcare resource use identification, measurement and valuation

L.4.4.1 Costs and resource use for intervention and comparators

List price for the technology

The list price for AVAL is [redacted] per 100 mg vial. AVAL is a weight-based treatment, with a dose of 20 mg/kg. The price per kg at 20 mg/kg is [redacted].

Acquisition and administration costs

AVAL and ALGLU are administered intravenously at a dose of 20 mg/kg qow. Acquisition costs (AVAL PAS price) and dosing information for AVAL and ALGLU are presented in Table 48. It was assumed that patients are 100% compliant with both treatments.

Table 48: IOPD, acquisition costs

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: after 3 months	£356.06	50 mg	1 vial	20 mg/kg	2	100%

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease.

In total, 26 administrations per year were modelled for AVAL. A total of 32 administrations were modelled in Year 1 for ALGLU to capture the additional doses in the first 12 weeks, followed by 26 doses in subsequent years.

As both AVAL and ALGLU use weight-based dosing, the model determined the patient's weight to calculate the total dose required for each administration. For patients <18 years, polynomial functions were fitted to weight-by-age data for girls and boys. Since the weight-by-age curves represent children in the general population at the 50th percentile, the weight for Pompe patients was adjusted using z-scores for boys and girls according to the following formula:

$$Weight_{Pompe}(age) = Weight_{50thPerc}(age) + (z - score) * SD$$

where $Weight_{Pompe}(age)$ is the Pompe patient's weight as a function of age, $Weight_{50thPerc}(age)$ is the 50th percentile weight as a function of age for the general population, and SD is the standard deviation. The SD was calculated for each age assuming a normal distribution by averaging the difference between the 15.9th percentile and the 50th percentile and the 84.1st percentile and the 50th percentile (one SD is approximately 34.1% from the mean). For patients ≥18 years, a weight equal to that of the general population was assumed and it remained constant until death. In line with clinical advice, the model did not consider vial wastage.

A cost of administration was applied to each dose of ALGLU and AVAL received by patients in the model. It was assumed that home-based nurse-led or semi-independent administrations incur the cost of [redacted]. Based on the draft SmPC, treatment administration takes 3.7 hours. Administration costs for infusions administered with a nurse were calculated assuming the cost per hour of an at-home nurse or outpatient visit, multiplied by the infusion time.

The first 3 administrations for both ALGLU and AVAL were assumed to take place in a hospital outpatient setting at the initiation of treatment. A summary of administration costs and the proportion of patients receiving ERT in each setting is presented Table 49, and the nurse time required for reconstitution and infusion was 4.7 hours for AVAL and 5.2 hours for ALGLU. For patients that administer at home either independently or semi-independently

the required nurse time for reconstitution was 45–60 minutes for AVAL and 75–90 minutes for ALGLU (52). The day case administration unit cost was sourced from the 2021/22 National Tariff Payment System (78) and was assumed as equal to the cost of delivering simple parenteral chemotherapy at first attendance (SB12Z).

An overview of the cost and distribution data applied to each treatment is presented in Table 19 and Table 20.

Table 49: IOPD, ERT administration costs for different settings

Category	Unit cost: AVAL	Unit cost: ALGLU	Source
At home: independent or semi-independent	£40.00	£60.00	Unit Costs of Health and Social Care, PSSRU (2020) (51) 2021/22 National Tariff Payment System (78)
At home: with nurse	£188.00	£208.00	
Outpatient	£165.00	£165.00	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 50: IOPD, ERT administration patient distribution across different settings

Category	% patients on AVAL	% patients on ALGLU	Source
At home: independent or semi-independent	[redacted]	[redacted]	Assumption
At home: with nurse	[redacted]	[redacted]	
Outpatient	[redacted]	[redacted]	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease.

Monitoring costs

The only treatment-related monitoring costs were those associated with antibody testing which were applied four times a year in the first two years of treatment, and then twice a year thereafter. A unit cost of £6.58 was applied (informed by the NHS reference costs 2019/20, code DAPS06 (53)).

L.4.4.2 Health state unit costs and resource use

Ventilation-related costs

Ventilation-related costs were applied as a one-off cost at the time of requiring ventilation, and as an annual ongoing cost (Table 51). Data were further divided into non-invasive ventilation (paediatric and adult) and invasive ventilation costs. Costs for invasive

ventilation were assumed to be the same for paediatric and adult patients due to insufficient data. Cost data were inflated to 2020 values where necessary.

Table 51: IOPD – Ventilation costs

Description	One-off cost	Annual cost	Source
Ventilation			
Non-invasive ventilation: home, paediatric	–	£22,729.26	Noyes 2006 (56)
Non-invasive ventilation: home, adults	£4,286.16	£654.83	Dretzke 2015 (55)
Invasive ventilation: home	£129,295	£149,025.09	Noyes 2006 (56)
Ventilation-related costs			
Outpatient assessment, paediatric	£329.14	–	Dretzke 2015 (55)
Outpatient assessment, adults	£389.63	–	NHS reference costs (2019/20) (53)

Abbreviations: IOPD, infantile-onset Pompe disease; NHS, National Health Service.

The one-off cost associated with invasive ventilation represents a 4-month stay for patients going on to invasive ventilation. Clinical experts estimated that patients would require a 4–6-month inpatient stay. The one-off cost associated with invasive ventilation therefore assumes patients spend 4 months in a high-dependency unit at a cost of £800 per day (56). This cost has been inflated from 2006 using the PSSRU pay and prices index.

Wheelchair-related costs

A one-off cost of a wheelchair and an annual wheelchair maintenance cost was captured (sourced from the 2019/20 NHS reference costs (53)) (Table 52). The annual cost includes the cost of a replacement wheelchair every 3 years for children and every 5 years for adults. A one-off cost for home adjustments, equal to the maximum disability facilities grant in England, and a hoist were also included.

Table 52: IOPD – Wheelchair costs

Description	One-off cost	Annual cost	Source
Wheelchair (powered)			
Paediatric	£1,375.63	£645.89	NHS reference costs WC08 and WC10 (2019/20) (53)
Adult	£1,306.48	£425.29	
Wheelchair-related cost			
Home adjustments	£30,000.00	–	Maximum disability facilities grant in England (2020) (58)
Hoist	£826.48	–	NRS Healthcare, sunlift mini mobile hoist (79)

Abbreviations: IOPD, infantile-onset Pompe disease; NHS, National Health Service; NRS, Nottingham rehab limited.

Disease-related monitoring and management

The model grouped the disease-related resource use costs into monitoring and management categories. Disease-related monitoring included pulmonary function, respiratory muscle strength, muscle strength, and sleep study. Within the management category, the model reported outpatient visits (day case, general practitioner visits), other provider visits (nurse visit, therapy, home aid visit), gastrostomy, port-a-cath, and hospitalisation costs as separate line items. Disease monitoring and management costs for infants and children and adults are presented in Table 54. Disease related costs were taken from an analysis of the CPRD (Section L.3.4.2) and are presented in Table 53. Costs were available only for the IOPD group as a whole and are assumed not to differ by health state.

Table 53: Disease-related costs from the CPRD analysis

Cost category	Cost per patient year
Elective and day-case	£798.42
Non-elective	£4,701.84
ITU	£3,083.14
Outpatient	£223.58
A&E	£90.99
Primary care consultations	£511.49
GP prescribing	£3,678.75
Total	**£13,088**

Abbreviations: A&E, accident and emergency; GP, general practitioner; ITU, intensive treatment unit.

Table 54: IOPD – monitoring and management costs associated with the health states in the cost-effectiveness model

Description	Unit Cost – Infants/children	Unit Cost – Adults	Not ventilation-dependent	Non-invasive ventilation-dependent	Invasive ventilation-dependent	Source
			Frequency			
Metabolic consultant	£448	£448	2	2	2	NHS reference costs (2019/20); EPOC guidelines (53)
Respiratory consultant	£220	£164	2	2	2	NHS reference costs (2019/20); EPOC guidelines (53)
Cardiologist	£172	£151	2	2	2	NHS reference costs (2019/20); EPOC guidelines (53)
Physiotherapy	£54	£54	2	2	2	NHS reference costs (2019/20) (53)
Sleep study	£309	£309	0.5	0.5	0.5	NHS reference costs (2019/20); EPOC guidelines (53)

[i]Frequencies are from the CPRD/HES analysis, assuming the same ratio of events between ventilated-/non-ventilated patients as observed in LOPD.
Abbreviations: GP, general practitioner; IOPD, infantile-onset Pompe disease; NHS, national health service; PSSRU, Personal Social Services Research Unit; EPOC, European Pompe Consortium.

L.4.4.3 Adverse event costs

No adverse events have been included in the model.

L.4.4.4 Indirect costs

As in LOPD, there is little quantifiable data on the indirect costs experienced by patients and carers in IOPD and a recent systemic review found no studies on the humanistic burden of IOPD (80). However, this burden can still be significant. Section B.1.3.6 summarises the burden of disease and highlights the impact that IOPD can have on education, mental health, and caregivers. Children with IOPD will require specialist schools and the disease can impact on their academic performance (81).

The impact on caregivers can also be high, impacting on both their physical and mental health as well as their ability to work. This is particularly pronounced when patients require invasive ventilation. One mother stated:

- "*As a single mother, it is very, very hard. 'I have' physical exhaustion, I was quite healthy before"* (48)

As with LOPD, though indirect costs have not been incorporated in the model, there is a significant burden of disease associated with home adaptations, transport needs and reduction in time at school or working that increases for both the patients and their carers as the disease progresses. The disease has a profound impact on physical and mental health of both patients and their carers.

L.4.5 Summary of base-case analysis inputs and assumptions

L.4.5.1 Summary of base-case analysis inputs

A summary of variables applied in the IOPD model is presented in Table 55.

Table 55: IOPD – Summary of variables applied in the cost-effectiveness model

Variable	Value	Source
Discount rate (outcomes)	0.035	NICE 2013 (17)
Discount rate (costs)	0.035	
Time horizon	50 years	
VFS, Weibull, shape parameter	0.843	Broomfield 2015 (69)
VFS, Weibull, scale parameter	4.722	

Variable	Value	Source
RR, CRIM+, VFS	0.55	
RR, CRIM-, VFS	1.52	
IVFS, Log-normal, Log mean	1.575	
IVFS, Log-normal, log SD	1.794	
RR, CRIM+, IVFS	0.51	
RR, CRIM-, IVFS	1.56	
Percent ambulatory, not ventilation-dependent, infants	30%	
Percent ambulatory, non-invasive ventilation-dependent, infants	30%	
Percent ambulatory, invasive ventilation-dependent, infants	0%	
Percent ambulatory, not ventilation-dependent, children	27%	
Percent ambulatory, non-invasive ventilation-dependent, children	27%	
Percent ambulatory, invasive ventilation-dependent, children	0%	
Percent ambulatory, not ventilation-dependent, adults	27%	
Percent ambulatory, non-invasive ventilation-dependent, adults	27%	
Percent ambulatory, invasive ventilation-dependent, adults	0%	
Age patients become ambulatory	18 months	Assumption
OS, CRIM-positive, Weibull, shape parameter	0.683	Broomfield 2015 (69)
OS, CRIM-positive, Weibull, scale parameter	54.904	
OS, CRIM-negative, Weibull, shape parameter	1.372	
OS, CRIM-negative, Weibull, scale parameter	2.790	
ALGLU, unit cost	£356.06	MIMS (82)
AVAL, unit cost	[redacted]	Sanofi Data on File
ALGLU, unit strength	50 mg	MIMS
AVAL, unit strength	100 mg	Mini-COMET trial protocol (83)
ALGLU, doses per 4 weeks	2	ALGLU SmPC (64)
AVAL, doses per 4 weeks	2	Mini-COMET trial protocol
ALGLU, initial period dose	20 mg	ALGLU SmPC (64)
AVAL, initial period dose	20 mg	Mini-COMET trial protocol
ALGLU, subsequent period dose	20 mg	ALGLU SmPC (64)
AVAL, subsequent period dose	20 mg	Mini-COMET trial protocol

Variable	Value	Source
ALGLU, compliance	100%	Assumption
AVAL, compliance	100%	Assumption
Cost – semi-independent administration, AVAL	£40.00	Unit Costs of Health and Social Care, PSSRU (2020) (51)
Cost – administration with nurse at home , AVAL	£188.00	Unit Costs of Health and Social Care, PSSRU (2020) (51)
Cost – semi-independent administration, AVAL	£60.00	Unit Costs of Health and Social Care, PSSRU (2020) (51)
Cost – administration with nurse at home , AVAL	£208.00	Unit Costs of Health and Social Care, PSSRU (2020) (51)
Cost – administration, outpatient, children	£165.00	2021/22 National Tariff Payment System (78)
Proportion of patients, self-administration, infants, ALGLU, infants	[redacted]	Assumption
Proportion of patients, self-administration, infants, AVAL, infants	[redacted]	Assumption
Proportion of patients, home administration with nurse, infants, ALGLU, infants	[redacted]	Assumption
Proportion of patients, home administration with nurse administration, infants, AVAL, infants	[redacted]	Assumption
Proportion of patients, outpatient administration, infants, ALGLU, infants	[redacted]	Assumption
Proportion of patients, outpatient administration, infants, AVAL, infants	[redacted]	Assumption
Proportion of patients, self-administration, infants, ALGLU, children	[redacted]	Assumption
Proportion of patients, self-administration, infants, AVAL, children	[redacted]	Assumption
Proportion of patients, home administration with nurse, infants, ALGLU, children	[redacted]	Assumption
Proportion of patients, home administration with nurse administration, infants, AVAL, children	[redacted]	Assumption
Proportion of patients, outpatient administration, infants, ALGLU, children	[redacted]	Assumption
Proportion of patients, outpatient administration, infants, AVAL, children	[redacted]	Assumption

Variable	Value	Source
Proportion of patients, self-administration, infants, ALGLU, adults	[redacted]	Assumption
Proportion of patients, self-administration, infants, AVAL, adults	[redacted]	Assumption
Proportion of patients, home administration with nurse, infants, ALGLU, adults	[redacted]	Assumption
Proportion of patients, home administration with nurse administration, infants, AVAL, adults	[redacted]	Assumption
Proportion of patients, outpatient administration, infants, ALGLU, adults	[redacted]	Assumption
Proportion of patients, outpatient administration, infants, AVAL, adults	[redacted]	Assumption
Wheelchair costs, one-off, children	£771.35	NHS reference costs (2019/20) (53)
Wheelchair costs, one-off, adults	£521.43	NHS reference costs (2019/20) (53)
Wheelchair costs, annual, children	£555.72	NHS reference costs (2019/20) (53)
Wheelchair costs, annual, adults	£262.47	NHS reference costs (2019/20) (53)
Wheelchair-related home adjustments	£30,000	Maximum disability facilities grant in England (2020) (58)
Cost of hoist	£826.48	Cost of Sunlift mini mobile hoist, NRS Healthcare
Non-invasive ventilation, one-off costs, adult	£4,286.16	Dretzke 2015 (55)
Non-invasive ventilation, annual costs, infant	£22,729.26	Noyes 2006 (56)
Non-invasive ventilation, one-off costs, children	–	Noyes 2006 (56)
Non-invasive ventilation, annual cost, adult	£654.83	Dretzke 2015 (55)
Invasive ventilation costs, one-off, all ages	£129,295.00	Noyes 2006 (56)
Invasive ventilation costs, annual, all ages	£149,025.09	Noyes 2006 (56)
Outpatient assessment, ventilation, infants	£329.14	Dretzke 2015 (55), NHS reference costs (2019/20) (53)
Outpatient assessment, ventilation, children	£329.14	Dretzke 2015 (55), NHS reference costs (2019/20) (53)

Variable	Value	Source
Outpatient assessment, ventilation, adults	£389.63	Dretzke 2015 (55), NHS reference costs (2019/20) (53)
IgG antibody monitoring	£6.58	NHS reference costs (2019/20) (53)
Antibody monitoring annual frequency, short-term	4	ALGLU SmPC (64)
Antibody monitoring annual frequency, long-term	2	
Not ventilation-dependent utility value, infants	0.684	Same ratio of utility vs. invasive ventilation as children assumed
Non-invasive ventilation-dependent utility value, infants	0.542	Average of not-ventilation dependent and invasive ventilation dependent
Invasive ventilation-dependent utility value, infants	0.399	Simon 2019 (36)
Not ventilation-dependent utility value, children	0.799	Simon 2019 (36)
Non-invasive ventilation-dependent utility value, children	0.633	Average of not ventilation-dependent and invasive ventilation-dependent
Invasive ventilation-dependent utility value, children	0.466	Simon 2019 (36)
Not ventilation-dependent utility value, adults	0.853	Simon 2019 (36)
Non-invasive ventilation-dependent utility value, adults	0.683	Average of not ventilation-dependent and invasive ventilation-dependent
Invasive ventilation-dependent utility value, adults	0.536	Simon 2019 (36)
Number of caregivers, infants	1.78	Average number of caregivers per child in the UK, ONS (84)
Number of caregivers, children	1.78	
Not ventilation-dependent disutility, infants	–0.099	Simon 2019 (36)
Non-invasive ventilation-dependent disutility, infants	–0.139	
Invasive ventilation-dependent disutility, infants	–0.180	
Not ventilation-dependent disutility, children	–0.072	
Non-invasive ventilation- dependent disutility, children	–0.102	

Variable	Value	Source
Invasive ventilation-dependent disutility, children	–0.131	

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CI, confidence interval, CRIM, cross-reactive immunological material; FVC, forced vital capacity; HR, hazard ratio; IOPD, infantile-onset Pompe disease; IVFS, invasive ventilation-free survival; MIMS, Monthly Index of Medical Specialities; NA, not applicable; NHS, National Health Service; ONS, Office for National Statistics; OS, overall survival; PSSRU, Personal Social Services Research Unit; RR, relative risk; VFS, ventilation-free survival.

L.4.5.2 Assumptions

Assumptions used in the IOPD model are presented in Table 56.

Table 56: IOPD model assumptions

Component of model	Assumption	Justification
Model structure	Time-to-ventilation and time-to-wheelchair did not impact OS	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 (69). It was assumed that the OS curve captures the additional risk of death that a patient will experience in the ventilation-dependent disease states
Clinical data	Ambulatory infants were assumed to become ambulatory at 18 months of age	A study by Broomfield 2015 followed 33 patients, of whom 28 had motor ability recorded (69). 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
Utility	Disutility associated with wheelchair-dependence was assumed to be captured in the ventilation-dependent health states	Utility scores were informed by Simon 2019 (36) and based on the severity of the disease. Vignettes for each state were provided and health state descriptions include an account of ambulatory status
	Child health state utilities were applied from aged 8 years	Utilities for the model were obtained from Simon 2019, which used a time-trade-off approach to elicit health state utilities in Pompe disease (36). The health states defined for LOPD assume child utilities began at 8 years. The model utility assumptions were chosen to align with this study
	The same ratio of utility values between invasive ventilation-dependent to not ventilation-dependent in	Given scarcity of utility data for children with Pompe disease, it was necessary to simplify assumptions where necessary

Component of model	Assumption	Justification
	children was applied to infants	
	The utility for the non-invasive ventilation health state was assumed to be the average of the not ventilation-dependent and invasive ventilation dependent health states	Given scarcity of utility data for children with Pompe disease, it was necessary to simplify assumptions where necessary
Costs	A one-off cost for wheelchair replacement and repair was applied every year, assuming a two-year replacement for children and 5-year replacement for adults	Clinical advice to the company stated that while children are growing, they require a new wheelchair every two years. Scenario analysis were presented in which children receive a replacement every three years in line with a previously published model in Duchenne muscular dystrophy which was used in a NICE evaluation (85)

Abbreviations: IOPD, infantile-onset Pompe disease; NICE, National Institute for Health and Care Excellence; OS, overall survival.

L.4.6 Base-case results

L.4.6.1 Base-case incremental cost-effectiveness analysis results

Table 57 presents the base-case results for the IOPD population. As treatment efficacy is conservatively assumed to be equal for AVAL and ALGLU there are no differences in QALYs or life-years. AVAL is associated with a cost saving due to the lower dose in the initial 3 months and a [redacted]; therefore AVAL dominates ALGLU in the base case. Table 58 and Table 59 present clinical and cost outcomes from the model respectively.

Table 57: IOPD – Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; LYG, life years gained; QALY, quality-adjusted life year.

Table 58: Clinical outcomes - IOPD

	ALGLU	AVAL	Incremental
Life years	[redacted]	[redacted]	[redacted]
Ventilator-free life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Patient	[redacted]	[redacted]	[redacted]
Caregiver	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease; LYG, life years gained; QALY, quality-adjusted life year.

Table 59: Disaggregated costs - IOPD

Outcome	ALGLU	AVAL	Incremental
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Ventilator	[redacted]	[redacted]	[redacted]
Ventilator-related	[redacted]	[redacted]	[redacted]
Wheelchair	[redacted]	[redacted]	[redacted]
Wheelchair-related	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]
Disease-related	[redacted]	[redacted]	[redacted]

Outcome	ALGLU	AVAL	Incremental
Disease management	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease.

L.4.7 Sensitivity analyses

As no treatment effect for AVAL compared with ALGLU has been estimated, no PSA has been estimated, as in all scenarios the health outcomes are equivalent between the two therapies and no ICERs can be estimated. OWSA has been run to look at differences in the incremental costs. The key parameters were ones associated with the cost of treatment and administration, or the treatment effects for AVAL, set to 1 in the base-case.

Figure 19: IOPD - Tornado diagram

Scenario analyses were performed, in which key structural assumptions were varied, and ICERs were reported. Considered scenarios are presented in Table 60. In all scenarios AVAL remains cost saving.

Table 60: IOPD – Scenario analyses performed

Area of uncertainty	Base case	Incremental costs
Discount rate set to 1.5%	3.5%	[redacted]
Discount rate set to 0%		[redacted]
Generalised gamma curve used for VFS	Weibull curve	[redacted]
Generalised gamma curve used for IVFS		[redacted]
Log-normal curve used for OS		[redacted]
CRIM+ only		[redacted]

Area of uncertainty	Base case	Incremental costs
CRIM- only	Combined population	[redacted]
No double dosing for ALGLU	Double dosing in the first 3 months	[redacted]
4.5 outpatient visits for dosing for AVAL on treatment initiation	33 visits	[redacted]
25-year time horizon	50 years	[redacted]

Abbreviations: AVAL, avalglucosidase alfa; CRIM, cross reactive immunological material; IOPD, infantile onset Pompe disease; IVFS, invasive ventilation-free survival; OS, overall survival; VFS, ventilation-free survival.

L.4.8 Validation

L.5 Validation of cost-effectiveness analysis

Both models have been validated by researchers not involved in their development using standard procedures:

- Cell-by-cell checks of logic and consistency,
- Logical check of model outputs.

L.5.1 LOPD external validation

The outcomes for ALGLU produced by the LOPD model are comparable to those seen in Kanters 2017 (8) when survival gains over standard treatment are extrapolated over a patient's lifetime. Kanters 2017 reported 21.84 discounted life years gained for a population of 49.1 years, compared with [redacted] in the present cost-effectiveness analysis (with discount rates set to 1.5% for comparability). The Kanters 2017 model produced more total QALYs (14.85 vs [redacted]), however it used the Dutch EQ-5D-3L tariff and outcomes are not directly comparable. Similarly, cost outcomes cannot be directly compared as the Kanters 2007 analysis takes a different perspective.

L.5.2 IOPD external validation

A single study considering the cost-effectiveness of ERT in IOPD from a UK perspective was identified. Castro-Jaramillo 2012 (6) assumed a 5% discount rate for costs and

outcomes and a 20-year time horizon, resulting in a total discounted cost of £1.34 million and 5.23 discounted QALYs for ALGLU. Using the same discount rates and time horizon, the current analysis predicts a total discounted cost of [redacted] and [redacted] discounted QALYs for ALGLU. Differences in outcomes are likely driven by the higher utility values assumed in the publication (a utility of 0.7 was applied for all patients alive and on ERT) and differences in the mortality data. Mortality in the Castra-Jaramillo model is not derived from survival data, rather mortality rate of 25% per year is assumed, based on two studies of ERT effectiveness.

The assumptions, inputs and outputs of the both the LOPD and IOPD models have been extensively validated at advisory boards.

L.6 Interpretation and conclusions of economic evidence

L.7 Strengths and limitations

L.7.1 LOPD

The economic analysis shows AVAL to be more effective than ALGLU in treating LOPD and cost-saving, leading to a dominant ICER. The model structure reflects the progression of both ventilatory and ambulatory elements of LOPD and clinicians have confirmed that the structure is representative of the course of the disease.

The data sources used to parameterise the model are robust, with long-term efficacy data from the Pompe Registry for ALGLU and from NEO1/NEO-EXT for AVAL. Resource use data were taken from the CPRD.

As AVAL is a new treatment for Pompe disease, a lack of data beyond six years is a limitation of this analysis. This resulted in a need for extrapolation of disease progression, using data from the Pompe Registry. For both AVAL and ALGLU, an equal linear decline over time was modelled. The assumption of linear progression in FVC% predicted and 6MWT distance was necessary due to the scarcity of the data, but it is known that in individual patients' progression may not be linear over time. It was not possible to capture all potential covariance between parameters for AVAL and ALGLU,

which may lead to an overstatement of the uncertainty in the model. However, assumptions around long-term efficacy and disease progression have been tested both with KOLs and in scenario analysis and AVAL remained cost-effective in all scenarios. Collection of more long-term data would delay patient access to a new treatment in a rare disease with a high unmet need.

L.7.2 IOPD

The economic analysis conservatively does not model any difference in outcomes for AVAL and ALGLU but shows AVAL to be a cost-saving treatment option for patients with IOPD. The model structure for IOPD captures the progressive nature of the disease, as patient move through ventilatory states to death.

Although there is a lack of head-to-head evidence comparing AVAL and ALGLU in IOPD, treatment with AVAL is associated with a trend for improvement or stabilisation across several clinical outcomes in patients with IOPD with clinical decline or suboptimal response to ERT. While this was largely in patients treated with 40 mg/kg of AVAL, it is comparing with a high dose of ALGLU. By cohort, the mean dose of ALGLU prior to entering the trial was equivalent to [redacted] Given the improvements observed with AVAL in LOPD, the assumption of equivalent efficacy in IOPD is likely to be a conservative assumption.

The clinical data used to inform the IOPD model are primarily taken from a retrospective case-note review from data collected between January 2000 and January 2014 (69). While this is considered the most appropriate data source, clinical practice has changed in this time and not all the CRIM negative patients will have been immunomodulated or given the same regimen as that currently used. As such, the response to treatment may be understated and the model may understate survival for these patients.

L.8 Conclusions

This analysis has demonstrated that compared with ALGLU, AVAL is an improved and cost-effective treatment option for both infantile- and late-onset Pompe disease. This result is consistent across the scenarios considered where AVAL is mostly cost-saving and is cost-effective in all scenarios considered. Therefore, AVAL offers an improved, cost-effective and cost-saving treatment option for patients with this severely disabling and fatal ultra-rare disease.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avalglucosidase alfa for treating Pompe disease [ID3737]

Clarification questions

January 2022

File name	Version	Contains confidential information	Date
		Yes/no	

Section A: Clarification on effectiveness data

A1. Company submission (CS) section B.2.3.1 states that results in the CS from the COMET study "are based on the interim CSR (data cut-off 19th March 2020, up to Week 97) and a more recent data cut (8th June 2021)."
(i) Please clarify which outcomes reported in the CS were analysed using data from the March 2020 data cut and from the June 2021 data cut.

The March 2020 and June 2021 data cuts were used to analyse Week 49 and Week 97 outcomes, respectively. Although some Week 97 data were available in the March 2020 data cut, patient numbers at later time points were low. Therefore, the June 2021 data cut was used for Week 97, as more patients had reached that timepoint.

(ii) Did the March 2020 cut include all patients who had completed the 49-week blinded primary analysis period (PAP)?

Yes. One-hundred patients were randomised in the PAP; 95 completed the PAP by the March 2020 data cut and five prematurely discontinued.

(iii) Please also clarify why results from the June 2021 data cut were not presented for all outcomes included in the CS.

Results from the June 2021 data cut were presented for all outcomes (Week 97) included in the submission.

(iv) On CS page 46 it is stated that "the ETP is ongoing and data are only available at later time points for a proportion of patients". Does this refer to the long-term results for COMET given in Appendix O? If not, please specify these time points and the proportion of patients with available data for each relevant outcome measure.

Yes, this refers to the ETP of COMET, where not all patients have completed longer-term follow up assessments.

A2. Similar to question A1 above, please clarify:

(i) which outcomes reported in the CS from the Mini-COMET study used data from the September 2019 and May 2021 data cuts.

All outcomes reported in the company submission from Mini-COMET used data from the May 2021 data cut, as data were more complete than those from the September 2019 data cut.

(ii) why the May 2021 data cut has not been used for all outcomes (CS section B.2.3.2).

The May 2021 data cut was used for all outcomes. We apologise for the ambiguous wording in Section B.2.3.2; the September 2019 data were included in the draft company submission but were updated when the May 2021 data became available.

(iii) Did the September 2019 data cut include all patients who had completed the PAP?

Yes, all patients who completed the PAP were included in the September 2019 data cut.

(iv) On CS page 46, It is stated that "the ETP is ongoing and data are only available at later time points for a proportion of patients". Please specify these time points and the proportion of patients with available data for each relevant outcome measure.

As with COMET, not all patients have completed longer-term follow up assessments. Results from the ETP are presented in the company submission (Section B.2.6.2).

A3. For each arm of the COMET trial please can the company provide the proportion of participants diagnosed with Pompe Disease when they were >1 but <18 years of age

In COMET, 4% of patients (2/51) in the AVAL arm and 2% (1/49) in the ALGLU arm were diagnosed with Pompe Disease when they were >1 but <18 years of age.

A4. Table 1 in CS Document B lists immunogenicity response as an outcome in the final scope and in the decision problem. Please can the company clarify where the results for immunogenicity response are reported in the CS.

Immunogenicity data were not included in the submission to provide a concise summary of the most important information. The immunogenicity endpoints did not suggest any concerning trends and the relevant information is provided below, as well as in the clinical study reports.

COMET

[redacted] Two patients in each group were always negative and two patients in each group were positive at baseline.

[redacted] Ten (19.6%) patients in the AVAL arm and 16 (33.3%) patients in the ALGLU arm had a peak titre of ≥12,800. For patients who had treatment-induced persistent ADA, a lower proportion of patients in the AVAL arm had a high response (10 [20.4%] patients) in comparison to the ALGLU arm (16 [34.8%] patients).

[redacted]

Table 1: Anti-drug antibody response, PAP, anti-drug antibody-evaluable population, COMET

	AVAL N=51 Anti-AVAL antibodies	ALGLU N=48 Anti-ALGLU antibodies
ADA status, n (%)		
Always negative	2 (3.9)	2 (4.2)

	AVAL N=51 Anti-AVAL antibodies	ALGLU N=48 Anti-ALGLU antibodies
Ever positive with negative baseline	47 (92.2)	44 (91.7)
Positive at baseline	2 (3.9)	2 (4.2)
Treatment-emergent ADA[†], n (%)	49 (96.1)	46 (95.8)
Treatment-induced ADA[‡], n (%)	47 (95.9)	44 (95.7)
Transient ADA	1 (2.0)	1 (2.2)
Persistent ADA	43 (87.8)	39 (84.8)
Low response	13 (26.5)	4 (8.7)
Intermediate response	20 (40.8)	19 (41.3)
High response	10 (20.4)	16 (34.8)
Tolerised ADA	3 (6.1)	4 (8.7)
Indeterminate ADA	[redacted]	[redacted]
Treatment-boosted ADA[¶], n (%)	2 (100)	2 (100)
ADA peak titre, n (%)		
Negative	[redacted]	[redacted]
100–800	17 (33.3)	8 (16.7)
1600–6400	20 (39.2)	20 (41.7)
≥12,800	10 (19.6)	16 (33.3)

Peak titre: highest ADA titre post baseline for patients that were seroconverted. The percentage calculations are based on denominator of total number of patients in ADA evaluable population of the treatment group if not specified.

[†]Treatment emergent ADA incidence is defined as 100 x (treatment boosted + treatment induced ADA positive patients)/(number of evaluable patients); [‡]Treatment induced ADA incidence is defined as 100 x (treatment induced ADA positive patients)/(number of evaluable patients with ADA negative at baseline); [¶]Treatment boosted ADA incidence is defined as 100 x (treatment boosted ADA positive patients)/(number of evaluable patients with ADA positive at baseline).

Abbreviations: ADA, anti-drug antibody; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PAP, primary analysis period.

Table 2: Seroconversion, time to seroconversion, and duration of anti-drug antibodies, PAP, anti-drug antibody-evaluable set, COMET

	AVAL N=51 Anti-AVAL antibodies	ALGLU N=48 Anti-ALGLU antibodies
Time to onset of ADA seroconversion from 1st infusion (weeks)[†]		
No.	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Time to ADA tolerised from seroconversion (weeks)[‡]		
No.	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

	AVAL N=51 Anti-AVAL antibodies	ALGLU N=48 Anti-ALGLU antibodies
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
Duration of positive ADA from seroconversion (weeks)¶		
No.	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

The percentage calculations are based on denominator of total number of patients in ADA evaluable population of the treatment group if not specified.
†Onset of ADA is defined as the time period (in days) between the first study drug administration and the first instance of treatment induced ADAs; ‡Time to ADA tolerised from seroconversion is defined as the time period (in days) between the first study drug administration and the first instance of ADA tolerised; ¶Duration of ADA will be calculated as the date of last treatment induced ADA sample minus date of first treatment induced ADA sample + 1.
Abbreviations: ADA, anti-drug antibody; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PAP, primary analysis period; SD, standard deviation.

Mini-COMET

The primary efficacy endpoint of Mini-COMET was to evaluate the safety profile of AVAL in patients with IOPD previously treated with ALGLU. The immunogenicity associated with AVAL treatment was assessed during the safety evaluation.

[redacted]

[redacted]

Table 3 presents a summary of seroconversion, time to seroconversion, and duration of ADA during the PAP of Mini-COMET.

Table 3: Seroconversion, time to seroconversion, and duration of anti-drug antibodies, PAP, anti-drug antibody-evaluable population, Mini-COMET

	Cohort 1 N=6		Cohort 2 N=5		Cohort 3, AVAL arm N=5		Cohort 3, ALGLU arm N=6	
	Anti-AVAL antibodies N=6	Anti-ALGLU antibodies N=6	Anti-AVAL antibodies N=5	Anti-ALGLU antibodies N=5	Anti-AVAL antibodies N=5	Anti-ALGLU antibodies N=5	Anti-AVAL antibodies N=6	Anti-ALGLU antibodies N=6
No. of patients with ≥2 post-baseline samples, n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients ADA positive at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median titre	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1:Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients with treatment boosted ADA[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median peak titre	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1:Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment boosted ADA incidence rate[‡] n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients ADA negative at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients always negative[¶]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment induced ADA positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geometric mean peak titre (Geo SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median peak titre	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Cohort 1 N=6		Cohort 2 N=5		Cohort 3, AVAL arm N=5		Cohort 3, ALGLU arm N=6	
	Anti-AVAL antibodies N=6	Anti-ALGLU antibodies N=6	Anti-AVAL antibodies N=5	Anti-ALGLU antibodies N=5	Anti-AVAL antibodies N=5	Anti-ALGLU antibodies N=5	Anti-AVAL antibodies N=6	Anti-ALGLU antibodies N=6
Q1:Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment induced ADA incidence rate[§], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients with Indeterminate ADA response[††]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients with transient ADA response[‡]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients with persistent ADA response[¶¶]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA prevalence rate[§§], n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA incidence rate[†††], n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence rate of neutralising antibodies[†††], n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence rate of neutralising antibodies (inhibition enzyme activity)[‡‡‡], n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incidence rate of neutralizing antibodies(inhibition uptake) [‡‡‡],n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Cohort 1 N=6		Cohort 2 N=5		Cohort 3, AVAL arm N=5		Cohort 3, ALGLU arm N=6	
	Anti-AVAL antibodies N=6	Anti-ALGLU antibodies N=6	Anti-AVAL antibodies N=5	Anti-ALGLU antibodies N=5	Anti-AVAL antibodies N=5	Anti-ALGLU antibodies N=5	Anti-AVAL antibodies N=6	Anti-ALGLU antibodies N=6
Time to onset of ADA seroconversion from 1st infusion (weeks)¶¶¶,§§§								
No.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of positive ADA from seroconversion (weeks)¶¶¶,††††	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The percentage calculations are based on denominator of total number of patients in ADA evaluable population of the treatment group.
†Pre-existing ADA positive was boosted to a higher level following administration of the study drug; ‡Treatment boosted ADA incidence= 100 x treatment boosted ADA subjects/ number of evaluable subjects ADA positive at baseline; ¶Patients with always negative ADA are those no positive samples detected post-baseline during PAP; §Treatment induced ADA incidence= treatment induced ADA subjects/ number of evaluable subjects ADA negative at baseline; ††Only the last post-baseline assessment is ADA positive or the last sample timepoint is positive and separated by <16 weeks from the first positive result; ‡‡Treatment induced ADA detected only at one assessment, then followed by all ADA negative assessments; or treatment induced ADA at ≥2 assessments, where first and last positive samples are less than 16 weeks, and the last assessment is ADA negative; ¶¶Treatment induced ADA at ≥2 assessments, where

first and last positive samples are separated by at least 16 weeks; §§ADA prevalence=100 x ((number of subjects with treatment induced ADA + pre-existing ADA)/ number of evaluable subjects in the treatment group); †††ADA incidence= 100 x ((Treatment boosted + treatment induced ADA subjects)/ number of evaluable subjects in the treatment group); ‡‡‡100 x (ever neutralizing antibody positive)/(number of evaluable patients); ¶¶¶Exclude the patients with positive ADA at baseline; §§§(date of initial seroconversion - date of first study drug +1) /7; ††††Duration of positive ADA = (last date of ADA positive - date of initial seroconversion)/7. Only calculated for patients with at least 2 positive ADA assessments.
Abbreviations: ADA, anti-drug antibody; ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; PAP, primary analysis period; SD, standard deviation.

NEO1/NEO-EXT

Of the treatment-naïve patients, 90% (9/10) developed treatment-emergent ADA, [redacted]

A5. Table 1 in CS Document B lists change in cardiac function as an outcome in the final scope and in the decision problem. B.2.6.2.3.5 reports Echo LVM Z scores for Mini-COMET. Can the company confirm whether there are any other cardiac outcomes reported for Mini-COMET and whether there are any cardiac outcomes reported for COMET and NEO-1/NEO-EXT? Please provide any such available cardiac data.

In Mini-COMET, left ventricular mass index (LMVI) M-MODE scores were measured from baseline up to Week 97 (Table 4).

Table 4: Echo-LVMI M-MODE (g/m^2): observed values and changes from baseline by study visit, safety population, Mini-COMET

	Cohort 1 N=6	Cohort 2 N=5	AVAL/AVAL N=5	ALGLU/AVAL N=6
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 25				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
% CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 49				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
% CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 97				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
% CFB (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; LVMI, left ventricular mass index; SD, standard deviation.

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.

A6. Table 11 in CS Document B lists GSGC, GMFM-88, QMFT, HHD and PedsQL-adult report as outcomes for NEO1/NEO-EXT. Can the company please clarify where the results for these outcomes are reported in the CS.

These were omitted for conciseness, as COMET is the primary source of efficacy data in LOPD. Results are provided below for NEO1. None of these were assessed in NEO-EXT.

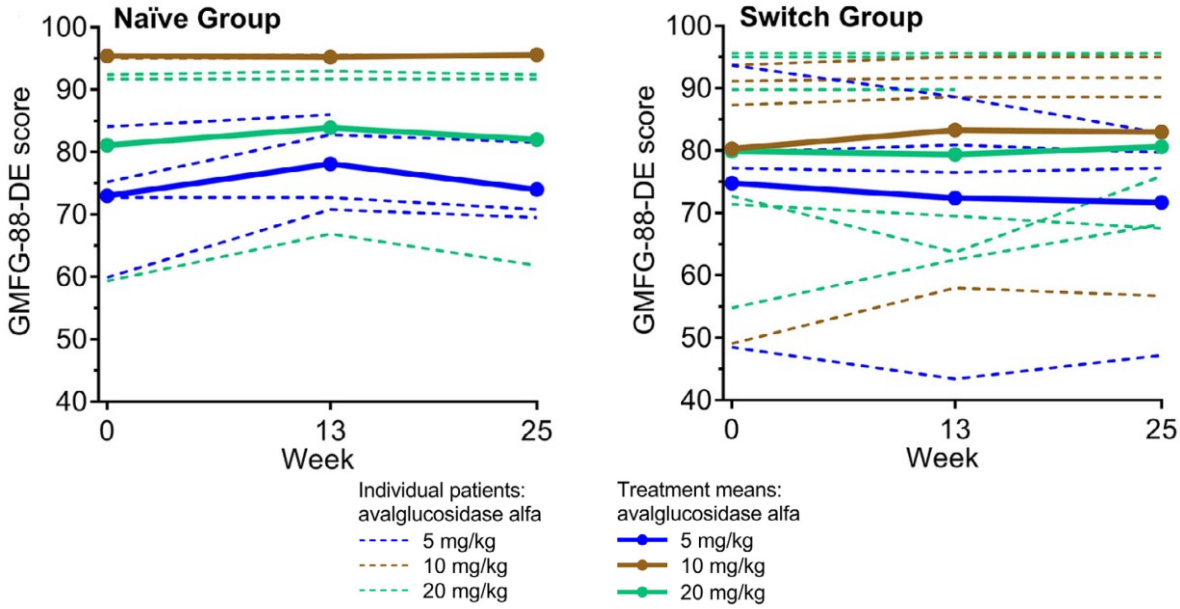
Gait, Stairs, Gowers, Chair ability (GSGC) and Gross Motor Function Measure-88 (Dimensions D and E; GMFM-88-DE)

In Group 1, mean scores for both the individual Dimensions D (standing) and E (walking, running, and jumping), and the combined GMFM-88-DE functional strength total measurement remained relatively unchanged from baseline at all dose levels throughout the study (Figure 1 left panel), with percentage mean (SD) changes from baseline of GMFM-88-DE measurement at Week 25 for Group 1 combined at 3.0% (5.85%).

In Group 2, mean scores for both the individual Dimensions D (standing) and E (walking, running, and jumping), and the combined GMFM-88-DE functional strength

total measurement remained relatively unchanged versus baseline at all dose levels throughout the study (Figure 1 right panel), with percentage mean (SD) changes from baseline of GMFM-88-DE measurement at Week 25 for Group 2 combined at 2.2% (9.01%).

Figure 1: Gross Motor Function Measure-88 for Dimensions D and E over time



Adapted from Pena 2019 (1).

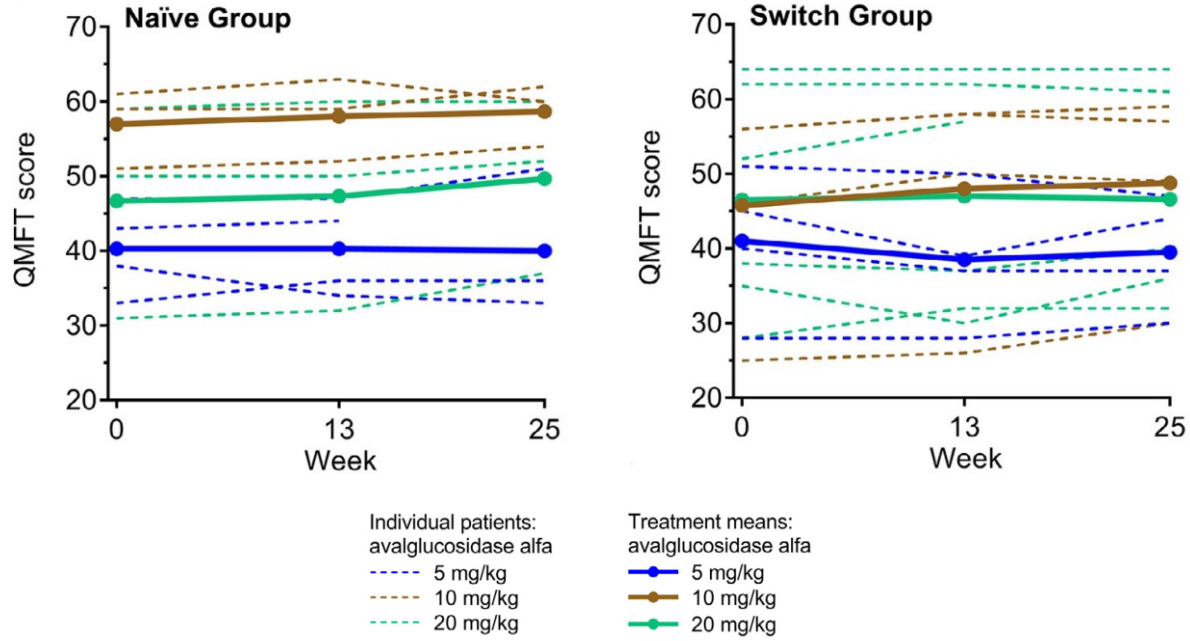
In Groups 1 and 2, mean changes from baseline at Week 25 for the functional ability GSGC score remained unchanged relative to baseline at all dose levels, with Group 1 combined mean of –0.8 and Group 2 combined mean of 0.2.

Quick motor function test

In Group 1, mean (SD) QMFT total scores increased relative to baseline at Week 25 in the 5, 10, and 20-mg/kg dose groups by 0.7 (4.93), 1.7 (2.31), and 3.0 (2.65) points respectively (on a 64-point scale) (Figure 2 left panel).

In Group 2, mean (SD) QMFT scores decreased slightly by –1.5 (2.65) relative to baseline at Week 25 in the 5 mg/kg dose group, and increased by 3.0 (1.63) and 1.2 (1.92) points in the 10 and 20 mg/kg dose groups, respectively (on a 64-point scale) (Figure 2 right panel).

Figure 2: Quick Motor Function Test over time



Adapted from Pena 2019 (1).

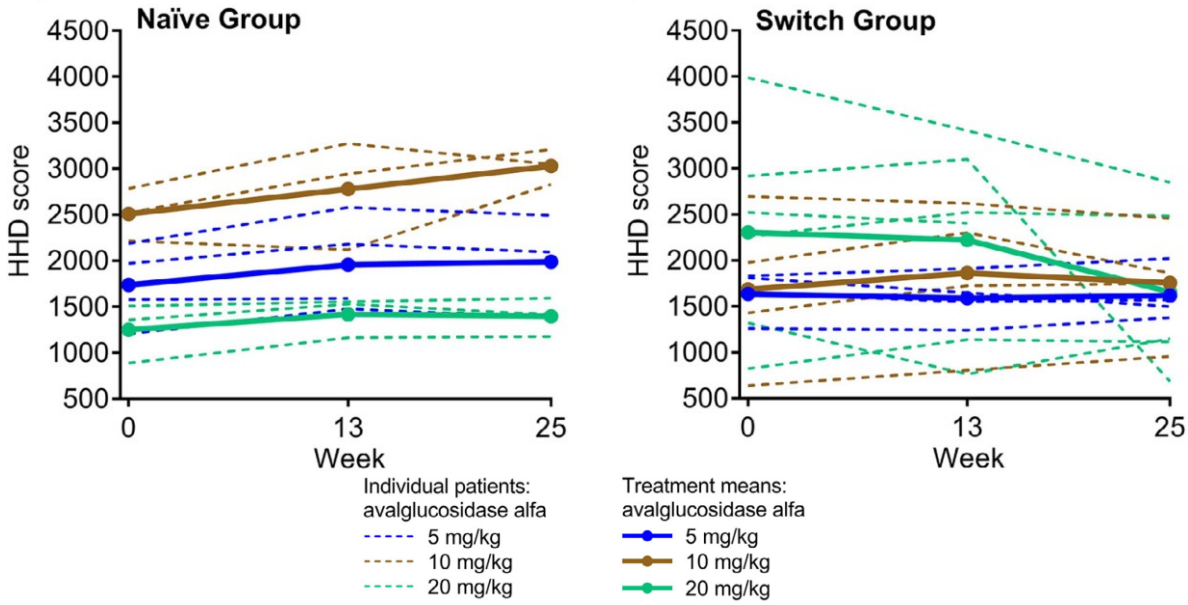
Hand-held dynamometry

In Group 1, lower body hand-held dynamometry assessments increased by a mean (SD) of 11.6% (4.69%), 21.4% (10.31%), and 14.2% (15.90%) at the respective 5, 10, and 20 mg/kg dose levels at Week 25 relative to baseline (Figure 3 left panel).

Upper body hand-held dynamometry assessments increased by a mean (SD) of 8.2% (25.88%) and 19.0% (7.49%) in the respective 5 and 10 mg/kg AVAL groups at Week 25 relative to baseline; a mean decrease of 9.9% (16.92%) was observed in the 20 mg/kg dose group.

In Group 2, lower and upper body HHD assessments increased at Week 25 by a mean (SD) of 14.3% (27.32%) and 10.8% (17.79%) relative to baseline, respectively, for the 10 mg/kg dose (Figure 3 right panel). At 5 and 20 mg/kg, mean upper and lower HHD values remained stable or tended to decrease by Week 25 (lower body average [SD] percentage changes from baseline at Week 25: 5 mg/kg = –0.5% [13.07%] and 20 mg/kg = –14.5% [42.23%]; upper body percentage changes from baseline at Week 25: 5 mg/kg = –8.1% [24.46%] and 20 mg/kg = –15.3% [27.69%]).

Figure 3: Hand-held dynamometry over time



Adapted from Pena 2019 (1).

Paediatric Quality of Life Inventory multidimensional fatigue scale

In Group 1, mean scores for cognitive fatigue, general fatigue, and sleep/rest fatigue remained unchanged relative to baseline across all AVAL dose groups, except for decreased cognitive fatigue and general fatigue in the 20 mg/kg dose group at Week 25 with a mean reduction of 11.1 (9.62) and 8.3 (7.22) points at Week 25 (100-point scale).

In Group 2, mean scores for cognitive fatigue, general fatigue, and sleep/rest fatigue remained unchanged relative to baseline across all AVAL dose levels.

A7. Priority question. The COMET study CSR includes hyperlinks to additional data sources, but these sources do not appear to be available to the ERG when clicking the link. For example, CSR section 19.3.4 Health Related Quality of Life states "Observed changes from baseline in EQ-5D-5L and PedsQL generic score in the PAP for the mITT and ETP population is presented in 16-2-6-eff-response-data [16.2.6.3.5.1] to [16.2.6.3.5.2] and [16.2.6.3.10.1] to [16.2.6.3.10.2"] Please provide all data referred to via these links in each CSR (where not already available).

The requested reference has now been provided.

A8. Priority question. Unless already submitted, please provide mean (plus standard deviation) EQ-5D-5L index values for both arms of the COMET trial at baseline and all other time assessment points, and any statistical analysis comparing these.

Observed values for each time point in the PAP and ETP are presented in Table 5. Estimates of changes from baseline in the PAP are presented together with nominal p-values in Table 6.

Table 5: Health-State Utility Values (5L) using UK tariff by treatment (crosswalk method) - Observed values and change from baseline by study visit - in PAP and ETP - mITT population

EQ-5D-5L index score (UK tariff, crosswalk method)	AVAL/AVAL (N=51)		ALGLU/AVAL (N=49)	
	Observed data	Change from baseline	Observed data	Change from baseline
Baseline				
Number	[redacted]	–	[redacted]	–
Mean (SD)	[redacted]	–	[redacted]	–
Median	[redacted]	–	[redacted]	–
Q1; Q3	[redacted]	–	[redacted]	–
Min; Max	[redacted]	–	[redacted]	–
Week 13				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 25				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 37				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D-5L index score (UK tariff, crosswalk method)	AVAL/AVAL (N=51)		ALGLU/AVAL (N=49)	
	Observed data	Change from baseline	Observed data	Change from baseline
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 49				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 61				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 73				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 97				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D-5L index score (UK tariff, crosswalk method)	AVAL/AVAL (N=51)		ALGLU/AVAL (N=49)	
	Observed data	Change from baseline	Observed data	Change from baseline
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 121				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 145				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 169				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 193				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D-5L index score (UK tariff, crosswalk method)	AVAL/AVAL (N=51)		ALGLU/AVAL (N=49)	
	Observed data	Change from baseline	Observed data	Change from baseline
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 217				
Number	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1; Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ETP, extended treatment period; mITT, modified intention-to-treat; PAP, primary analysis period; SD, standard deviation; UK, United Kingdom.

Table 6: Health-State Utility Values (5L) using UK tariff by treatment (crosswalk method) - Estimates of Change from Baseline by visit - in PAP - mITT population

Change from baseline in EQ-5D-5L index score (UK tariff, crosswalk method)	AVAL (N=51)	ALGLU (N=49)	Difference (N=100)
Week 13			
Number	[redacted]	[redacted]	–
Mean (SD)	[redacted]	[redacted]	–
Median	[redacted]	[redacted]	–
Min; Max	[redacted]	[redacted]	–
Estimate	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
p-value	–	–	[redacted]

Change from baseline in EQ-5D-5L index score (UK tariff, crosswalk method)	AVAL (N=51)	ALGLU (N=49)	Difference (N=100)
Week 25			
Number	[redacted]	[redacted]	–
Mean (SD)	[redacted]	[redacted]	–
Median	[redacted]	[redacted]	–
Min; Max	[redacted]	[redacted]	–
Estimate	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
p-value	–	–	[redacted]
Week 37			
Number	[redacted]	[redacted]	–
Mean (SD)	[redacted]	[redacted]	–
Median	[redacted]	[redacted]	–
Min; Max	[redacted]	[redacted]	–
Estimate	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
p-value	–	–	[redacted]
Week 49			
Number	[redacted]	[redacted]	–
Mean (SD)	[redacted]	[redacted]	–
Median	[redacted]	[redacted]	–
Min; Max	[redacted]	[redacted]	–
Estimate	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

Change from baseline in EQ-5D-5L index score (UK tariff, crosswalk method)	AVAL (N=51)	ALGLU (N=49)	Difference (N=100)
p-value	–	–	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CI, confidence interval; mITT, modified intention-to-treat; PAP, primary analysis period; SD, standard deviation; SE, standard error; UK, United Kingdom.

A9. Priority question. On CS page 50, with reference to the NEO1 study, it is stated that "Results in this submission are based on the final CSR and study publication (105)." However, the CSR does not appear to have been submitted in the reference pack. We also note that on page 50 in relation to the NEO-EXT study it is stated "Results in this submission are based on the interim CSR (data cut-off 27th February 2020) and include the two periods of treatment from NEO1 and NEO-EXT". Are we correct in assuming the NEO-EXT interim CSR replaces/subsumes the final NEO1 CSR? If not, please can the latter be provided.

The requested reference has now been provided.

A10. Priority question. The CSRs submitted for the COMET, Mini-COMET and NEO-EXT studies are labelled as 'Interim'. Please provide any available updated or finalised CSRs for these studies.

All these documents are reported as "Interim", as the ETP is still ongoing. The final CSRs are planned for approximately:

- Q1 2022 for NEO-EXT
- Q4 2023 for COMET
- Q4 2026 for Mini-COMET.

Data tables summarising the most recent data cuts for COMET and Mini-COMET have been provided, however formal CSRs are not yet available.

A11. Priority question. Please provide the Statistical Analyses Plans (the most up-to-date versions) for each of the four avalglucosidase alfa clinical evidence studies.

The requested references have now been provided.

Section B: Clarification on cost-effectiveness data

B1. Priority question. CS Document B reports the parameters and results of a cost comparison study while the submitted economic models show the results for the cost-utility analyses presented in Appendix L.
(i) Please clarify why the model results do not match the results reported in Document B (i.e. cost comparison).
(ii) Please provide versions of the models with the parameters, assumptions and results the same as in CS Document B

It has now been clarified that in addition to the cost-utility models (described in the Appendix L), a cost-comparison model was also submitted (described in Document B).

B2. Priority question. It is unclear to the ERG how to access the coding in the DICE simulation model, in order to check the technical accuracy of the model. Please comment on whether it is possible to access and modify this coding and if so, provide instructions on how to do this.

The unlocked code has been provided to NICE.

B3. Priority question. CS Table 48 presents a summary of the variables applied in the LOPD cost-comparison model. The baseline characteristics of LOPD patients (age, % male, weight) as well as the cost of nurse and cost of administration (outpatient) are different from the ones in the economic model. We understand that the submitted model reflects the cost-utility analysis in Appendix L, but what is the justification for these parameters to differ between the cost comparison and cost utility analyses?

The cost-comparison model used the baseline characteristics from COMET directly, while the cost-utility analysis used baseline characteristics from the eight profiles described in Appendix L, Section L3.2.1. These profiles were generated using data from COMET but will not exactly match the baseline characteristics in the cost-comparison model. The costs of nurse time and the cost of administration in document B were aligned with the cost-minimisation model used in the base-case.

B4. Priority question. Similar to question B2 above, CS Table 61 presents a summary of the variables applied in the lOPD cost-comparison model. The

baseline characteristics of IOPD patients (age, % male, % CRIM+) are based on the study by Broomfield 2015 but they are not the same as the ones used in the model (based on Kishani 2007). Please clarify the reason for not using the Broomfield 2015 baseline estimates in the model.

This was a mistake in the model; the Broomfield 2015 data should have been used in the base-case. This has been updated in the model and updated results are provided in the appendix.

B5. Table 3 in CS Appendix L and the "Profiles" sheet in the LOPD model both present the eight patient profiles used in the model. Please explain the discrepancy of the weight of each profile (values under column "share") between these two tables.

This was a transcription error in Appendix L. The values in the model are correct.

B6. CS Appendix L Table 4 reports the efficacy outcomes observed in COMET trial at week 49:

- **%FVC predicted: 2.89 for AVAL and 0.46 for ALGLU (difference of 2.43);**
- **6MWT: 32.21m for AVAL and 2.19m for ALGLU (difference of 30.01).**

In the model, these efficacy inputs are entered as the absolute values for ALGLU (0.46% and 2.19m) but as the relative/additive values for AVAL (2.43% and 30.01m). Can you please explain why the company did not use the absolute estimates of AVAL in the model?

The model is set up in this way to enable the user to vary the absolute ALGLU effect depending on the source used; and to have AVAL relative to this unchanged as the only source of AVAL effect is COMET. This allows the sensitivity analyses to measure the uncertainty around the relative effect and not the absolute effect, while still using alternative inputs for the baseline impact of ALGLU.

B7. Please provide the Kaplan Meier and the extrapolated survival curves for OS used in the LOPD model. In addition, please clarify the reason why the

other parametric models (apart from Weibull and Gompertz) were not used to extrapolate baseline OS.

The fits with all parametric distributions have been provided alongside this response. Distributions included in the analysis were exponential, Weibull, Gompertz, lognormal, loglogistic and generalized gamma. The assessment of fit was based on AIC and BIC values as well as visual fit and clinical validity. According to these criteria, Gompertz is recommended for the base case (it has the lowest AIC and BIC except for generalized gamma) with Weibull recommended for sensitivity analyses as these models produced the most plausible fits and allow for an increasing hazard over time, which is not the case with the exponential, log-normal and log-logistic models.

The long-term projections for exponential, lognormal, and loglogistic were deemed inappropriate and are not included in the CEM. According to clinical experts interviewed during an advisory board, a life expectancy of 45 years from time of diagnosis for a patient treated with ERT was clinically valid. The life expectancies predicted by the exponential, lognormal and loglogistic parametric curves for patients on BSC from Güngör 2011 (2) were high at 48, 41 and 39 years, respectively. These were considered too optimistic and would predict very high survival once the HR for ERT (0.41) is applied in the CEM.

B8. CS Appendix L, Table 60, IOPD model

Please, provide details of the changes to the parameters that are needed to conduct the following scenarios:

- **No double dosing for ALGLU**
- **4.5 outpatient visits for dosing for AVAL on treatment initiation**

The response to this question also covers the scenarios in question B9. Some transcription errors had been made in Appendix L, however in response to question B4 all results have been updated.

<u>No double dosing for ALGLU</u>

The formulas in cells BC7 and BD7 should be replaced with the following formulas:

*=(BB7*IF(D7<INDEX(m.init.dur.comp1,AE7),INDEX(m.init.dose.comp1,AE7),INDEX(m.sub.dose.comp1,AE7))/m.strength.comp1)*m.cost.comp1/m.packsize.comp1*INDEX(m.compliance.comp1,AE7)*(INDEX(m.freq4wks.comp1,AE7)*weeksinmonth/4)*

*=IF(D7=1,m.upfront.cost.comp1,0)-IF(D1215=1,'Treatment Costs'!$K$61*2,0)-IF(D1215=2,'Treatment Costs'!$K$61,0)+CHOOSE(AE8,IF(D7<INDEX(m.init.dur.comp1,1),'Treatment Costs'!$L$61,'Treatment Costs'!$L$62),IF(D7<INDEX(m.init.dur.comp1,2),'Treatment Costs'!$L$77,'Treatment Costs'!$L$78),IF(D7<INDEX(m.init.dur.comp1,3),'Treatment Costs'!$L$93,'Treatment Costs'!$L$94))*cycle.length*

In the updated model provided, a dropdown has been included on the 'Treatment Costs' sheet to allow the user to select this functionality more easily.

4.5 outpatient visits for dosing for AVAL on treatment initiation

Replace the values in cell 'Treatment costs'!F47 with the value 742.50.

Log-normal curve used for OS

Set the dropdowns in cells 'Trt Effect and Disease Prog.'!F55 and 'Trt Effect and Disease Prog.!'F61 to 'Log-normal'.

CRIM+ only

Set cell 'Settings!E30' to 100%.

B9. In CS Appendix L Table 60, IOPD model, there are two scenarios that the ERG is not able to reproduce the same results:

- **log-normal curve used for OS;**
- **CRIM+ only.**

Please provide information on how to reproduce these scenarios

Please see response to question B8.

B10. Similar to question B9, there are a few scenarios we are unable to reproduce in the LOPD model (CS Appendix L Table 35). Please provide information on how to reproduce the following scenarios:

- **Patients below the median age only;**
- **No caregiver disutility;**
- **Hospital administration for the first 4 AVAL infusions;**
- **Alternative disutility from DMD.**

Patients below the median age

On the profiles sheet, set the adjusted 'AdjShare' column to 0 for all patients above the median age (profiles 3,4, 7 and 8) and reweighted the remaining profiles according to their share.

No caregiver disutility

Set the caregiver disutilities in the range 'Disease!D25:H25' to 0.

Hospital administration for the first 4 AVAL infusions

In the base-case, 3 administrations are assumed. For the scenario, the cost in range 'isInitHospAdultAval' is multiplied by 4/3.

Alternative disutility from DMD

The values in cells 'Disease!D25:H26' should be replaced with the values in Table 16 of the CS. The caregiver disutility associated with the 'Ventilator and wheelchair state' is assumed to be the sum of the non-invasive ventilator and wheelchair-dependent disutilities. Disutilities are presented in Table 7. There is a transcription error in the results in Appendix L. The incremental QALYs should be [redacted], rather than [redacted].

Table 7: Scenario disutilities

Disutilities	Not dependent on ventilator or wheelchair	Non-invasive ventilator	Wheelchair-dependent	Invasive ventilator-dependent	Ventilator & wheelchair
Caregiver	0.00	0.062	0.055	0.063	0.117
Patient	-	0.389	0.383	0.467	-

B11. Priority question. The CS states that in the IOPD model, patients receive an additional 6 administrations with ALGLU in the first year. Please explain why this assumption should not also be applied to patients receiving AVAL?

This assumption was made for ALGLU based on the advice received in the UK advisory board, that in England the initial dose of 20 mg/kg every week for the first three months is routinely covered by the NHS. There is currently no experience of differential dosing of AVAL in this initial period and it is not anticipated to be included in the license. Therefore, no such assumption on increased initial dose could be made for AVAL.

B12. Please provide the NHS reference costs codes for outpatient visits and outpatient assessments in Appendix L Tables 19, 22, 49 and 51.

The cost of outpatient administration in Tables 19 and 49 was taken from the 2021/22 National Tariff Payment System and is assumed to be the cost of HRG code SB12X – 'Deliver simple parenteral chemotherapy at first attendance'. The value in Tables 22 and 51 is the cost of DZ37A – 'Non-invasive ventilation support assessment'. This value has been updated to reflect the 2021/22 National Tariff Payment System and has subsequently been changed to £181 in adults and £217 in children.

B13. The disease-related costs per patient reported in Appendix L Table 25 and Table 53 do not appear to match those in the CPRD report (Table 10-4). Please explain the reason for this discrepancy.

The costs in the model were entered incorrectly by error and have now been updated to match the CPRD report and the updated results provided in the Appendix. The updated costs are presented in Table 8.

Table 8: Disease-related costs per patient year by category

Cost category	Cost	Reference
Elective and day-case	£338	CPRD analysis (3)
Non-elective	£386	
ITU	£65	
Outpatient	£217	
A&E	£49	
Primary care consultations	£270	
GP prescribing	£615	
Total	£2,186	–

Abbreviations: A&E, Accident and emergency; CPRD, Clinical Practice Research Datalink; GP, general practitioner; ITU, intensive treatment unit.

B14. The cost of a nurse per hour is £39/hr in the LOPD model. This differs from the value used in the IOPD model and the values reported in the Appendix L Tables 19 and 49. Please explain the reason for this discrepancy. In addition, please state which NHS staff band was used for the costing of nurse time.

This is an error in the model. The cost of nurse time in all models has now been updated to £44 per hour, based on the most recent cost per working hour of a Band 5 community-based nurse in the PSSRU Unit Costs of Health and Social Care 2021. The updated results provided in the Appendix.

B15. The cost of the hoist is reported in Appendix L Table 52 as £826.48, whereas the value used in the IOPD model is £669.99. Please explain this discrepancy.

The cost reported in Appendix L is correct and the model has now been rerun with the updated cost. The updated results are available in the Appendix.

B16. It is unclear to the ERG how the ventilation costs reported in Appendix L table 22 and 51 have been estimated from the Noyes 2016 and Dretze 2015 references. Please provide more information on the how the estimates have been calculated, including the source table number and details of any adjustment made.

The cost of non-invasive ventilation in children was assumed to be the mean cost of 'simple' ventilator dependency in Noyes 2006 (4) (£17,876 per year, inflated to £24,460.56). The cost of non-invasive ventilation in adults was taken from Table 34 of Dretzke 2015 (5). The one-off cost includes the cost of NIC equipment, the set-up

costs, and additional monthly costs in the first 3 months. Where possible costs were updated using the 2021/22 National Tariff Payment System; otherwise, they were inflated to 2020/21 costs using the PSSRU NHSCII, assuming a start year of 2014/15 for costs (Table 9).

Table 9: Costs of non-invasive ventilation

Element of cost	Cost	Source
Equipment costs		
NIV device and humidifier	£4,049	Inflated
NIV equipment for home use monthly cost	£75	Inflated
Setup costs		
NIV set-up and assessment in Month 1†	£181	2021/22 National Tariff Payment System, DZ37A
NIV follow-up in month 3: 1 × consultant-led outpatient appointment + 1 × blood gas test	£225 £195	2021/22 National Tariff Payment System, Consultant led outpatient attendance, respiratory medicine National Schedule of NHS Costs Year: 2019-20 v2. Outpatient: DZ57Z
Annual costs thereafter		
2 x blood gas check conducted at routine follow up	£390	National Schedule of NHS Costs Year : 2019-20 v2. Outpatient: DZ57Z
1 x annual NIV equipment check	£618.56	Inflated
Monthly costs		
Monthly costs in first 3 months	£313.78	Inflated
Monthly costs beyond 3 months	£159.02	Monthly equipment costs plus annual costs divided by 12
Total costs		
One-off	£4,878.20	Sum of one-off equipment costs, set up cost and additional monthly costs in the first three months
Annual	£1,908.19	12 multiplied by the monthly cost beyond 3 months

†Not included in total costs, as this is applied separately in the model.
Abbreviations: NHS, National Health Service; NIV, non-invasive ventilation.

The annual cost of invasive ventilation is assumed to be the mean grand total cost in Table 6 of Noyes 2006 (£104,352) (4). This was inflated from 2005/06 to 2020/21

costs using the PSSRU NHSCII, to a value of £142,790. The one-off cost associated with invasive ventilation assumes four patients spend four months in a high-dependency unit at a cost of £800 per day (Table 8 Variable B of Noyes 2006 (4)). This was inflated to £1,095 per day, giving a total cost of £133,277. The cost of paediatric and adult outpatient assessments was taken from the 2021/22 National Tariff Payment System.

These values differ from those in the submission as not all inflation factors were calculated using the PSSRU NHSCII, and those that had 2020/21 values were calculated using the updated PSSRU published in December 2021.

B17. The company suggests that 'doses are generally rounded to the nearest vial in order to obtain the correct dose as an average of two infusions' (CS page 162). However, the cost calculations in the IOPD model do not appear to include this rounding, please explain this discrepancy.

The model does not include any rounding, as the number of vials used may be rounded up or down, thus the average number of vials across two infusions is used.

B18. Appendix L refers to the company's use of Pompe Registry data to estimate parameters such as decline in 6MWT and in FVC% predicted. The reference cited is "Sanofi Genzyme. Pompe Registry Report. 2017". In the reference pack we found a pdf 'Sanofi Genzyme Pompe Registry.pdf' which, upon examination, appears to be a patient information leaflet for alglucosidase alfa which includes a brief description of the Pompe Registry and the process of enrolling as a patient in the registry. We are unclear of the relevance of this in relation to the citation in Appendix L. We assumed the report would contain information and data relevant to FVC and 6MWT. Please can the company clarify if this is the document supplied is as intended.

We have used the submitted patient information leaflet as a source of background information on the registry.

We do not have a permission from the Pompe Registry to submit the report that was used to estimate the parameters mentioned above; however, all the relevant available data was included in the submission.

Section C: Textual clarification and additional points

None

Appendix: Updated results

Cost-minimisation

Table 10: Base-case results, discounted – LOPD

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

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Figure 4: Tornado diagram – LOPD

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 11: Scenario analysis results, LOPD

Scenario	Incremental cost	% change
Base case	[redacted]	-
Discount rates set to 0%	[redacted]	[redacted]
Discount rates set to 1.5%	[redacted]	[redacted]
Time horizon set to 15 years	[redacted]	[redacted]
Time horizon set to 30 years	[redacted]	[redacted]
Weibull curve used for mortality	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AVAL, avalglucosidase alfa.

Table 12: Base-case results - IOPD, discounted

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

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Figure 5: Tornado diagram, IOPD

[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 13: Scenario analysis results, IOPD

Scenario	Incremental cost	% change
Base case	[redacted]	[redacted]
Discount rates set to 0%	[redacted]	[redacted]
Discount rates set to 1.5%	[redacted]	[redacted]
Time horizon set to 10 years	[redacted]	[redacted]
Time horizon set to 20 years	[redacted]	[redacted]
Log-normal curve used for mortality	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
No double dosing for ALGLU	[redacted]	[redacted]
CRIM-positive only	[redacted]	[redacted]
CRIM-negative only	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; CRIM, cross-reactive immunological material.

IOPD CE model

Table 14: IOPD – Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; LYG, life years gained; QALY, quality-adjusted life year.

Table 15: Clinical outcomes - IOPD

	ALGLU	AVAL	Incremental
Life years	[redacted]	[redacted]	[redacted]
Ventilator-free life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Patient	[redacted]	[redacted]	[redacted]
Caregiver	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease; LYG, life years gained; QALY, quality-adjusted life year.

Table 16: Disaggregated costs - IOPD

Outcome	ALGLU	AVAL	Incremental
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Ventilator	[redacted]	[redacted]	[redacted]
Ventilator-related	[redacted]	[redacted]	[redacted]
Wheelchair	[redacted]	[redacted]	[redacted]
Wheelchair-related	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]
Disease-related	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; IOPD, infantile-onset Pompe disease.

Figure 6: Tornado diagram - IOPD

Abbreviations: IOPD, infantile-onset Pompe disease.

Table 17: IOPD – Scenario analyses performed

Area of uncertainty	Base case	Incremental costs
Discount rate set to 1.5%	3.5%	[redacted]
Discount rate set to 0%		[redacted]
Generalised gamma curve used for VFS	Weibull curve	[redacted]
Generalised gamma curve used for IVFS		[redacted]
Log-normal curve used for OS		[redacted]
CRIM+ only	Combined population	[redacted]
CRIM- only		[redacted]
No double dosing for ALGLU	Double dosing in the first 3 months	[redacted]
4.5 outpatient visits for dosing for AVAL on treatment initiation	3 visits	[redacted]
25-year time horizon	50 years	[redacted]

Abbreviations: AVAL, avalglucosidase alfa; CRIM, cross reactive immunological material; IOPD, infantile onset Pompe disease; IVFS, invasive ventilation-free survival; OS, overall survival; VFS, ventilation-free survival.

LOPD CE model

Table 18: Base-case results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; LYG, life years gained; QALY, quality-adjusted life year.

Table 19: Disaggregated QALYs (discounted)

	ALGLU	AVAL	Difference
Patient Life years	[redacted]	[redacted]	[redacted]
Total QALYs			
Patient QALYs			
Caregiver disutility			

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; QALY, quality-adjusted life year.

Table 20: Proportion of patients reaching each milestone (not mutually exclusive)

	ALGLU	AVAL	Difference
Non-invasive ventilator	[redacted]	[redacted]	[redacted]
Invasive ventilator	[redacted]	[redacted]	[redacted]
Wheelchair	[redacted]	[redacted]	[redacted]
Ventilator and wheelchair	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 21: Time on treatment and to reaching milestones

	ALGLU	AVAL	Difference
On treatment	[redacted]	[redacted]	[redacted]
To non-invasive ventilator*	[redacted]	[redacted]	[redacted]
To invasive ventilator*	[redacted]	[redacted]	[redacted]
To wheelchair*	[redacted]	[redacted]	[redacted]

*Among patients that reached these endpoints.
Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Table 22: Disaggregated costs (discounted)

	ALGLU	AVAL	Difference
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration			
Drug initiation			
Ventilator			
One-off costs			
Annual costs			
Wheelchair			
One-off costs			
Annual costs			
Disease management			
Treatment-related monitoring	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa.

Figure 7: Tornado diagram - LOPD

Abbreviations: AE, adverse event; Alg, alglucosidase alfa; Ava, avalglucosidase alfa; HR, hazard ratio; 6MWT, six-minute walk test.

Table 23: Scenario analysis results - LOPD

Scenario	Incremental cost	Incremental QALYs	ICER
Base-case	[redacted]	[redacted]	Dominant
Effect persistence for AVAL equal to ALGLU	[redacted]	[redacted]	Dominant
Effect persistence for AVAL set to 6 years	[redacted]	[redacted]	Dominant
Effect persistence for AVAL set to 4 years	[redacted]	[redacted]	Dominant
Discount rates set to 0%	[redacted]	[redacted]	£41,638
Discount rates set to 1.5%	[redacted]	[redacted]	£3,260
Time horizon set to 15 years	[redacted]	[redacted]	Dominant
Time horizon set to 30 years	[redacted]	[redacted]	Dominant
FVC decline no treatment -0.832% per year	[redacted]	[redacted]	Dominant
FVC decline no treatment -1.248% per year	[redacted]	[redacted]	Dominant
6MWT decline no treatment -9.528m per year	[redacted]	[redacted]	Dominant
Weibull curve used for mortality	[redacted]	[redacted]	Dominant
Patients below the median age only	[redacted]	[redacted]	£12,875
No caregiver disutility	[redacted]	[redacted]	Dominant
[redacted]	[redacted]	[redacted]	Dominant
Alternative disutilities from DMD	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; QALYS, quality-adjusted life year; 6MWT, six-minute walk test.

Table 24: LOPD – Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
ALGLU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 8: LOPD - cost-effectiveness plane

Abbreviations: LOPD, late-onset Pompe disease; QALYs, quality-adjusted life years.

Figure 9: LOPD - CEAC

Abbreviations: CEAC, cost-effectiveness acceptability curve; LOPD, late-onset Pompe disease.

References

1. Pena LDM, Barohn RJ, Byrne BJ, Desnuelle C, Goker-Alpan O, Ladha S, 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.
2. Gungor D, de Vries JM, Hop WC, Reuser AJ, van Doorn PA, van der Ploeg AT, 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.
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4. 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.
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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pompe disease - avalglucosidase alfa [ID3737]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Association for Glycogen Storage Disease UK
3. Job title or position	CEO
4a. Brief description of the organisation (including who funds it). How many members does it have?	The charity was founded in 1986 to promote the interests of people affected by Glycogen Storage Disease. This is achieved through provision of information, support and education for people affected, their families and professions in the field. We engage widely with our 122 charity members and 1506 registered community members and work closely with other charities and professional partners to drive up standards of care. The charity receives funding from charitable donations and trusts and wide range of treatment industry organisations.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? If so, please state the name of manufacturer, amount, and purpose of funding.	£21,484 received in total from Sanofi Genzyme for on-line conference series, patient education, benefits support and community services. No comparator company is listed by NICE in the appraisal matrix (funding also received from others with an interest in Pompe disease) No published position on the technology or comparator or any other relevant interest.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

5. How did you gather information about the experiences of patients and carers to include in your submission?	In July 2021 AGSD-UK issued a survey to better understand the impact of the condition in the UK. Wide distribution elicited 56 responses from people with Pompe, along with 29 from carers/family members of those affected. Of these 85 responses, 71 related to people with Late Onset Pompe Disease (LOPD) and 14 to people with Infantile Onset Pompe Disease (IOPD). These responses have informed this submission, along with follow up interviews with a small number of people affected and previously published background information.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Background and diagnosis** Pompe is a rare, life threatening and life changing condition with variable rates of progression and age of onset. First symptoms can occur at any age from birth to late adulthood. Earlier onset is usually associated with the most rapid progression and even greater disease severity. At all ages the condition is characterised by skeletal muscle weakness causing increasingly severe respiratory and mobility problems. The most severely affected infants usually present within the first 3 months after birth. They have characteristic cardiac problems due to heart enlargement in addition to generalised skeletal muscle weakness, with a life expectancy of less than 2 years if untreated. In contrast to classic infantile-onset Pompe, late-onset generally refers to all cases in which hypertrophic cardiomyopathy did not manifest or was not diagnosed at or under the age of 1 year, as well as to all cases with symptom onset above the age of 1 year. Though people with late onset during childhood, adolescence, or adulthood rarely manifest cardiac problems, progressive muscle weakness leads to increasing dependency on mobility aids and respiratory support, affecting independence, quality of life and life expectancy. In the absence of a new-born screening programme for Pompe, the route to diagnosis is uncertain and can be challenging. Among survey respondents, those with infantile onset were generally diagnosed in the first months of life, following symptoms such as floppy baby syndrome and persistent chest infections. They first saw a range of specialists including gastrointestinal and metabolic physicians and cardiologists. Parents of infants affected described the anxiety and devastation of their journey to diagnosis and treatment: *"The whole experience has been an emotional rollercoaster and has been mentally draining. Both my partner's and my mental health have suffered from watching our son deteriorate rapidly before showing some improvement, but the hardest thing is knowing that this condition is going to eventually claim his life."* - Father of a child with IOPD Among those with late onset only 26% were diagnosed within 12 months of symptoms such as breathing or mobility problems.14% waited over 10 years for diagnosis. The delay reflected the number and range of specialists that patients and carers reported seeing before receiving a diagnosis. Those affected expressed frustration at the impact of delayed diagnosis on

	their access to treatment to stave off degeneration and maintain function and independence: *"If I had an early diagnosis and been able to start ERT earlier I might have been able to continue to work. I felt better and saw some improvements after 6 months, but too much muscle damage had already occurred"...Had been very independent, travelled, I might have been able to do more without the obstacles I face now."* - LOPD patient in their 60s. More than 10 years before diagnosis from first onset of symptoms. **Use of health, welfare and social care services** The survey pointed to extensive use of health and welfare services, as well as highlighting unmet need in areas such as counselling/psychology. The overwhelming majority of respondents reported using physiotherapy services (99%) and accessing a Disability Living Allowance or Personal Independence Payment ((85%) All those with infant onset had used dieticians, and most had used speech and language therapy (92%) and occupational therapy (75%). Half reported accessing paid carers. A third had used a social worker while a quarter accessed NHS psychology services. The same number had educational needs identified through a Special Educational Needs or Disabilities Coordinator. Among those with late onset 57% had accessed dieticians and 53% occupational therapy services. 28% had accessed speech and language therapy, 26% had accessed psychology services, while 21% had used a paid carer and 21% a social worker. Access to aids and adaptations was seen as particularly important: *"… we need to be extremely careful and use appropriate supports such as a bath board, inflatable seats, rails or a bath lift to assist with getting in and out. A fall in a bath can be extremely painful and dangerous." – person with LOPD in his 30s* **Living with Pompe** For people affected, their symptoms and prognosis take a huge toll in terms of their physical and psychological wellbeing: *"My breathing and mobility are both getting worse. I feel worried that I will end up with breathing support fulltime and dread the thought that I won't be able to move around independently" – person with* LOPD in their 60s Physical symptoms reported by respondents were wide ranging. For the majority these included significant issues with pain (61%), sleep (58%) and digestive problems (62%) as well as muscle problems (93%), debilitating fatigue (88%) respiratory impairment (64%) and delayed motor skills (52%). In addition, a substantial minority of respondents reported other symptoms including: difficulty regulating temperature (41%), continence issues (40%) scoliosis (28%) cardiac symptoms (18%) problems with hearing (15%) and speech problems (8%). For people with late onset the most challenging symptoms were ranked as muscle weakness (72%) and respiratory problems (37%). For those with infant onset the most challenging symptoms were ranked as feeding and digestive problems (86%)

	muscle weakness (71%) and respiratory symptoms (50%). These symptoms have a significant impact on the everyday lives of people affected, with most reliant on some form of respiratory support (60%) and walking aids (75%). 53% were wheelchair users (46% for those with late onset, 64% for those with infant onset). Survey respondents overwhelmingly reported that they had missed out on doing activities they enjoyed in the last 12 months because of Pompe (92%): *"… can't go out and do the things I want to do without someone else to get me there and help me around"* – person with LOPD in their 20s 85% reported an impact on their ability to work, including restrictions in the types of roles possible. 40% of respondents reported having to leave work altogether or feeling incapable of working, with a knock on effect on their sense of self worth: "*[I] retired early from work as it became too difficult and I felt I couldn't do what I wanted and had done previously, which made me feel guilty as I became less and less productive*" – person with LOPD in their 50s Many respondents commented on the impact on independence: *"I cannot go anywhere alone for the fear of falling or struggling with energy levels*" – person with LOPD in their 30s "*Overwhelming fatigue and how to manage treatment has prevented him from going to uni and he's unsure what to do next*" - Mother of a teenager with LOPD *"[He worries about] how he'll earn an income and manage if he doesn't live with us*" - Mother of a teenager with LOPD The symptoms and prognosis had a significant impact on respondents' mental health and caused considerable anxiety for the future: *"Getting worse. Being unable to look after my children. Being unable to look after myself. Needing help from others more often. Having to use a wheelchair or ending up on a ventilator 24 hours a day. Losing independence. No longer being able to work. Possibly dying." – person with* LOPD in their 40s *"How fast I will decline. Lack of income if things decline quickly. Inability to be the mother my children deserve. Inability to eat food - have an NG tube at present as can't eat without vomiting"* – person with LOPD in her 40s *"Lack of independence and being left alone"* – person with LOPD in their 40s *"Being hopeless and a burden"* –person with LOPD in their 40s **What do carers experience when caring for someone with the condition?** Respondents with caring responsibilities for people living with Pompe described the impact this had on their lives. This included 88% reporting an effect on their finances and 83% on their ability to work their preferred hours or at all:

	"Being a carer for my son for the last 12 years has taken a huge toll on my life. Being a single mother of 4 children (2 with Pompe) has been a massive juggling act between being there to support them and trying to earn." - Mother of adult with LOPD "*As a single parent I left my job when my son was diagnosed to be able to attend the many appointments and infusion days*." - Mother of an under-10 living with LOPD *I am currently in the process of reducing my hours as I can't cope with working as much as my caring demands have increased"* - Mother of teenager living with IOPD 80% of parents or carers reported an impact on their social activities and many mentioned the effect on other family members: *"Long hospital stays in Birmingham taking us away from friends, family and our home...We cannot volunteer or carry out our hobbies as we used to due to his health, equipment and oxygen requirements. To be honest, the list is never ending."* - Mother of a child living with IOPD *"My other children don't always get the attention, and opportunities to do things because of their brother's Pompe disease"* - Mother of an under-10 living with IOPD 71% reported an effect on their physical health: "*I now feel like I am doing two jobs and get quite tired near the end of days despite not necessarily doing what I previously would say would be strenuous. The mental and physical side of caring has been an eye-opener*" - Husband of person with LOPD An overwhelming 93% of parents and carers reported an impact on their mental health: *"[I] worry that he's still breathing all the time. Having to provide good balanced meals. Stressed as not seen a specialist since diagnosed. I went into depression over it last year. I don't sleep the night before treatment, as I'm worried about messing it up."* - Wife of person with LOPD in his 60s *"Emotional distress and poor mental health raising a child who isn't expected to live for long. Tiring and exhausted. No time for self care, cooking, exercise, social activities"* - Mother of a child with IOPD When asked about their hopes and concerns for the future a major concern among parents and carers was how the person they care for would cope if they were unable to continue to provide support.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available	87% of people represented in the study had received regular myozyme infusions, the standard treatment for Pompe. Of these three were no longer using myozyme. Those with late onset receiving regular infusions reported that they were given fortnightly. Those with infantile onset were evenly split between weekly or fortnightly infusions, Four were awaiting the start of enzyme replacement therapy and 18 had been in clinical trials.

on the NHS?	Perceptions of current treatment were mixed with 16% of late onset respondents receiving the standard therapy reporting that it had little or no impact on the condition whilst 35% reported only a moderate impact: *"Was hoping to see an increase in muscle strength to make legs more stable but hasn't happened"* –person with LOPD in their 40s Just under half of respondents were more positive: *"It has definitely slowed the progression of the disease significantly*" – person with LOPD in their 50s "*After treatment his energy levels are up and his overall wellbeing is drastically improved*." - Mother of a child with late-onset Pompe. Among those with infantile onset and their carers 23% reported a little impact on standard therapy and 15% a moderate impact. None reported no impact while 62% said standard treatment had a lot or a great deal of impact: *"Everything has helped and made a difference to the quality of his remaining life, but the ERT is giving him days and months of relative normality that he would otherwise [not] have had."* - Father of a child diagnosed with IOPD Some respondents reported side effects from treatment: "*Tiredness after infusion lasts for several days, I just recover and then I seem to be back in it... it's an endless routine*." – person with LOPD in their 40s Most were able to receive their infusions at home rather than travelling to specialist centres and this was welcomed: "*Very pleased to be able to have it at home."* – person with LOPD in their 50s "*Being able to be mobile at home while infusion running,*" - Parent of an under-10 with IOPD However, treatment continues to have an impact on patients' day to day lives: "*I'm very grateful for the treatment but I feel limited by the nurse coming to the house which means I have to plan my whole day around this and it wipes out 2 days a month that I can't do other things*" – person with LOPD in their 40s 31% of respondents mentioned difficulties cannulating and problems with needles as a disadvantage of current treatment: "*Long days, trouble cannulating, mental effects of feeling like a patient rather than a person*." – person with LOPD in their 20s

8. Is there an unmet need for patients with this condition?	Whilst the current standard therapy has significantly improved life expectancy and quality of life, it is still the case that patients who have been responsive to treatment experience debilitating symptoms and disease progression. Meanwhile, those with a limited or waning response to standard therapy describe a desperate and urgent need for more effective treatments. One respondent described the impact of seeing their independence ebb away and expressed that: 'without more effective treatment the only thing that would improve things for me is a change in the law around assisted dying' - person with LOPD in their 60s Respondents described losing hope as a levelling off in their response to standard therapy led to increasing dependence on walking aids and assisted respiration. They expressed the feeling that their lives were 'shrinking' and that improved therapy may come too late: 'Whilst the current treatment regime has had some efficacy there is a general sense for us in the Pompe community that better treatment options are urgently needed in order to slow down the rate of disease progression and improve our quality of life.' Person with LOPD in their 40s
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Among the small number of people with experience of avalglucosidase alfa who were followed up by interview there was optimism expressed for the future: *"Hoping to get some of my lost strength and mobility back. If I could walk again unaided or with just a walking stick, that would be wonderful.*" – person with LOPD in their 50s" *[I feel optimistic] that I have been given opportunity to partake in a clinical trial and that compared to the start of my journey with Pompe, the future doesn't look as scary…hope that one day, no one with Pompe will face some of the difficulties and pain that I have endured…having access to treatment that will enable them to have a near normal life, contributing to society and not faced with the obstacles and barriers that being disabled bring*" – person with LOPD in their 60s For a parent of a child with infant onset there was a significant reduction in the need for emergency admissions, while recipients of the new therapy commented on its impact in terms of their stamina and consequently their independence: "Before it was such a struggle to function. I felt constantly worn out. I didn't even want to meet friends. After 6-9 months the change was significant. I had more energy and fewer headaches. I was doing more. I could climb the stairs and was falling much less. I wasn't getting injured all the time." –person with LOPD in their 40s. The sentiment "*I feel like I have been given my life back"* –LOPD patient in their 40s –was echoed by other respondents.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The need for treatment with fortnightly infusions continued to place the same practical disadvantages and restrictions for those receiving the new technology, who expressed a wish for: "*Treatment that doesn't involve infusions every 2 weeks*" - LOPD patient in their 60s
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why	While the need for more effective treatment feels particularly urgent for those whose response to existing therapy is limited or waning, all those with this degenerative condition would benefit from the earliest possible access in order to slow progression, maintain function and independence and improve quality of life.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For those with this rare, degenerative, life limiting condition, the absence of screening and delays in diagnosis make the need for access to effective treatment to stave off muscle wastage and dependence on respiratory support still more urgent.
Other issues	
13. Any other issues that you would like the committee consider?	

Key messages - in up to 5 bullet points, please summarise the key messages of your submission:
• Pompe is a severe, degenerative, life limiting and life changing condition that affects every aspect of daily living. • The huge impact of Pompe on quality of life was demonstrated in AGSD's recent survey, involving 85 people directly affected, their parents and carers. The vast majority reported problems with muscle weakness, mobility and frequent falls, tiredness or overwhelming fatigue, pain, sleep problems, digestive issues and difficulties with respiration. A substantial minority reported a range of other symptoms including continence problems and difficulties with temperature regulation. The majority were reliant on respiratory support and mobility aids, with a substantial need for health, welfare and social care support. Over half were wheelchair users. Respondents described severe restrictions on their independence and ability to work and socialise, with a major detrimental effect on their mental wellbeing and significant anxiety about the future. • The overwhelming majority of parents and carers for those with Pompe reported that their mental and physical health, financial security, ability to work and take part in social activities were affected and many described a significant toll on their wellbeing. • The survey also showed the limitations of the standard therapy myozyme for those who do not tolerate it, whose response is limited or who are experiencing waning effectiveness. Just over half of those with late onset reported no, little or only moderate impact from standard therapy while in 38% of those with infant onset little or moderate impact was reported. Respondents articulated an urgent need for access to more effective treatments. • The small number of respondents who had experienced treatment with avalglucosidase alfa expressed optimism for the future, reflected on increased stamina and independence and spoke about 'getting [their] life back."

Kohler, L., Puertollano, R. & Raben, N. Pompe Disease: From Basic Science to Therapy. ***Neurotherapeutics*** 15, **928–942 (2018). https://doi.org/10.1007/s13311-018-0655-y**

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Avalglucosidase alfa for treating Pompe disease ID3737

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Muscular Dystrophy UK
3. Job title or position	Director of Care, Campaigns and Support
4a. Brief description of the organisation (including who funds it). How many members does it have?	Muscular Dystrophy UK is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 70,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them. We are also a member of NHS England's Paediatric Neurosciences Reference Group. Collaboration lies at the heart of our work and as well as our own response to this consultation we are supportive of that being submitted by the Association of Glycogen Storage Disease (AGSD).
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Yes, In March 2021, MDUK received £2,500 from Sanofi as a sponsorship for a translational research conference. We have received no other funding from Sanofi, nor have we published any position on the technology or comparator in the last 12 months.

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered by: - Published evidence on disease burden - Media case studies and reports - Collaboration with the Association for Glycogen Storage Disease (AGSD)
Living with the condition	
6. What is it like to live with the condition? What do carers	Pompe disease is a severe, degenerative, life limiting and life changing condition that affects every aspect of daily living. The huge impact of Pompe on quality of life was demonstrated in the Association of Glycogen Storage Disease (AGSD)'s recent survey, involving 85 people directly affected or their parents and carers. The vast majority reported problems with muscle weakness, mobility and frequent falls, tiredness or overwhelming fatigue, pain, sleep problems, digestive issues and difficulties with respiration. A substantial minority reported a range of other symptoms including continence and difficulties with

experience when caring for someone with the condition?	temperature regulation. The majority were reliant on respiratory support and mobility aids, with a substantial need for health, welfare and social care support. Over half were wheelchair users. Respondents described severe restrictions on their independence and ability to work and socialise, with a major detrimental effect on their mental wellbeing and significant anxiety about the future. Case studies have supported these findings. Many people say that by the time they are diagnosed, they are already unable to properly walk and rely on a walking aid and may also already struggle to breath and are on a ventilator. Some have also said that they were unprepared for the speed at which their disease progressed and the way it affected their everyday activities such as needing to sleep with a ventilator, and the exhaustion that follows simple tasks. As the disease progresses, patients struggle to hold a cup to drink, or hold a pen to write. Additionally, patients are at higher risk of fracturing their pelvis or hip, leading to needing orthopaedic intervention and reducing the mobility of these patients even further. As their breathing deteriorates, they also may need to use a cough assist machine to clear secretions from their lungs. The ASGD survey results also showed the overwhelming majority of parents and carers affected by Pompe disease reported that their mental and physical health, financial security, ability to work and take part in social activities were affected and many described a significant toll on their wellbeing.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The treatments currently available can help with symptom management but do not treat the underlying cause of Pompe disease. Even accounting for that distinction, currently available treatments have limitations. The AGSD survey showed the limitations of the standard therapy – myozyme - for those who do not tolerate it, whose response is limited or who are experiencing waning effectiveness. Just over half of those with late onset Pompe diseases reported no, little or only moderate impact from standard therapy while in 38% of those

	with infant onset Pompe disease little or moderate impact was reported. Respondents articulated an urgent need for access to more effective treatments. Similarly, case studies have shown the limited effectiveness of Enzyme Replacement Therapy with some saying that it 'doesn't work' and can 'knock you out for days'.
8. Is there an unmet need for patients with this condition?	Yes, as all treatments currently focus on alleviating the symptoms rather than addressing the underlying cause of the disease.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The small number of respondents who had experienced treatment with Avalglucosidase alfa expressed optimism for the future, reflected on increased stamina and independence and spoke about 'getting [their] life back."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	No disadvantages have been raised.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The population as described in the scope document (paediatric and adult) are defined appropriately. We do not feel that any other groups would benefit more or less.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	That this treatment is available through home infusion helps reduce the inequality that can be experienced around access to other treatments, due to both geographical disparity of access and the burden of travel costs to receive treatment.

Other issues	
13. Are there any other issues that you would like the committee to consider?	No other issues to raise.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission:	

- Pompe disease is a severe, degenerative, life limiting and life changing condition that affects every aspect of daily living
- In the AGSD survey, a vast majority reported problems with muscle weakness, mobility and frequent falls, tiredness or overwhelming fatigue, pain, sleep problems, digestive issues and difficulties with respiration.
- The treatments currently available can help with symptom management but do not treat the underlying cause of Pompe disease.
- The AGSD survey showed the limitations of the standard therapies for those who do not tolerate it, whose response is limited or who are experiencing waning effectiveness.
- Respondents who had experienced treatment with Avalglucosidase alfa have told us how positively life-altering the treatment is.

Thank you for your time.

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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

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Date completed	25th February 2022

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- Dr Robin Lachmann, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust

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- Lois Woods, Senior Research Assistant, Southampton Health Technology Assessments Centre (SHTAC) for performing literature searching and critically appraising search strategies.

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).
- Dr Lachman has received consultancy fees, meeting expenses and honoraria for speaking from SanofiGenzyme. He has received one honorarium related to Pompe disease (an educational talk on receptor mediated uptake of lysosomal enzymes, including pre-clinical data for avalglucosidase).

- 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.

This report should be referenced as follows:

Souto-Ribeiro, I; Maund, E; Cooper, K; Pickett, K; Tomie Takahashi, M; Scott, DA; Shepherd, J. Avalglucosidase alfa for treating Pompe disease - A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2022

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
6	The lifetime incremental survival advantage for AVAL is likely to be underestimated (LOPD)	4.2.6.2.1
7	The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs (IOPD) and LOPD)	4.2.8
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)	4.2.8.1
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 (IOPD)

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.

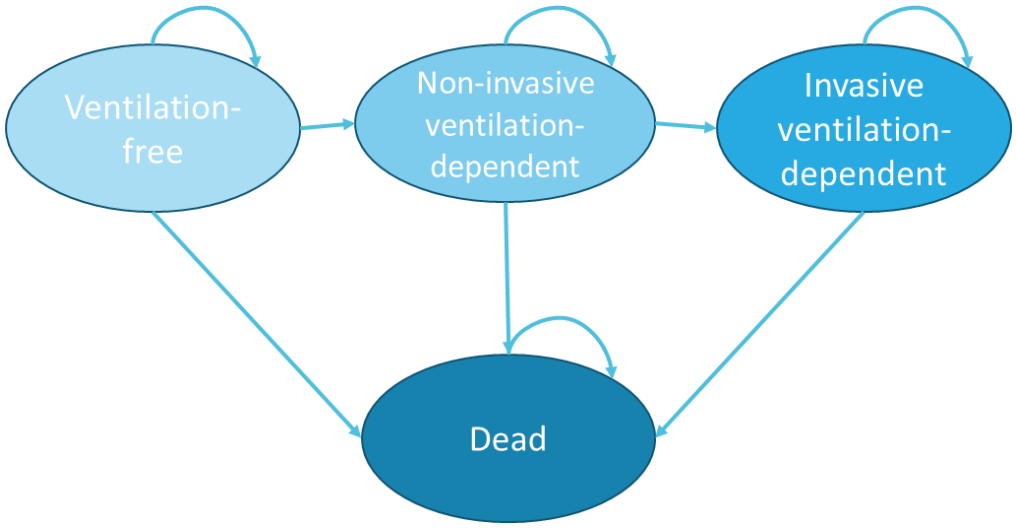

Figure 1 IOPD Model Structure

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

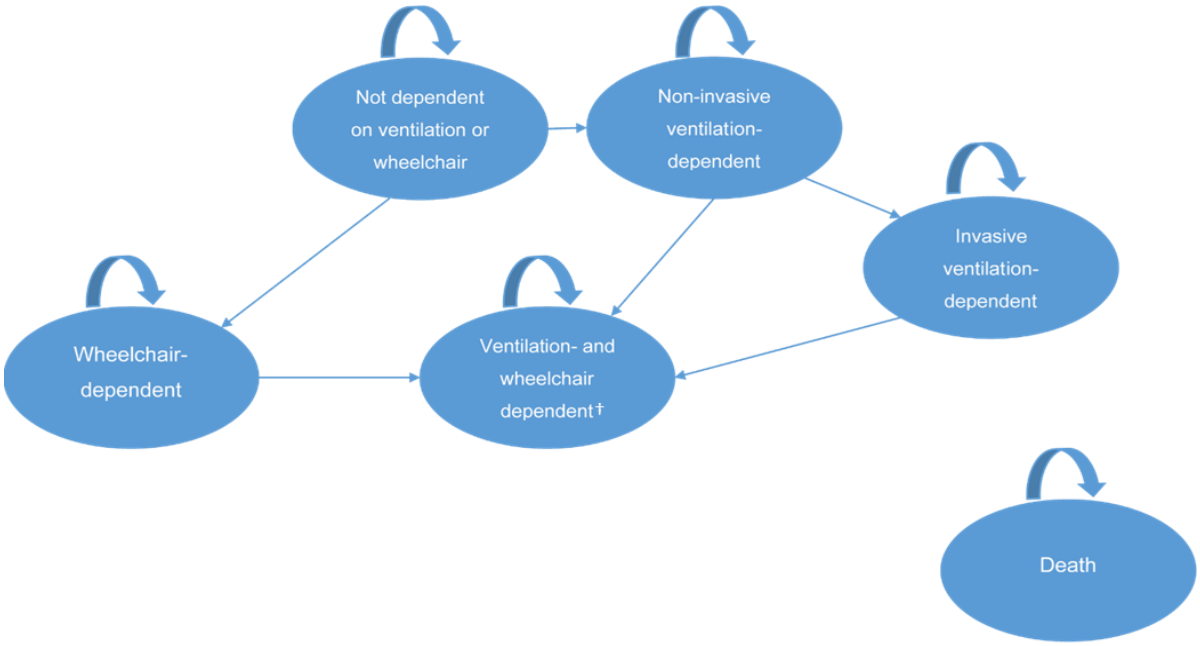

Figure 2 LOPD economic model schematic

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]		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]	

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

		Drug amount required (mg)	Number of vials required		Difference (round up) fraction of vials		Difference (round up) in amount (mg)	
Profile	Weight		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.

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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 (lOPD)		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 (lOPD)		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 (lOPD)		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.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

ERG response to the Factual accuracy check

Avalglucosidase alfa for treating Pompe disease [ID3737]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **12pm on Thursday 10 March 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

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

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that the cost-comparison approach is not adequately justified and does not meet the NICE reference case criteria, as AVAL may offer a clinical benefit compared to ALGLU.	We propose that wording on the cost-comparison approach not being adequately justified or not meeting reference case criteria is removed.	The Addendum to the Guide to the methods of technology appraisal states that a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than the comparators (1). Following the routing of AVAL through the STA rather than the HST process, the company made the conservative assumption that AVAL provides similar health benefits to ALGLU to facilitate quick decision-making and not delay patient access to AVAL, given the uncertainty in the clinical data inherent in a rare disease setting.	Not a factual inaccuracy, no change made. The ERG's assessments of the company's models against the NICE reference case are shown in the ERG report section 4.2.1. On the basis of this, it is the ERG's view that the cost utility models better fit the NICE reference case and should therefore be the focus of decision making.

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

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG considers the only available evidence for IOPD to come from the randomised part of the Mini-COMET trial (n=11).	We propose the ERG correct this statement (and similar statements throughout the report) to reflect the	It is inappropriate to discard evidence from a single-arm trial in IOPD, an ultra-rare subpopulation of Pompe disease with a high level of unmet	Not a factual inaccuracy, no change made.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	evidence from the entire Mini-COMET trial (n=22).	need. This evidence shows improvement or stabilisation in patients who were previously declining or sub-optimally responding to the current standard of care, ALGLU. We are concerned with this approach to evaluating a treatment that has been routed through the STA process, but would have been better suited for HST. We also believe that this decision by the ERG contradicts the new NICE HTA manual (2) which recognises that rare diseases are an area where evidence generation is particularly challenging, and where more acceptance of uncertainty is recommended.	The company has chosen to mis-quote the ERG. Issue 4 in section 1.5 of the ERG report states: "The only available *comparative* evidence for the clinical effectiveness of AVAL in the IOPD population is the phase 2 mini-COMET trial. However, with a sample size of n=11 participants the results are highly uncertain." Furthermore, we do not discard evidence, rather, we prioritise it in terms of its relevance to the decision to be made. ERG report Table 8 report clearly shows that mini-COMET enrolled 22 patients, 11 of whom were in the cohort (#3) in which AVAL was compared with ALGLU. Since the decision problem assess efficacy and safety of AVAL *in comparison to* ALGLU, this cohort of 11 patients is therefore pivotal. The outcomes of AVAL treatment in the other 11 patients in the study (from cohorts 1 and 2) is less informative because there is no direct comparison to AGLU. The NICE appraisal committee, however, may choose to take these non-comparative data into

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
			account as supporting, contextual information, but ultimately their decision will be most informed by evidence based on the 11 patients in cohort 3. We would also like to point out that in our report we have indeed acknowledged the challenges of evidence generation in rare diseases such as this. Finally, as a point of clarification, the new NICE manual does not apply to this appraisal. Only NICE appraisals started after 1st February 2022 are subject to the methods and processes in the new manual. Nonetheless, this is a red herring because our approach to assessing the evidence would be the same irrespective of whether old or new methods and process.

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

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG considers that there is no 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. The ERG proposes that the same duration of effect should be used in the economic model for ALGLU and AVAL.	We propose changing the text to acknowledge that there is evidence showing the duration of the treatment effect of AVAL.	NEO-EXT provides these data (for example, Tables 25 and 27 in Document B). In addition, as described in Issue 6, the ERG proposal is inconsistent with their approach to modelling an OS benefit of AVAL. We therefore believe a similar consideration should be given to the duration of effect as was given to OS.	We acknowledged in ERG report section 4.2.6.2 that the NEO-EXT study provides data on the effect of AVAL until week 312. However, the data is very limited and uncertain since the NEO-EXT is a single-arm study with a small sample size, and only two patients at risk at week 312. To better reflect this, we rephrased the first sentence as follows: "The ERG considers that there is **limited** evidence showing the duration of the treatment effect of AVAL."

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

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
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.	We propose the ERG amend the wording to clarify that the company assumed dose rounding between two infusions (as explained in the response to clarification questions).	Based on clinical advice provided to the company, the assumption is that the dose may be rounded up or down, not always up and the dose can be averaged across infusions. The assumption is not that vials may be shared, but that the dose required at	Not a factual inaccuracy, no change made. We would like to point out that ERG report section 4.2.8.1 mentions that doses are generally rounded to the whole vial to obtain the correct dose as an average of two infusions, as

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		each infusion is not rounded up for every infusion. By assuming vial wastage when there isn't any, the ERG is underestimating the potential savings associated with AVAL use. The company will seek further clinical input on what is the current clinical practice regarding vial wastage.	stated in the company submission. However, we do not find any evidence of this approach in the models though, as no wastage has been assumed. Clinical advice to the ERG suggested that the calculation of drug acquisition costs should be rounded up to the whole vial. This is the assumption used in the ERG base case analysis. We agree that additional clinical input would 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)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG changed the dose frequency of AVAL from every other week to weekly during the first 12 weeks, to match the dosing frequency of ALGLU in the IOPD model.	We propose this change is removed.	There is no clinical evidence or established practice to support the initial higher dose of AVAL.	Not a factual inaccuracy, no change made. There is no established practice for AVAL in any respect because it is not currently used in the NHS. 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. Hence, our assumption is justified on the basis expert clinical opinion and does not purport to be fact.

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)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state it is unreasonable to assume no differences between AVAL and ALGLU in the proportion of patients requiring a dose increase.	We request the statement on the assumption being unreasonable is removed.	We believe in the light of the available evidence this assumption may be considered conservative, but not unreasonable. Further, it is in line with the ERG preferred base case, which assumes no difference in effectiveness between the ERTs.	Not a factual inaccuracy, no change made. Our job is to assess the appropriateness and validity of the company's analyses using reason, amongst other considerations. In the interests of balance we point out where the company's assumptions and use of data is reasonable and unreasonable. We would like to point out that there are several instances of the former in our report.

Table 1: Factual/textual errors

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
Section 2.2.1; page 27	The following sentence contains a spelling error: *The cause of Pompey disease is mutations in the gene…*	Change 'Pompey' to 'Pompe'.	We have now corrected this.
Section 2.2.1; page 27	The following sentence is imprecise: *All people with IOPD have GAA activity of less than 1%...*	Please change to: *All people with IOPD have GAA activity of less than 1% of normal range*	We have now amended this on page 28 by adding the words "*of normal range*"
Section 2.2.1.1; page 28	The following sentence is incorrect, as CRIM positive patients have some enzyme activity (<1% of normal range): ***CRIM-positive** people make a non-functional form of GAA*	Please change to: ***CRIM-positive** people make a form of GAA with severely impaired activity*	We have now amended this on page 28 by changing the words "*a non-functional form of GAA"* to "*form of GAA with severely impaired activity"*
Section 2.2.1; page 27	The following sentence implies that ALGLU and BSC are comparable treatment options: *Currently Pompe disease is managed with enzyme replacement therapy (ERT) comprising the drug ALGLU, or with best supportive care.*	Please amend to clarify that they are not comparable treatment options.	We have now changed the text on page 27 to read: *"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.* We believe this accurately reflects the treatment management for Pompe disease

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
Section 2.2.1.2; page 28	The following paragraph contains duplicate text: *Our clinical expert on LOPD advised that patients diagnosed at a younger age experience faster disease progression. 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.*	Remove text highlighted in green.	We have amended this text on p28 by deleting the sentence "*Our clinical expert on LOPD advised that patients diagnosed at a younger age experience faster disease progression"*
Section 2.2.1.3; page 29	The following sentence contains a spelling error: *As highlighted by one of our clinical experts, the purpose of ERT is to slow the inevitable progresson of Pompe disease, thus it is not a curative treatment.*	Change 'progresson' to 'progression'.	We have now corrected this.
Section 2.2.1.3; page 29	The following sentence likely contains an error: *Following these transfusions, patients are transferred to a home care company, under contract to NHS England…*	Please check intended meaning and correct the statement.	We have deleted this sentence and replaced it with the following on page 29: *"Patients receive subsequent transfusions at home, provided by a home care company contracted to NHS England."*
Section 2.2.1.3; page 29	The following statement is not consistent with company sales data implemented in the model and suggests all patients eventually become independent:	We propose the ERG correct the statement to reflect the fact that only a proportion of patients become fully independent in their infusions.	We have corrected this text on page 29 by deleting the word "they" and replacing it with the word "some". The sentence now reads "*Over time, as patients and their families become familiar with the*

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
	Over time, as patients and their families become familiar with the process, they are able to manage the infusion themselves with the role of the home care company reduced to delivering the drug and supplies only		*process, some are able to manage the infusion themselves"*
Section 2.2.1.4; page 29	The following statement is ambiguous and potentially inconsistent with clinical expert opinion received and with the rest of the document: *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.*	Please correct the statement to reflect clinical opinion.	This sentence accurately reflects the opinion of our clinical expert. We have clarified our meaning by amending the sentence that follows it, by deleting "would" and adding "in England". That sentence on p29 now reads *"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."*
Section 2.2.1.5; page 31	The following sentence contains an error: *A large Dutch cohort study of LOPD patients, including 88 patients receiving ALGLU 20mg/g every week…*	Please correct the dose in the statement to 20 mg/kg.	We have now corrected this.
Section 2.3.2; page 34	The following statement does not accurately reflect the company position: *However, the company argue that the data are not strong enough to model long-term events.* We do not believe the data are not strong enough, but that Mini-COMET did not provide sufficiently long-term results to use	Please correct the statement to reflect this.	The sentence is not incorrect as written, but for clarity we have amended so it now says "However, the company argue that the data are insufficient to model long-term events.

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
	in an economic model (as stated in Appendix L to CS). In addition, due to the ultra-rare nature of IOPD there is insufficient evidence to support an extrapolation from the Mini-COMET endpoints to longer-term outcomes such as OS, wheelchair and ventilator use.		
Section 2.3.2; Table 6; page 35	Table 6 states: *The ERG notes the following omissions :* • *Change in respiratory function (IOPD)* • *Immunogenicity response* • *Cardiac outcomes (LOPD)* Immunogenicity data was provided, while change in respiratory function and cardiac outcomes were deemed inappropriate outcome measures to a particular population	Please correct the statement to reflect the data that were submitted or irrelevant.	We have deleted the following text in table 6: "*The ERG notes the following omissions :* • *Change in respiratory function (IOPD)* • *Immunogenicity response* • *Cardiac outcomes (LOPD)"*
Section 3.1; page 39	With regard to the following statement, details of why the four studies were included in the CS are presented in Appendix D: *It is unclear, however, how the four studies that were included in the CS were subsequently identified from these*	Please refer to the following statement in Appendix D: *Publication database searches were supplemented with unpublished data of completed and ongoing Sanofi studies of avalglucosidase alfa.*	Not a factual inaccuracy. Our meaning here was that it is unclear what process was used to determine that four of the 147 studies identified as meeting the eligibility criteria for the review were relevant to the CS decision problem. For example, was another round of screening conducted, using more specific eligibility criteria? We have, however, amended the sentence

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
			to improve the clarity of our main point in this paragraph, as follows: “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…”.
Section 3.1; Table 7; page 41	The following response in Table 7 is unclear: *Yes and no*	Please clarify	We have clarified our meaning here by changing the answer to the question in the table to: “No – the eligibility criteria were specified, but these were not appropriate to the decision problem”. As a consequence of this change, we have also amended the decision for the same question in Table 58 in Appendix 2 (which provides the ERG’s full critical appraisal of the company’s systematic review) to the same text.
Section 3.1; Table 7; page 41	The following question was marked as ‘unclear’, however, details of data extraction were provided in Appendix D: *Was data extraction performed by two or more reviewers independently?* Appendix D, page 13 provides the following information: *Data were independently captured from each included study by a single investigator, with validation performed by a second, senior investigator. This validation*	Please amend the text	Not a factual inaccuracy; no change made. The ERG’s judgement for this question was “Unclear” and remains so. We provided our reason for this judgement in Table 58 (Appendix 2) of our report. We were aware of the text in CS Appendix section D.1.1 describing how data extraction was carried out (and we have referenced this section in Table 58). However, we believe the text reads ambiguously, and it is difficult to determine if it means that the reviewers carried out data extraction independently of each other or if the second

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
	step included confirming the accuracy of data against the source article as well as completeness, to ensure that no relevant data were missed during extraction		reviewer just checked the data the first reviewer had extracted.
Section 3.2.1.1; page 44	The following paragraph (in particular the highlighted part) is unclear, and Sanofi therefore cannot comment on its factual accuracy: *A clinical expert consulted by the ERG believes that the participants in the Mini-COMET study are not 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. In the experts' experience, there are only a minority of people who do not experience progression on this dose (and thus, the study will only not represent a minority of treatment-experienced patients), but the expert stated that they were aware of reports of good progress on the 20 mg/kg qow dose. 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.*	Please amend paragraph, as the statement appears contradictory and the messaging is unclear.	We have amended this paragraph to improve clarity, including removing the text highlighted in green by the company.

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
Section 3.2.1.1; page 44 **Section 3.2.1.2; Page 49**	Statements that appear contradictory are included regarding the clinical expert opinion: *A clinical expert consulted by the ERG believes that the participants in the Mini-COMET study are not 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 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*	Please provide a consistent statement regarding the clinical expert's opinion on how representative Mini-COMET patients are of clinical practice.	We have clarified that the expert's opinion stated in the paragraph starting "A clinical expert consulted…" relates to their view about the representativeness of the Mini-COMET study's participant inclusion and exclusion criteria. The expert's view stated in the paragraph beginning with "The ERG's IOPD clinical expert…" relates to how representative they perceive the baseline characteristics of the Mini-COMET study participants presented in the CS (plus baseline CRIM status, which was not included in the CS) are of the patients treated in practice. These are different aspects of the study and we have provided our expert's views on each of these aspects; we cannot reconcile these views into one consistent statement.
Section 3.2.1.2; page 48	The following sentence is missing a word: *As noted in CS section B.2.3.6.2, there were multiple imbalances in baseline characteristics between the two arms Mini-COMET*	Add the word 'in' between 'arms' and 'Mini-COMET', like so: As noted in CS section B.2.3.6.2, there were multiple imbalances in baseline characteristics between the two arms in Mini-COMET	We have now corrected this.
Section 3.2.1.2; page 49	The following statements are incorrect: *We note from the Mini-COMET CSR[23] that the study included*	To acknowledge the single-arm portion of Mini-COMET, where [redacted] with CRIM-negative IOPD was treated with AVAL	We have clarified on page 50 that [redacted] with CRIM-negative disease was assigned to ALGLU in Cohort 3 and, additionally, that [redacted] with

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
Section 3.2.1.2; page 52 **Section 3.2.5.1, page 62**	[redacted] *(page 49)* *A further limitation of the Mini-COMET study is that it only included* [redacted] *with CRIM-negative disease, who happened to be randomised to the ALGLU arm.* Consequently, there are no data currently available on the efficacy and safety of AVAL in CRIM-negative IOPD… *(page 52)* *The* [redacted] *with CRIM-negative disease included in the study, who had had an abnormal baseline score on this measure, moved into the normal range (page 62)* [redacted] with CRIM-negative disease was assigned to Cohort 2 in Mini-COMET, and received AVAL 40 mg/kg for 6 months		CRIM-negative disease was assigned to Cohort 2 and was treated with AVAL. We have amended the text on page 53 to read as follows: "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." We have also amended the text on p. 62 to read as follows: "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."
Section 3.2.2.3; page 54	The ERG appears to have provided a risk of bias assessment of NEO1/NEO-EXT using a tool designed to assess comparative studies (3). We therefore believe the conclusions that the trial is at high risk of bias are not based on fact. The ERG also did not assess the non-RCT part of Mini-COMET.	We propose the text regarding high risk of bias is removed.	After consideration, we have removed the risk of bias assessment of NEO1/NEO-EXT so that the assessments presented in the ERG report relate to the risk of bias assessments presented in the CS only.

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
Section 3.2.5.3; page 65	The following statement is not factually correct: *In the COMET trial, participants assigned to AVAL showed statistically significantly greater mean improvements in 6MWT at Week 49 compared to baseline than those assigned to ALGLU (based on the 95% CIs)*	Based on the hierarchical design of the COMET trial, statistical testing of the difference between treatments for secondary endpoints is not appropriate due to the non-inferiority for the primary endpoint. The ERG should remove the statement regarding statistical significance.	We have now removed reference to statistical significance in this sentence, as suggested by the company. The sentence has been amended to: "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…". We would like to point out that the company's statement that "statistical testing the difference between treatments for secondary endpoints is not appropriate due to the non-inferiority for the primary endpoint…" is ambiguous as written. In the ERG's interpretation, statistical testing for secondary outcomes was not done the because the superiority test of the primary outcome (FVC% predicted) (which was permitted only because non-inferiority for the primary outcome was reached) – returned a p value of 0.0626, just missing superiority at the 5% significance level defined in the study protocol.
Section 3.2.5.4; page 68	The statement below does not take into account the hierarchical design of COMET and the fact that in the ETP all patients were receiving AVAL and therefore statistical testing of the significance of the observed differences is not appropriate:	Please correct the statement to reflect the trial design.	We have now removed the following sentence: "The company did not report, however, if differences between the arms were statistically significant."

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
	During the ETP, [redacted] *(clarification response A8, Table 5). The company did not report, however, if differences between the arms were statistically significant*		
Section 4.2.2.2.2; Table 24; page 84	In the company's justification column, the following statement was unclear: *…therefore the treatment effect was assumed to stop at* [redacted] *for AVAL and* [redacted] *(FVC) and* [redacted] *(6MWT) for ALGLU.*	The ERG could make it clearer that the assumption is [redacted] for FVC and 6MWT for AVAL	Text changed to: *"…therefore the treatment effect was assumed to stop at* [redacted] *(**both for FVC and 6MWT**) for AVAL and* [redacted] *(FVC) and* [redacted] *(6MWT) for ALGLU."*
Section 4.2.3.1; page 86	The following statement is not consistent with the corrected model provided as part of the clarification questions: *The IOPD patient characteristics in the 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 (4), while the characteristics reported in the CS (document B Table 61) are based on Broomfield et al.(5)*	Please correct the statement to reflect the final model provided.	The ERG report clearly states that the updated model provided by the company corrected this mistake and used the Broomfield study to inform the baseline characteristics of the population. However, to make it clearer, we have amended the text: *"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 (4), while the characteristics reported in the CS (document B Table 61) are based on Broomfield et al.(5)"*

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
Section 4.2.6.2, page 94	The following statement concerning the ongoing NEO-EXT trial may be misunderstood: *We note that only seven patients were still at risk at week 104 and only two at week 312.*	We propose correcting this to: *We note that data for only seven patients are available for Week 104 and for only two for Week 312.*	We changed the text as the company suggested.
Section 5.2.3.2; page 114	Furthermore, we consider that the PSA results do not appear stable at 300 simulations.	The report should note that cost differences across the PSA simulations are in the order of 100's of GBP, which is a fraction of 1% of the overall cost for the AVAL or ALGLU arm. There are differences between the deterministic and the probabilistic analysis, likely a non-linear effect of the model.	The ERG analysed the PSA results stability in more detail in section 5.3.2.3.2 and Appendix 4 of the ERG report. Therefore, to make this sentence clearer, the text in section 5.2.3.2 was changed to: *"Furthermore, we analysed the model stability of the company PSA"*
Section 6.2.2; Table 54; page 129	The base case and the PSA are both giving an incremental QALY gain of 0.42, but the PSA results cannot be so different to the base case. This must be either a transcribing error, or an error in a parameter in the PSA (presumably a HSUV because the costs align).	Please review and amend accordingly.	We agree. The base case considered total QALYs, and the PSA considered only the discounted patient QALYs. Table 54 was amended and now considers the total QALYs in the PSA. We also included the error in the model validation section (5.3.2.2) and amended Table 45 as well as Appendix 4.
Section 6.2.2; Figure 5; page 130	Figure 5 suggests an entire vial is wasted for patients over 80 kg.	Please correct the figure to reflect potential vial wastage accurately.	We agree. Figure 5 has now been amended to reflect the potential vial wastage accurately.

Location of factual/textual errors	Description of factual/textual errors	Proposed amendments	ERG response
Section 6.3; page 132	We believe the following statement contains an error, since the ERG base case does not include a QALY benefit: *For the ERG's base case for IOPD, AVAL has an [redacted] per QALY vs ALGLU*	Please correct the statement.	We have corrected the text as suggested.

References

1. National Institute for Health and Care Excellence. Addendum to the Guide to the methods of technology appraisal. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf (last accessed 8th March 2022).
2. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. Process and methods [PMG36]. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. 2022.
3. Cochrane Effective Practice and Organisation of Care (EPOC). Suggested risk of bias critieria for EPOC reviews. EPOC Resources for review authors. Available at: https://epoc.cochrane.org/resources/epoc-resources-review-authors. 2017.
4. 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.
5. Broomfield A, Fletcher J, Davison J, Finnegan N, Fenton M, Chikermane A, 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.

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Technical engagement response form

Avalglucosidase alfa for treating Pompe disease [ID3737]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **26th April 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Sanofi
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	Yes	The NICE methods guide states that cost-comparison analyses are suitable for technologies that are likely to provide similar or greater health benefits at similar or lower costs than the relevant comparator. The phase 3 trial COMET has shown that based on the primary endpoint AVAL is non-inferior to ALGLU in the treatment of LOPD, with a trend for improved respiratory function (FVC% predicted), mobility (6MWT) and other outcomes across 49 weeks compared with ALGLU. Establishing comparative efficacy in IOPD is more challenging, given the extremely rare nature of the disease, however, the phase 2 trial Mini-COMET has shown a trend for improvement or stabilisation with AVAL across several clinical outcomes in patients with IOPD who were previously in clinical decline or had suboptimal response to ERT. An updated PAS has been submitted, which brings the acquisition cost for AVAL below that of ALGLU. The company considers that despite uncertainty in the comparative efficacy of AVAL and ALGLU, a cost-comparison approach remains appropriate. The Company previously submitted a cost-utility analysis alongside the cost-comparison analysis, however, the cost-comparison analysis may be more useful to support the decision. Results of the cost-comparison analysis including the new PAS are presented in Table 1 and Table 2.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 2: It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	Yes	All the details are now available in Table 4; Appendix B.
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 for the late onset Pompe disease (LOPD) population	Yes	The decision to not prioritise these studies for data extraction was a pragmatic one. All studies that were not selected for data extraction provided only data on ALGLU or natural history (rather than AVAL) and data from large registries were already available. Studies conducted outside the UK and the Netherlands were also not prioritised so that only data most generalisable to the UK were extracted. Table 5 (Appendix B) presents a list of all full texts that were not selected for data extraction: • studies with a sample size of <100 people, conducted outside the UK and the Netherlands • Excluded systematic reviews • Studies reporting only humanistic (and no clinical) outcomes and that do not report SF-36 or EQ-5D.
Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD) population is a major uncertainty in the economic evaluation		The IOPD population is an ultra-orphan subpopulation of patients with Pompe disease, characterised by more rapid progression of the disease compared to LOPD. There is also a substantial variability in the treatment of IOPD across different countries, as reflected by the range of ALGLU doses that patients were treated with prior to inclusion in the trial. In spite of these limitations, the Mini-COMET trial has shown improvement or stabilisation across several outcomes in patients treated with AVAL who were previously declining or suboptimally responding to ALGLU. Therefore, a conservative assumption that AVAL has the

Key issue	Does this response contain new evidence, data or analyses?	Response
		same efficacy as ALGLU was made in both the cost-comparison and cost-utility model.
Issue 5: The duration of the AVAL treatment effect is very uncertain in the LOPD population	Yes	While there is uncertainty in the duration of the treatment effect (plateau period), the evidence from NEO-EXT supports the halting of disease progression for a period of at least five years following the initial improvement at one year. In addition, this does not lead to a significant amount of decision uncertainty. Scenarios have been provided using both the company's preferred assumptions (5 years plateau for 6MWT and %FVC), and the ERG's preferred assumptions (AVAL equivalent to ALGLU). In both cases, AVAL remains the dominant treatment option.
Issue 6: The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population	Yes/No	The survival gains for AVAL are driven by slower disease progression, meaning that patients remain in less severe disease states with lower mortality rates. Therefore, no direct impact on mortality has been included in the company base case. This is in part due to the lack of long-term comparative data available to provide an estimated hazard ratio for AVAL compared with ALGLU. However, it is likely that the model underestimates the survival gains expected with LOPD, and therefore, the company base case has been altered to align with the ERG's preferred assumptions (HR of 0.85) for AVAL.
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	Yes	A survey conducted across eight treatment centres within the UK concluded that there is little to no vial wastage in real-world clinical practice. The results of the survey are provided as a data-on-file document. We have also provided a revised base case for the LOPD population which considers that doses can be rounded up or down to the nearest vial. No change has been made in the approach to modelling the number of vials required in the IOPD model. As this is a cohort model, variation in patients weight, and therefore the number of vials required, is not captured and when the number

Key issue	Does this response contain new evidence, data or analyses?	Response
		of vials can be rounded up or down an average number of vials is more appropriate.
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment in the IOPD population	Yes	There is no clinical evidence or established practice to support the initial higher dose of AVAL. A scenario analysis including increased dosing frequency for AVAL has been included and AVAL remains dominant in this scenario.
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 in the IOPD population.	No	No information is currently available on how dose escalation may occur in clinical practice and as such it is not possible to model any informative scenarios around dose escalation. As currently the dose of ALGLU is in practice escalated when response to treatment becomes insufficient, it is anticipated that a similar approach would apply to AVAL.

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; ERT, enzyme replacement therapy; %FVC, percentage predicted force vital capacity; HR, hazard ratio; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; PAS, patient access scheme; SF-36, short-form 36-item questionnaire; SLR, systematic literature review; 6MWT, six-minute walk test.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Outcomes from PSA	Section 6.2.2, page 129	Yes	Results of the PSA presented in the ERG report present the total QALYs for patients, but do not include the caregiver disutility. This is due to an error in the model noted in cells I41 and I42 of the 'PSA results' sheet. When corrected, the total QALYs are closely aligned to the base case analysis. Updated PSA has been presented in Table 3.

Abbreviations: ERG, evidence review group; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate (LOPD)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issues 1–9	The PAS made AVAL available at [redacted] per vial.	In response to the ERG report, an updated PAS has been submitted and the new cost per vial is [redacted].	This reduces the incremental drugs costs and leads to a larger saving with AVAL, from [redacted] to [redacted] and therefore AVAL remains dominant.
Issue 6	No additional survival benefit was modelled for AVAL over ALGLU beyond that inferred by slower disease progression.	In line with the ERG's preferred analysis, a HR of 0.85 for AVAL vs ALGLU has been included.	The additional survival benefit leads to longer durations of treatment with AVAL and the incremental cost increases to [redacted], with an increase in incremental QALYs to [redacted]. This leads to an ICER of £92,183.
Issue 7	No adjustment of dose based on patients' weight.	The dose is rounded up or down to the nearest number of vials based on a patient's weight.	This reduces the incremental drugs costs and leads to a larger saving with AVAL, from [redacted] to [redacted] and therefore AVAL remains dominant.
Not related to any key issues	The rate of progression of 6MWT with BSC was assumed	In line with the ERGs preferred assumptions, the rate of	The impact on results is minimal; there is a small decrease in cost savings, however AVAL remains dominant.

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Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
	to be equal to that for AVAL and ALGLU.	progression has been set to [redacted] m/year.	
Not related to any key issues	A disutility of 0.117 was applied to caregivers in the 'Not dependent' state, and 0.131 in the non-invasive ventilator state.	In line with the ERG preferred analysis, these disutilities have been changed to 0.072 and 0.102.	This leads to an increase in the incremental QALYs with AVAL and therefore AVAL remains dominant.
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted].	Incremental costs: [redacted].	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; BSC, best supportive care; ERG, evidence review group; ERT, enzyme replacement therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; PAS, patient access scheme; QALY, quality-adjusted life year; 6MWT, six-minute walk test.

Table 4 Changes to the company's cost-effectiveness estimate (IOPD)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Not related to key issues	N/A	ERG corrections to the base case for drug administration and CPRD costs.	A small increase in cost saving to [redacted].
Issues 1–9	The PAS made AVAL available at [redacted] per vial.	In response to the ERG report, an updated PAS has been submitted and the new cost per vial is [redacted].	Increase in cost saving to [redacted].
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted].	Incremental costs: [redacted].	Dominant.

Abbreviations: AVAL, avalglucosidase alfa; CPRD, clinical practice research datalink; ERG, evidence review group; N/A, not applicable; PAS, patient access scheme; QALY, quality-adjusted life year.

Appendix A

Sensitivity analyses around revised base case

Table 1: Scenario analyses (LOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
Base case	[redacted]	[redacted]	Dominant
AVAL plateau period equal to the ALGLU plateau period (ERG's preferred assumptions)	[redacted]	[redacted]	Dominant

Abbreviations: ALGLU, alglucosidase alfa; AVAL, avalglucosidase alfa; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease.

Table 2: Scenario analyses (IOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
Base case	[redacted]	[redacted]	Dominant
Exponential distribution used to model OS	[redacted]	[redacted]	Dominant
Double dosing for AVAL in the first 12 weeks	[redacted]	[redacted]	Dominant
ERGs preferred assumptions	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year.

Table 3: Updated PSA for LOPD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
ALGLU	[redacted]	[redacted]	[redacted]	–	–	–	–
AVAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Appendix B

Table 4: List of 40 studies, Issue 2

First author, Year	Title	Population
Van der Ploeg 2010	A randomized study of alglucosidase alfa in late-onset Pompe's disease	LOPD
Forsha 2011	Cardiovascular abnormalities in late-onset Pompe disease and response to enzyme replacement therapy	LOPD
Baek 2016	The influence of a polymorphism in the gene encoding angiotensin converting enzyme (ACE) on treatment outcomes in late-onset Pompe patients receiving alglucosidase alfa	LOPD
Harlaar 2019	Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease	LOPD
Harlaar 2019	O.23A 10 year prospective study on the effects of enzyme replacement therapy in adult Pompe patients	LOPD
Poelman 2020	Effects of higher and more frequent dosing of alglucosidase alfa and immunomodulation on long-term clinical outcome of classic infantile Pompe patients	IOPD
Poelman 2019	P.72 Optimizing long-term outcome in classic infantile Pompe patients: effects of higher dosing and immunomodulation	IOPD
Hug 2019	Mini-comet study: safety data and immunogenicity for repeat avalglucosidase alfa dosing in patients with infantile-onset pompe disease who were previously treated with alglucosidase alfa and demonstrated clinical decline	IOPD
Kronn 2020	Mini-COMET study: safety, immunogenicity, and preliminary efficacy for repeat avalglucosidase alfa dosing in patients with infantile-onset Pompe disease (IOPD) who were previously treated with alglucosidase alfa and demonstrated clinical decline	IOPD
Chien 2019	Mini-COMET: safety/immunogenicity of avalglucosidase alfa in IOPD patients with clinical decline on alglucosidase alfa	IOPD
Kishnani 2021	Mini-COMET study: Individual participant-level responses to treatment in patients with infantile-onset Pompe disease receiving repeated dose regimens of avalglucosidase alfa or alglucosidase alfa who were previously treated with alglucosidase alfa	IOPD

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First author, Year	Title	Population
Sanofi 2020	An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa (neoGAA, GZ402666) in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response. 2020. SANOFI interim clinical study report.	IOPD
Pena 2019	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	LOPD
Schoser 2019	P.69 NEO1 and NEO-EXT studies: exploratory efficacy of repeat avalglucosidase alfa dosing for up to 5 years in participants with late-onset Pompe disease (LOPD)	LOPD
Dimachkie 2020	NEO1 and NEO-EXT studies: Long-term safety and exploratory efficacy of repeat avalglucosidase alfa dosing for 5.5 years in late-onset pompe disease patients	LOPD
Dimachkie 2020	NEO1/NEO-EXT: Safety and exploratory efficacy of repeat avalglucosidase alfa dosing for up to 6 years in participants with late-onset pompe disease	LOPD
Dimachkie 2021	NEO1/NEO-EXT studies: Safety and exploratory efficacy of repeat avalglucosidase alfa dosing after up to 6 years in participants with late-onset pompe disease (LOPD)	LOPD
Schoser 2020	AUTOPHAGIC MYOPATHIES / MYOFIBRILLAR MYOPATHIES / DISTAL MYOPATHIES / POMPE DISEASE: P.03 NEO1/NEO-EXT studies: Safety and exploratory efficacy of repeat avalglucosidase alfa dosing after up to 6 years in late-onset Pompe disease (LOPD)	LOPD
Schoser 2020	NEO1/NEO-EXT studies: Trends over time in exploratory efficacy of repeat avalglucosidase alfa dosing for up to 5.5 years in late-onset Pompe disease (LOPD) patients	LOPD
Pena 2019	NEO1 and NEO-EXT studies: Long-term safety of repeat avalglucosidase alfa dosing for 4.5 years in late-onset Pompe disease patients	LOPD
Sanofi 2015	An open-label, multicenter, multinational, ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of repeated biweekly infusions of neoGAA in naïve and alglucosidase alfa treated late-onset Pompe disease patients. 2015. SANOFI clinical study report.	LOPD

First author, Year	Title	Population
Sanofi 2020	An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease. 2020. SANOFI interim clinical study report.	LOPD
Kishnani 2007	Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease	IOPD
Spiridigliozzi 2012	Early cognitive development in children with infantile Pompe disease	IOPD
Kishnani 2009	Early treatment with alglucosidase alfa prolongs long-term survival of infants with pompe disease	IOPD
Young 2009	Long-term monitoring of patients with infantile-onset Pompe disease on enzyme replacement therapy using a urinary glucose tetrasaccharide biomarker	IOPD
Schoser 2019	PRECLINICAL APPROACHES AND EARLY CLINICAL RESULTS: O.22First-in-human study of ATB200/AT2221 in patients with Pompe disease: 24-month functional assessment results from the ATB200-02 trial	LOPD
Schoser 2018	NEW THERAPEUTIC APPROACHES AND THEIR READOUT: O.20Results from ATB200-02: first-in-human, open-label, phase 1/2 study of ATB200 co-administered with AT2221 for Pompe disease	LOPD
Schoser 2019	First-in-human study of ATB200/AT2221 in patients with Pompe disease: Preliminary functional assessment results from the ATB200-02 trial	LOPD
Clemens 2019	Safety and efficacy of advanced and targeted acid α-glucosidase (AT-GAA) (ATB200/AT2221) in ERT-switch nonambulatory patients with Pompe disease: preliminary results from the ATB200-02 trial	LOPD
Kishnani 2019	First-in-human study of advanced and targeted acid α-glucosidase (AT-GAA) (ATB200/AT2221) in patients with Pompe disease: preliminary functional assessment results from the ATB200-02 trial	LOPD
Schoser 2019	Preliminary patient-reported outcomes and safety of advanced and targeted acid α-glucosidase (AT-GAA (ATB200/AT2221) in patients with Pompe disease from the ATB200-02 trial	LOPD
Schoser 2021	Efficacy and safety results of the avalglucosidase alfa phase 3 COMET trial in late-onset Pompe disease patients	LOPD

First author, Year	Title	Population
Diaz-Manera 2021	Initial Results of the Avalglucosidase alfa Phase 3 COMET Trial in Late-Onset Pompe Disease Patients	LOPD
Sanofi 2020	A Phase 3 randomized, multicenter, multinational, double blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment-naïve patients with late onset Pompe disease. 2020. Sanofi interim clinical study report.	LOPD
Mozaffar 2021	Efficacy and safety of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in late-onset Pompe disease (LOPD): a Phase 3 trial (PROPEL)	LOPD
Schoser 2021	Efficacy and safety of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in late-onset Pompe disease: PROPEL study	LOPD

Table 5: List of excluded studies, Issue 3

First author, Year	Country	Population	Intervention	Comparator	Outcomes	Design
Clinical observational LOPD studies with a sample size <100, conducted outside the UK and the Netherlands, and without humanistic outcomes						
Filosto 2019	Italy	LOPD; N=64	ALGLU	–	Clinical	Retrospective cohort study
Ravaglia 2012	Italy	LOPD; N=21	ALGLU	–	Clinical	Single centre, observational, prospective, non-randomised, open-label study
Ravaglia 2010	Italy	LOPD; N=11	ALGLU	–	Clinical	Single centre, observational, prospective, non-randomised, open-label study

Technical engagement response form.

First author, Year	Country	Population	Intervention	Comparator	Outcomes	Design
Montagnese 2015	Italy	LOPD; N=14	ALGLU	–	Clinical	Retrospective cohort study
Papadopoulos 2017	France	LOPD; N=12	ALGLU	–	Clinical	Prospective (registry) study
Ripolone 2018	Italy	LOPD; N=18	ALGLU	–	Clinical	Retrospective study
Sechi 2017	Italy	LOPD; N=11	ALGLU	–	Clinical	Prospective interventional study
Masat 2016	France	LOPD; N=24	ALGLU	–	Clinical	Prospective (registry) study
Angelini 2012	Italy	LOPD; N=40	ALGLU	–	Clinical	Prospective (clinical) study
Angelini 2012	Italy	LOPD N=74	ALGLU	–	Clinical	Open-label observational study
Carlier 2015	France	LOPD; N=23	ALGLU	–	Clinical	Retrospective cohort study
Alandy-Dy 2019	US	LOPD; N=18	ALGLU	–	Clinical	Retrospective cohort study
Gutschmidt 2021	Germany, Italy, Spain, Taiwan	LOPD; N=68	ALGLU	–	Clinical	Retrospective study
Korlimarla 2021	US	LOPD; N=58	ALGLU	–	Clinical	Prospective study
Korlimarla 2021	US	LOPD; N=58	ALGLU	–	Clinical	Prospective study
Papadimas 2021	Greece	LOPD; N=14	ERT	–	Clinical	Retrospective study
Wenninger 2021	Germany	LOPD; N=12	ERT	–	Clinical	Cohort study
Studies reporting only humanistic (and no clinical) outcomes and that do not report SF-36 or EQ-5D						
McNamara 2015	US	LOPD; N=35	ERT	–	QoL/PROs	Cohort study

Technical engagement response form.

First author, Year	Country	Population	Intervention	Comparator	Outcomes	Design
Hagemans 2007	Multiple countries	LOPD; N=225	NR	–	QoL/PROs	Retrospective cohort study
Lefeuvre 2019	France	LOPD; N=65	NR	–	QoL/PROs	Prospective (registry) study
Chen 2021	China	LOPD; N=68	None	–	QoL/PROs	Cross-sectional survey
SLRs						
Milverton 2019	–	LOPD	ERT	–	Clinical	SLR
Berger 2019	–	LOPD	–	–	Clinical	Meta-analysis
Manta 2021	–	Mixed	Mixed – includes ERT	–	Clinical	SLR
Berli 2021	–	LOPD	ERT	–	Clinical	SLR and meta-analysis
van Kooten 2021	–	LOPD	NR	–	Clinical	SLR
Schoser 2019	–	Mixed	ERT	–	Economics	SLR

Abbreviations: ALGLU, alglucosidase alfa; ERT, enzyme replacement therapy; LOPD, late-onset Pompe disease; NR, not reported; PRO, patient-reported outcome; QoL, quality-of-life; SLR, systematic literature review; US, United States.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Avalglucosidase alfa for treating Pompe disease ID3737

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Pompe disease or caring for a patient with Pompe disease. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report section 1.3.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **26th April 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with Pompe disease or caring for a patient with Pompe disease

Table 1 About you, Pompe disease, current treatments and equality

1. Your name	Celia Thomas
2. Are you (please tick all that apply)	☒ A patient with Pompe disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Pompe disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Muscular Dystrophy UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with Pompe disease? **If you are a carer (for someone with Pompe disease) please share your experience of caring for them**	My experience of living with Pompe Disease is that it is very debilitating in so many ways. In the last twenty years, I have lost a lot of mobility, and now have to use a wheelchair. I cannot now get off ordinary chairs, a bed, a toilet seat or a car seat without help. I cannot climb stairs or steps of any kind. My voice is now affected and I cannot speak clearly. My swallowing is also affected and I have to drink very carefully taking small sips. I get breathless and now need to use a ventilator during the day as well as every night. I cannot now take showers myself or dress myself. I have lost my taste for food and drink which is a blow. I eat very little which someone else has to cook. I need help getting up in the morning and going to bed at night.
7a. What do you think of the current treatments and care available for Pompe disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. The current treatment of Myosyme for Pompe is probably better for younger patients but not very effective in older patients like me. As for care, I'm afraid I can't answer that. It would depend on so many things. 7b.) I'm afraid I'm not in touch with others about treatments. We are all at different stages of our journey through life.
8. If there are disadvantages for patients of current NHS treatments for Pompe disease (for example, how avalglucosidase alfa is given or taken, side effects of treatment, and any others) please describe these	As for avalglucosidase alfa, I'm afraid I cannot comment on it. All I have heard from one doctor is that it sometimes gives people diarrhoea. I don't know anyone who is being trialled, or treated with it. It may be the case that the earlier this treatment is given, the more effective it is.
9a. If there are advantages of avalglucosidase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does avalglucosidase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of avalglucosidase alfa over current treatments on the NHS please describe these. For example, are there any risks with avalglucosidase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from avalglucosidase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering Pompe disease and avalglucosidase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	
Issue 2: It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	

Patient expert statement

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 for the late onset Pompe disease (LOPD) population	
Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD)population is a major uncertainty in the economic evaluation	
Issue 5: The duration of the AVAL treatment effect is very uncertain in the LOPD population	
Issue 6: The lifetime incremental survival advantage for AVAL is	

Patient expert statement

likely to be underestimated in the LOPD population	
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment in the IOPD population ***We consider patient perspectives may particularly help to address this issue***	
Issue 9: The option for ERT dose escalation is excluded from the company's cost utility models.	

Patient expert statement

The impact on cost effectiveness of different dose escalation approaches is unknown in the IOPD population ***We consider patient perspectives may particularly help to address this issue***	
Are there any important issues that have been missed in ERG report?	

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- My experience of living with Pompe Disease is that it is very debilitating in so many ways. In the last twenty years, I have lost a lot of mobility, and now have to use a wheelchair. I cannot now get off ordinary chairs, a bed, a toilet seat or a car seat without help. I cannot climb stairs or steps of any kind. My voice is now affected and I cannot speak clearly. My swallowing is also affected and I have to drink very carefully taking small sips. I get breathless and now need to use a ventilator during the day as well as every night. I cannot now take showers myself or dress myself. I have lost my taste for food and drink which is a blow. I eat very little which someone else has to cook. I need help getting up in the morning and going to bed at night.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

Patient expert statement

For more information about how we process your personal data please see NICE's privacy notice.

Personal statement from Celia Thomas

I was wrongly diagnosed in 1991, when I was 46, with Limb Girdle Muscular Dystrophy. This was changed in 2018 to Late Onset Pompe Disease during a two month stay in the National Hospital when a PEG was put in place and I had my first infusion of Myozyme.

I have been physically active all my life, my chief hobby being singing in choirs. I have been on walking holidays involving climbing hills, and often cycled five miles to work and back. I developed a limp in my early forties and found singing rather tiring, so sought a diagnosis. From then on I stopped singing but was able to live normally with my mobility only very slowly deteriorating. I had a lot of massage and did quite a lot

of exercises. I had a fall resulting in a broken leg in 2007 and after that I walked with a rollator. Then I fell again some years later and broke my kneecap. Eventually I started to use a mobility scooter, and now use an electric wheelchair. Now my speech is badly affected, as is my breathing and swallowing. I have used a ventilator overnight for the last three years and often during the afternoon and evening.

I long to be able to enjoy life again, but it is difficult when all physical activity, including speaking, is tiring. I can't really taste anything and I now have eczema on my wrists and lower arms. My face is like a battleground! Roll on a better treatment for Pompe.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Avalglucosidase alfa for treating Pompe disease ID3737

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A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Patient expert statement

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Patient expert statement

Part 1: Living with Pompe disease or caring for a patient with Pompe disease

Table 1 About you, Pompe disease, current treatments and equality

1. Your name	Gemma Seyfang
2. Are you (please tick all that apply)	☒ A patient with Pompe disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Pompe disease? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Association for Glycogen Storage Disease - UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐X I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I volunteer as a peer coordinator with AGSD-UK. This brings me into contact with many people living with Pompe and gives me an insight into their experience of the

	condition and of the existing therapy. My sibling also has Pompe disease and is treated with the existing therapy. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐**x** I have not completed part 2 of the statement
6. What is your experience of living with Pompe disease? **If you are a carer (for someone with Pompe disease) please share your experience of caring for them**	**I was diagnosed in August 2016, but my first symptoms started when I was around 13 years old.** **Before diagnosis I was really struggling with the following symptoms: -** **Daily morning headaches which caused my whole body to be fatigued due to the build up of CO2 in my bloodstream and this feeling would last until early afternoon when my blood would become reoxygenated. I used to struggle to concentrate at work, my focus was all about how tired I felt, running a business became increasingly difficult.** **This had a knock-on effect to the rest of my day I was withdrawn and unsociable.** **Walking up the stairs was becoming increasingly difficult to the point of me crawling up the stairs on my hands and feet as this was the easiest way to get up without causing the most amount of pain and fatigue.** **Going out in public caused me massive anxiety particularly if this was a place I had never been to before, I would search on the internet to find photos and information about the place to see if they had a lift or worst case a handrail or two.** **I would often injure my body where I was straining to force myself to climb the stairs.**

	Rising from a seated position was a real struggle, if I was sat at a table, I would push off that, if I would walk into a room I would choose a chair that had arms if available as pushing up without arms would mean I would have to spin around on the seat and climb up the back of the chair. **If I was offered a seat without arms I would rather stand as then I wouldn't injure my body straining to stand back up.** **Falling over was often a daily occurrence, in public and in my home, my weakened hip and leg muscles and the fact that I barely have any reflexes in my knees meant that if I stumbled, I couldn't stop my body from falling from the ground.** **This would result in many injuries and then I would be faced with the task of standing back up. If there was something I could crawl up to assist me standing back up, then I would crawl over to it. If there wasn't then I would really struggle to get myself back up off the floor taking a long time to complete this task. If in public people would try to assist which then results in more injuries as they were trying to pull on my limbs or shoulders which were very weak.** **Completing daily tasks such as housework were extremely difficult such as putting washing in and out the machine as reaching down low resulted in a huge struggle to stand back up particularly if trying to retrieve something and worse so if this object was heavy such as a washing basket.** **If I dropped something often it would have to remain there until someone could assist me.** **Cooking was a huge safety risk as I would find it almost impossible to lift things in and out of the oven, often dropping them or burning myself, in the same way lifting a pan of boiling water.**

	Also, reaching for things up high would normally result in me dropping the object as my muscle weakness meant I couldn't hold my arms up plus the object. **My breathing was becoming a real issue, particularly when talking or walking as I felt I couldn't catch my breath.** **When lying down I would feel as though I was suffocating at times and would struggle to fall asleep.** **Walking was slow, shuffled and a real worry particularly if it was outside, I felt I was unfit and lazy.** **Every day I was faced with massive challenges, I felt I was thinking through my every movement I made and struggling to get my body to respond, this was very tiring.** **Since starting on the trial of Avalglucosidase alfa (AVAL) my life has changed dramatically for the better.** **Drawing on my experience and that of my sibling, who was diagnosed at the same time as me, I have noted that all my symptoms were much worse than theirs, I qualified for the trial, but they did not as their symptoms were not severe enough.** **My sibling went on to start the current NHS treatment, Alglucosidase alfa, whilst I started the trial drug, AVAL. Our journeys since then have been very different.** **Their progression has been slowed by the treatment but now their symptoms are much worse than mine, my improvements greatly outweigh theirs.**

Patient expert statement

7a. What do you think of the current treatments and care available for Pompe disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a/b. The current treatment Alglucosidase alfa has been successful in slowing down deterioration of muscular myopathy, with an overall improvement in patients' lives. However, many affected describe how their treatment is no longer as effective as they have plateaued over time. There is an urgent need for an alternative treatment to slow deterioration.** **Supportive care from specialist centres such as physiotherapists, dieticians etc is good in terms of supportive therapy, but the treatment is crucial to slow progression and improve quality of life.** **My siblings' views are that the current treatment is not as effective as AVAL upon experiencing deterioration themselves whilst accessing the current treatment and seeing my progress on AVAL.**
8. If there are disadvantages for patients of current NHS treatments for Pompe disease (for example, how avalglucosidase alfa is given or taken, side effects of treatment, and any others) please describe these	**AVAL is given intravenously in the same way that the current treatment Alglucosidase alfa is given.** **Disadvantages of Alglucosidase alfa are that some patients react to the drug and there is currently no alternative treatment option available for them.**
9a. If there are advantages of avalglucosidase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does avalglucosidase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**With AVAL the quality of my life has improved greatly: -** **I no longer experience morning headaches or fatigue, this in turn means I have improved energy levels which overall has improved the quality of my life.** **Before I would crawl up the stairs or if I was in public, I would shuffle up one step at a time, side stepping, both hands on the rail, twisting my body to swing so that I could lift the next foot up. Now I can walk up alternate steps holding just one rail, facing forward and I can hold something in my free hand, and when I reach the top, I am not completely exhausted as I was once before. I no longer get anxious going to new places, I have become much less isolated and more sociable because if this.**

	I can stand up from a seated position now with either one hand pushed off my thigh, or if the chair is sturdy and high enough, I can stand up by pushing off the back of my legs and using no hands. such as on my sofa. **I no longer worry about sitting on a chair that is low or has no arms.** **I rarely ever fall, but if I do, I can stand up much more easily, I don't need an object to push off. I can even just sit on the floor to do a task and then stand back up within seconds.** **This has given me so much more confidence and independence.** **Completing daily tasks is so much easier, I have more energy, can pick something up off the floor or reach for high places with more ease.** **I have improved lung capacity beyond expectation.** **At the beginning of the trial, I was close to requiring night time bipap but 6 months later I was retested, and every year I have tests, and this is no longer the case as my lung function has improved. I can breathe whilst talking and walking without experiencing any breathing issues. I can lie flat and breathe.** **My walking stride and stamina has improved greatly, I don't feel fatigue in my legs in anywhere near the time I was previously. This has given me so much independence before I would not go out without someone assisting me.** **9b. In my opinion all these advantages are important, they all contribute to a significant overall improvement in the quality of my life. I do feel like I have gotten my life back which in turn has meant an improvement in my children's and partner's lives. I feel blessed to have been part of this trial.**

	9c. AVAL could help those who are reacting to Alglucosidase alfa and those who have stopped responding to the treatment as an alternative treatment option.
10. If there are disadvantages of avalglucosidase alfa over current treatments on the NHS please describe these. For example, are there any risks with avalglucosidase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	**I have never experienced any issues or side effects from taking AVAL, so cannot comment on any disadvantages.**
11. Are there any groups of patients who might benefit more from avalglucosidase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	**Those who may benefit are those who experience side effects from taking the existing treatment Alglucosidase alfa.** **Also, those who have found that the existing treatment, Alglucosidase alfa, is no longer slowing their progression down and its impact has plateaued.**
12. Are there any potential equality issues that should be taken into account when considering Pompe disease and avalglucosidase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	**I do not believe there to be any**

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	**Through my involvement of volunteering with the patient organisation, I know what a huge impact Pompe Disease has on the lives of both children with IOPD and their parents and the importance of optimal treatment.**

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	
Issue 2: It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	

Patient expert statement

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 for the late onset Pompe disease (LOPD) population	
Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD)population is a major uncertainty in the economic evaluation	
Issue 5: The duration of the AVAL treatment effect is very uncertain in the LOPD population	
Issue 6: The lifetime incremental survival advantage for AVAL is	

Patient expert statement

likely to be underestimated in the LOPD population	
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment in the IOPD population ***We consider patient perspectives may particularly help to address this issue***	
Issue 9: The option for ERT dose escalation is excluded from the company's cost utility models.	

Patient expert statement

The impact on cost effectiveness of different dose escalation approaches is unknown in the IOPD population ***We consider patient perspectives may particularly help to address this issue***	
Are there any important issues that have been missed in ERG report?	

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Pompe Disease is a hugely debilitating, life limiting disease and speedy access to the best possible treatment to slow the progression down is essential to maximise quality of life for people affected.
- My quality of life has improved way beyond my expectations due to being part of the trial treatment Avalglucosidase alfa (AVAL).
- Having an alternative treatment option for those who do not respond well to current treatment or have plateaued is crucial to continue to slow the progression of the disease.
- I have not experienced any side effects at all in my 5.5 years of receiving AVAL
- Optimal treatment is vital to help all those affected by Pompe Disease, including those with infant and late onset Pompe and their parents, loved ones and carers.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

Patient expert statement

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Avalglucosidase alfa for treating Pompe disease ID3737

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report section 1.3. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.
Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **6th May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating Pompe disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr James Davison
2. Name of organisation	Great Ormond Street Hospital London
3. Job title or position	Consultant Paediatric Metabolic Medicine
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Pompe disease? ☐ A specialist in the clinical evidence base for Pompe disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links with the tobacco industry.
8. What is the main aim of treatment for Pompe disease	To improve quality and duration of life for patients with Pompe by treating cardiac disease, and ameliorating skeletal motor and respiratory decline.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	For IOPD, increased survival/life expectancy. Improved (decreased) cardiac hypertrophy and improved (increased) cardiac function. Lower rate of needing non-invasive ventilation (NIV) initiation or decreased requirement for NIV support (hours needed, pressures needed). Improved gross motor developmental milestones attained and retained.
10. In your view, is there an unmet need for patients and healthcare professionals in Pompe disease?	Yes – despite current treatment with alglucosidase alfa which has improved outcome for IOPD patient survival but with significant requirement for non-invasive ventilation, and suboptimal gross motor outcome with a very significant rate of motor decline, and further many requiring gastrostomy feed support.
11. How is Pompe disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients with Pompe disease are managed under a Lysosomal Storage Disorder Highly Specialised Service (HSS) Centre. Treatment follows the previously issued guideline documents for IOPD/LOPD. Patients receive multidisciplinary supportive treatments including physiotherapy, speech/language therapy, feed support including enteral tube feed if required, respiratory interventions including non-invasive ventilation/invasive ventilation, cardiology treatment as required. Disease-modifying treatment with current available enzyme replacement therapy (alglucosidase alfa) is commenced in line with guidelines and continued long-term. This is initiated in-hospital but continued via homecare delivery where possible.

	This technology would be incorporated within the current pathway of care replacing alglucosidase alfa.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology is being deployed in some patients under the current Early Access to Medicines Scheme (EAMS). In IOPD patients this is used in the same way as current care. The technology would be prescribed and managed by the specialist LSD HSS service. It would be administered in-hospital at initiation but then continued to be delivered via homecare administration where possible.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect the technology to provide clinically meaningful benefits compared to current care with increased life expectancy, greater preservation of skeletal motor function, and decreased need for non-invasive ventilatory support in patients with IOPD. As a result, it is expected to increase HRQOL more than current care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Potential to benefit all patients with Pompe disease.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	No significant difference compared to current care.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing. Agreed start/stop criteria in line with current practice for alglucosidase alfa. Dose escalation criteria required to be agreed
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Measures in the appraisal do capture health-related benefits.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The provision of recombinant enzyme replacement therapy is an innovative step in treatment of Pompe disease, and this second-generation technology aims to improve the mechanistic efficacy of the enzyme replacement by increasing uptake to the target organs. The technology addresses the unmet need of the population for whom existing treatment is sub-optimal.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects/ adverse effects of the technology are similar to those of current care.
20. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials included do represent the current practice within the UK, noting variation between patients for their current alglucosidase alfa dosing regimens.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The trials included measures to capture the most important outcomes, encompassing: • Cardiac outcomes (eg LVMi) • Respiratory outcomes (need for non-invasive ventilation) • Motor function • There are other emerging phenotypic features seen in long-term survivors of IOPD that are not fully assessed in the short-term clinical trials (see eg Davison J, *J Mother Child* 2020 Oct 2;24(2):3-8. PMID 33554498 for summary). It is unclear whether ALGLU or AVAL have any effect on addressing these aspects of the disease.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Clinical expert observation supports the findings of the trial data.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	No specific concerns.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

	Please note that I have not been part of any previous discussions/clinical expert meetings as part of this Technology appraisal and so comments are based on my reading of the ERT report (25/2/22) and the Technical Engagement Papers provided to me on 29 April 2022.
Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	Agree that the phase 2 trial evidence in IOPD may not be sufficient to confirm equal efficacy of AVAL and ALGLU, given that the trial primary objective was to demonstrate safety. However, clinical observation of patients included would agree that AVAL provides at least equivalent if not better outcome than ALGLU in clinical parameters and biomarker response. Some of the patients included had very advanced disease that the assessment criteria would not necessarily capture improvement in. Agree that assuming at least efficacy equivalence between AVAL and ALGLU is appropriate.
Issue 2: It is unclear if all relevant clinical effectiveness	Agree it is important to review the excluded studies however I am not aware of relevant publications relating to AVAL that have not been included.

Clinical expert statement

evidence has been included in the company submission	
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 for the late onset Pompe disease (LOPD) population	Agree optimal to maximise numbers of patients included in the overall analysis. While UK/Netherlands populations may be similar, other populations eg in US may also reflect UK population.
Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD) population is a major uncertainty in the economic evaluation	Agree the efficacy evidence is limited, although the short term safety data is robust for both infusion-associated acute reactions and immunogenicity (anti-drug antibody). If a survival benefit was seen with AVAL as a result of improving motor function outcome, lower need for non-invasive ventilation, then the incremental survival may be significantly more than the maximal 6 months modelled in the Hazard Ratio adjustments. What effect would be seen for 1-5 years survival benefit? Very short term personal clinical observation of patients treated with AVAL in the EAMS supports increased efficacy with some carers reporting improvements in motor function noted in short term.
Issue 5: The duration of the	

AVAL treatment effect is very uncertain in the LOPD population	
Issue 6: The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population	
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	Clinical practice in paediatric setting is to use "dose rounding" to utilise a full vial, with alternating dosing to achieve target dose for a patient (i.e. average over alternating doses). Practically not possible to vial-share where being administered at home (and patients do not live in proximity).
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment in the IOPD population	This is important to consider. For newly diagnosed IOPD patients who have significant cardiac dysfunction/ hypertrophy, the established use of higher ALGLU dosing at treatment initiation aims to achieve rapid improvement in the cardiac component which would otherwise be fatal. This is achieved with use of ALGLU 20mg/kg weekly for (at least) 12 weeks. Weekly infusions may provide pharmacokinetic benefit compared to every-other-week administration of the same overall dose. There has been no evaluation yet of AVAL treatment for ERT-naïve patients; this is being addressed as noted by the ERG in the Baby-COMET study. **Of note, the Baby-COMET study uses AVAL 40mg/kg every other week, with scope for increasing to 40mg/kg weekly where there is inadequate response**. It is therefore anticipated that the higher dosing regimen (at least 40mg/kg every other week, or 20mg/kg weekly) AVAL would be the dose utilised for ERT-naïve IOPD patients at treatment initiation.

	Also to note that the dosing used in the Mini-COMET study included 40mg/kg every other week for the majority of patients. This is also the dose schedule being used for ERT-experienced patients with IOPD who are switching to AVAL under the EAMS. The BabyCOMET study does not include a comparison group, however the parallel prospective observational study ("OBS17003") also sponsored by Sanofi aims to collect clinical outcome data from an equivalent cohort treated with ALGLU (ClinicalTrials.gov identifier NCT04848779) that would be suitable as a comparison group.
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 in the IOPD population	As noted, dose escalation for ALGLU is used in clinical practice where there has been suboptimal response or clinical decline, with a variety of regimens (higher dose and/or frequency). It is difficult to model dose-escalation effect for AVAL given that this would be used in patients who are already showing suboptimal response. Clinicians are likely to prospectively use the available higher dose on assumption that this will provide greater benefit, and maintaining skeletal muscle function is better than trying to rescue damage that has already occurred. The appraisal has already noted the on-going proposal for standardised adjustment to the current ALGLU dosing used in England with proposed higher dosing.
Are there any important issues that have been missed in ERG report?	Higher dose AVAL requires longer infusion time compared to higher dose ALGLU (experience from patients in EAMS). This may impact on associated nursing costs with longer infusion time if higher dose needed.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is clear unmet need in IOPD patients despite ALGLU treatment.
- AVAL is expected to provide greater efficacy than ALGLU in IOPD. Personal clinical observation of efficacy of AVAL supports the (limited) clinical efficacy data provided in the MiniCOMET study for IOPD.
- Consideration of appropriate dosing regimens needs to be made, with distinction between IOPD and LOPD, and in particular the requirement for high dosing at treatment initiation in IOPD patients.
- Personal clinical observation is that AVAL is well tolerated in long term use (trial patient) and short term in a wider cohort of IOPD patients treated with AVAL in the EAMS system with early reports of improved outcome from carers.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Avalglucosidase alfa for treating Pompe disease ID3737

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report section 1.3. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.
Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **6th May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating Pompe disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Robin Lachmann
2. Name of organisation	Royal College of Physicians, London
3. Job title or position	Consultant in Inherited Metabolic Disease
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Pompe disease? ☒ A specialist in the clinical evidence base for Pompe disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for Pompe disease	In adults, to prevent progression of muscle weakness

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Any improvement in muscle strength would be highly significant. Pompe isa progressive disease and the muscle damage is largely irreversible so stabilisation of muscle strength would also be a significant response.
10. In your view, is there an unmet need for patients and healthcare professionals in Pompe disease?	Yes. Current disease modifying treatment can slow progression of disease significantly but does not stop progression.
11. How is Pompe disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients would be referred to one of the national LSD Services. Disease modifying therapy in the form of alglucosidase alfa would be offered to all IOPD and any LOPD patient with demonstrable muscle weakness. All patients would be assessed for respiratory insufficiency and started on non-invasive ventilation if required. Other services which might be offered would be physiotherapy and pain management. The pathway of care is well defined (only specialist centres are allowed to prescribe alglucosidase alfa) but there are currently no published NHSE policies relating to Pompe (although a policy for the use of double dose alglucosidase alfa in IOPD is under consideration). In general, adult centres would follow the European consensus guidelines for starting and stopping therapy (https://onlinelibrary.wiley.com/doi/10.1111/ene.13285) The availability of avalglucosidase alfa would nt affect the pathway of care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Avalglucosidase would be a like for like replacement for alglucosidase alfa. Prescription would be limited to the highly specialised national LSD service. There might be a need to perform some additional infusions in hospital when transferring patients from alglucosidase alfa to avalglucosidase alfa. Homecare nurses would need to be trained about the new product.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Preclinical and clinical data suggests that the new technology does result in more enzyme entering the target tissue. There is some evidence that patients already treated with alglucosidase alfa show improved muscle strength when transferred to avalglucosidase alfa. This would imply that the curve of disease progression is shifted to the left, which would be expected to improve quality of life and survival. I don't think it is yet clear whether the slope of the curve can also be decreased by the new technology, which would have a more profound effect on QoL and survival, but that would be the hope.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As with alglucosidase alfa, it is likely going to be important to start treatment as early as possible in the progression of the disease.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Should be equivalent to current care
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	For adults, patients will need to have demonstrable weakness and still have useful muscle function to preserve.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	I don't think so

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is a second generation enzyme replacement therapy. The alterations which have been made to the enzyme are not especially innovative and are designed to improve the efficiency of treatment rather than being a step change in management.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	On the whole ERTs are very well tolerated. Immune responses can be an issue, especially in infants, but this is unlikely to be any different to alglucosidase alfa.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In UK clinical practice we have a large cohort of LOPD patients who have already been treated with alglucosidase alfa for many years. The trials of avalglucosidase alfa really don't tell us what might happen to these patients when they are switched over to avalglucosidase alfa. The trials in IOPD suggest that switching can stabilise disease in patients who were declining on alglucosidase alfa, but IOPD is very different to LOPD and I don't think these results are directly transferrable. 6MWT measures both motor function and respiratory reserve and is probably a more important outcome measure than FVC for the majority of patients.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There is no data on real world experience which I am aware of.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Not that I am aware of

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	As I understand it the suggestion here is that if AVAL were to be more effective than ALGLU and lead to patients surviving longer then, even though AVAL would be cheaper than ALGLU on the basis of annual cost, the extra cost of treating patients for those extra years of life would end up making it less cost-effective. This argument might make sense to a health economist but seems specious to me.
Issue 2: It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	I think it is unlikely that any high quality data from patients treated with AVAL has been omitted.

Clinical expert statement

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 for the late onset Pompe disease (LOPD) population	I tend to agree with the ERG. Pompe is a rare disease and reports of sample sizes of >100 will be very limited. It is likely that the excluded studies may contain useful information.
Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD) population is a major uncertainty in the economic evaluation	It probably would be possible to do a head to head study of AVAL vs ALGLU in treatment naïve patients, but it would take a long time to recruit enough patients. Even if it was possible to show a mortality benefit in the first year of life, it would take decades to collect long-term outcome data. I find the argument that a drug is less cost effective because it leads to longer survival difficult if the result is that NHSE can only provide the less effective treatment which has never had its cost effectiveness assessed.
Issue 5: The duration of the AVAL treatment effect is very uncertain in the LOPD population	I think this uncertainty is going to apply in all cases of lifelong treatment for slowly progressive diseases as companies can't do clinical trials which last more than a few years. It is important to bear in mind that ALGLU treatment has significantly altered the natural history of the disease already.

Issue 6: The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population	I think any conclusions about overall survival are speculation. Most LOTS patients live for many years after diagnosis and the difference between 1 and 3 months extra survival doesn't really seem to be clinically meaningful. It is notable that for issue 5 the argument is that the company have overestimated the effects of AVAL on function, making it less cost effective, whilst here the argument is that they have underestimated the effects on life expectancy, which also makes it less cost effective. As with IOPD, I find it hard to understand how successfully prolonging life, with the accompanying need for longer duration of treatment, makes something less cost effective. If the argument is that there is a point where quality of life declines to a point where treatment is no longer cost effective, then that would be an argument for developing stopping criteria.
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	Current NHS practice does not allow for vial sharing. All doses are rounded up or down to the nearest whole vial.
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly	I am not a paediatrician, but I would agree that dosing of AVAL would be expected to be the same as ALGLU when initiating therapy.

treatment in the IOPD population	
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 in the IOPD population	Dosing in OPD is an active area of research and of NHSE policy development. It does seem that high doses of ALGLU are related to better outcomes. This would likley be the case for AVAL as well
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

ERT for is lifesaving in IOPD
ERT leads to demonstrable improvements in muscle function in LOPD
LOPD continues to progress despite ERT, although the rate of deterioration is likely slower than without treatment
AVAL has shown incremental benefits compared with ALGLU in a variety of short-term clinical trials.
It seems likely that in long-term use AVAL will be at least as effective as ALGLU and may significantly slow disease progression when compared to AGLU

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Avalglucosidase alfa for treating Pompe disease ID3737

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report section 1.3. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.
Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **6th May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating Pompe disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Mark Roberts
2. Name of organisation	Salford Royal NHS Foundation Trust
3. Job title or position	Consultant Neurologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Pompe disease? ☒ A specialist in the clinical evidence base for Pompe disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NIL
8. What is the main aim of treatment for Pompe disease	The aim of current treatment is to maintain mobility, respiratory and cardiac function, and to slow disease progression

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Pompe is a progressive disease and particularly severe in infants. In IOPD in a clinically significant response would include achievement of normal motor milestones, reduced left ventricular mass, and avoidance of ventilatory requirements and delayed death. In LOPD a response would include continued independent ambulation and avoidance of artificial ventilation.
10. In your view, is there an unmet need for patients and healthcare professionals in Pompe disease?	There is unfortunately considerable unmet needs IOPD patients continue to decline often becoming wheelchair and ventilator dependant. LOPD often show initial stabilisation or modest improvement for 1-2 years but then decline with a reduced life expectancy
11. How is Pompe disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	All symptomatic Pompe patients can access current treatment (ALGLU). The EPOC guidelines are used. The pathway of care is well defined, with treatment initiated and monitored through NHS England LSD centres. The technology could be incorporated into the current pathway more frequent monitoring would be prudent to obtain more Real World Data on treatment response, and would require more clinic visits for patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	The technology will use the existing NHS care pathway provided through specialist clinics. It is likely that patients will need to return to site for initial treatment infusions prior to a return to home therapy. The familiarity with the existing treatment and the similarity with the proposed technology should minimise training for example in making up the treatment vials.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It is likely that the technology will delay disease progression in the short to medium term and so improve quality of life and have a modest effect on length of life compared to existing treatment
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology should be more effective in all patient groups. The design of the Phase 3 COMET study in which treatment naïve patients were randomised to ALGLU or AVAL (Technology) means that when declining patients are switched to AVAL whether a treatment effect is seen will need to be monitored closely.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Most HCPs are likely to want to introduce the technology in a hospital setting for several treatment visits as many patients are declining this will have a temporary but significant effect on in-hospital care particularly at a time when hospitals are trying to upscale their response to delayed patient care consequent on the COVID pandemic. I anticipate that individual patients will have to be prioritised and arrangements made to initiate treatment in cohorts.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Because of non-inferiority of the technology, assuming its approval, it is likely that all symptomatic treatment naïve patients full filling the EPOC guidelines will be offered this technology. The impact of COVID on monitoring including practical problems with vital capacity measurements in LOPD (with safety concerns as an aerosol generating procedure) will require clinicians to make an judgment on patients clinical status and it is likely that all centres will need to

	agree criteria to define a decline, particularly as treatment effects are small and LOPD patients are clinically highly heterogeneous.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The technology has the same treatment regime and is in unlikely to have any other benefits not captured by QALY calculation.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology represents an evolutionary advance in Pompe and will impact on health status, deferring progression. The technology is not a revolutionary step-change, but an incremental advance in supportive care while we await future, hopefully more effective genetic therapies.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The available data from the Phase 3 COMET study suggest that the technology is not associated with any additional side effects compared to current treatment.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	The clinical trials on the technology in LOPD support its use in Enzyme Replacement Therapy naïve patients in the UK, and the outcome measures chosen (6MWT and VC) are appropriate and do reflect clinical practice. The measures used do reflect impact on quality of life and longevity. There is little data on the technology's benefits in ERT experienced patients, and close monitoring and a registry will be required to assess the treatment effect. In the future it is likely that Muscle MRI and actigraphy will be use as secondary

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	outcome measures but these are not yet established in Pompe. I am not aware of any adverse effects that were not apparent in clinical trials but have come to light subsequently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	The trial data does reflect real-world experience of ERT in Pompe ie a modest benefit with stabilisation and initial benefit in the majority of patients.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	No

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	The question on the cost comparison versus cost utility is a highly complex, is an economic evaluation and not something I can have an informed view on, I accept the reviewers comments.
Issue 2: It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	It would be reasonable to request access to all data, even if there is limited cardiac data in IOPD.

Clinical expert statement

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 for the late onset Pompe disease (LOPD) population	Whilst I accept that there are many clinical similarities between the UK and Netherlands Pompe cohorts, I cannot understand the decision not to include data from other European cohorts eg Spain Italy France and Germany, all of whom have published there Real-World data on the existing treatment. Pompe is a rare disease, and even country cohort sizes will be small, furthermore LOPD is heterogeneous, and given this to use as much data as possible including meta analysis would seem prudent.
Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD) population is a major uncertainty in the economic evaluation	I agree if approved Real-World data will be important.
Issue 5: The duration of the AVAL treatment effect is very uncertain in the LOPD population	I agree the duration of the treatment effect of AVAL is unclear, and the results of open extension studies and if approved Real-World data will be important.

Issue 6: The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population	From the data available the AVAL benefits are likely to be underestimated particularly as changes in respiratory function predict ventilatory requirements and respiratory insufficiency and pneumonia are the main modes of death in LOPD
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	Whilst vial sharing is used in specific Botulinum toxin injection clinics for Dystonia and migraine, I agree that vial sharing is unlikely in Pompe, as it would need a highly co-ordinated system which is unlikely to be possible particularly in the home care setting.
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment in the IOPD population	As suggested by one of your reviewers many IOPD patients will be on weekly infusions, and depending on costing model, AVAL may be cheaper intervention. The CS may reflect a cautious approach given the limited data from Mini-COMET and the time lines on Baby-COMET
Issue 9: The option for ERT dose escalation is excluded from the company's cost	I suspect this reflects genuine uncertainty as to the dose used in IOPD pateints in contrast to the very standardised dose which will be used in Adult LOPD. However to give a standard charge for this technology, being so very expensive, would seem reasonable.

utility models. The impact on cost effectiveness of different dose escalation approaches is unknown in the IOPD population	
Are there any important issues that have been missed in ERG report?	I would just comment that with such an expensive treatment with so little long term data to propose a Managed Access agreement or similar would seem reasonable.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There are significant un-met needs in both IOPD and LOPD
The technology is an evolution from current standard of care
There is a trend towards enhanced benefit in treatment naïve LOPD patients
There is limited data on efficacy in IOPD
There is limited data on long term data of efficacy in LOPD real world data will be important

Click or tap here to enter text.

Thank you for your time.

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Clinical expert statement and technical engagement response form

Avalglucosidase alfa for treating Pompe disease ID3737

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report section 1.3. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Clinical expert statement

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Deadline for comments by **5pm** on **6th May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating Pompe disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	DR AYESHA ALI
2. Name of organisation	NHS ENGLAND
3. Job title or position	MEDICAL ADVISOR, HIGHLY SPECIALISED SERVICES
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with Pompe disease? ☐ A specialist in the clinical evidence base for Pompe disease or technology? ☒ Other (please specify): Commissioning organisation for the clinical service and the drug if approved
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for Pompe disease	Stop or slow progression, facilitate mobility and ability to undertake activities of daily living and participate in social/community/family life

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in Pompe disease?	This technology, if approved, will provide an additional option for patients
11. How is Pompe disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are no national NHS England clinical commissioning policies for the treatment of this disease. The pathway of care is well defined for this patient group and there are no significant differences of opinion between the professionals This technology, if approved, will provide an additional option for patients
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will be administered through current commissioning arrangements and used in the same settings as current ERT

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No significant difference to current practice
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There remains considerable uncertainty about long term clinical effectiveness
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	

23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	No additional equality considerations

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	
Issue 2: It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	

Clinical expert statement

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 for the late onset Pompe disease (LOPD) population	Although a larger sample size has statistical benefits, given the size of the prevalent population, studies with smaller samples sizes should have been considered for inclusion
Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD) population is a major uncertainty in the economic evaluation	There is an imbalance in the quality and quantity of evidence between the two patient groups
Issue 5: The duration of the AVAL treatment effect is very uncertain in the LOPD population	

Issue 6: The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population	
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment in the IOPD population	
Issue 9: The option for ERT dose escalation is excluded from the company's cost	This is an important factor and one that has arisen in the administration of algucosidase where there is often use of an off label higher dose particularly in the first twelve months of life

utility models. The impact on cost effectiveness of different dose escalation approaches is unknown in the IOPD population	
Are there any important issues that have been missed in ERG report?	This is picked up in the ERG report but the impact on carers does not appear to be fully captured.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Imbalance between evidence between infant and late onset populations
Studies with smaller patient sample sizes should have been considered for inclusion
Uncertainty in evidence on long term benefits
Possibility of dose escalation requires better modelling/consideration
Carer impact not fully captured and assessed in the model

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avalglucosidase alfa for treating Pompe disease [ID3737]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **26th April 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Association of British Neurologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 2: It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
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 for the late onset Pompe disease (LOPD) population	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Issue 4: The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD) population is a major uncertainty in the economic evaluation	No	AVAL appears of similar efficacy to ALGLU in LOPD and given the same disease mechanism there should be no reason to expect lesser effectiveness in IOPD. So although the numbers studied with IOPD were very small it would be reasonable to assume a similar response as to that in LOPD
Issue 5: The duration of the AVAL treatment effect is very uncertain in the LOPD population	No	It is uncertain but there would be no reason to assume any different duration than in ALGLU treatment and potentially could be better. Data on this can still be prospectively gathered.
Issue 6: The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population		Possibly so because there appears a trend towards greater efficacy for AVAL compared with ALGRU. However, the length of follow-up as yet, does not make it clear whether this trend persists or may be a short-lived initial effect which is not sustained and would not therefore reflect better survival.
Issue 7: The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs	Yes	This would appear to be the case although the dosing is suggested to be averaged over two treatments.
Issue 8: The increased dosing frequency for the comparator treatment alglucosidase alfa (ALGLU) during the first 12 weeks is not assumed for AVAL, making ALGLU a more costly treatment in the IOPD population	**Yes**	The higher dose of ALGLU is used in those with poor response or worse disease burden. It appears there is the same intention to increase the dose of AVAL in such situations which would reduce the cost difference between ALGLU and AVAL in IOPD..
Issue 9: The option for ERT dose escalation is excluded from the company's cost utility models. The	Yes	

impact on cost effectiveness of different dose escalation approaches is unknown in the IOPD population.		

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

CONFIDENTIAL

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

Avalglucosidase alfa for treating Pompe disease ID3737

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	13th May 2022

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Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

1. Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Sanofi, to the key issues for technical engagement (TE) proposed in the ERG report for this appraisal (submitted to NICE on 25th February 2022). The ERG received the company's response form on 29th April 2022.

The company's response form contains the following information:

- A written response to each of the 9 key issues, seven of which include new evidence and/or analyses (see Table 1).
- A set of updated company cost-effectiveness results, incorporating:
    - An updated confidential Patient Access Scheme (PAS) price discount for avalglucosidase alfa
    - Additional evidence and/or analyses provided by the company in response to some of the key issues for TE.
- An updated version of the company's economic model accompanies the response form.

In this report we present the following:

- Our critique of the company's response to each of the 9 issues for technical engagement (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of an updated ERG base case and scenario analyses (Section 3)

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	The company's justification for cost-comparison analysis as the primary economic evaluation is subject to uncertainty	Yes
2	It is unclear if all relevant clinical effectiveness evidence has been included in the company submission	Yes
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 for the late onset Pompe disease (LOPD) population	Yes
4	The limited available evidence on the efficacy and safety of avalglucosidase alfa (AVAL) in the infantile onset Pompe disease (IOPD) population is a major uncertainty in the economic evaluation	No
5	The duration of the AVAL treatment effect is very uncertain in the LOPD population	Yes
6	The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population	Yes
7	The assumption that AVAL medication vials are shared underestimates AVAL's acquisition costs (IOPD) and LOPD)	Yes
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)	Yes
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 in the IOPD population.	No

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2. Critique of the company's response to key issues for technical engagement

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

The company's preferred approach of cost-comparison analysis is not adequately justified based on the limited available clinical effectiveness evidence for AVAL. Our focus, therefore, has been on a critique of the company's cost-utility model, though this itself is subject to uncertainty due to limited available data for some input parameters.

At technical engagement the company reiterated their preference for a cost-comparison analysis by citing the previously presented results of the phase 3 COMET trial. These results show AVAL to be non-inferior to ALGLU in the LOPD population, and the mini-COMET study show a trend for improvement or stabilisation with AVAL in the IOPD population.

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

Reference details of 40 of the 103 clinical trials and observational studies included in the company's systematic review of clinical effectiveness were not provided in the submission to NICE. The ERG was unable to check whether all relevant clinical effectiveness studies had been included in the CS.

At technical engagement the company provided a bibliography of the 40 studies (company response document, Appendix B Table 4). The ERG counts a total of 37 publications in the bibliography which raises the possibility that the remaining three (out of 40 studies) publications are not present in this list (assuming each study is reported in at least one publication). It is possible that some of the publications report more than one study, but the ERG has not been able to check each publication to verify this. Furthermore, the total number of studies versus the total number of publications is not discussed.

None of the 37 references appear relevant to the decision problem, based on the ERG's examination of their titles. Thus, it does not look like the list contains any references that should have been included in the CS. However, as noted above, there are three missing references.

2.3 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)

In their systematic review of clinical effectiveness, the company did not extract data from certain LOPD studies, namely those:

- With a participant sample size <100 conducted outside the UK and the Netherlands
- Only reporting humanistic outcomes (and no clinical outcomes),
- Not reporting SF-36 or EQ-5D.

Bibliographic details of the 17 studies with a participant sample size <100, conducted outside the UK and the Netherlands were not reported in the submission and no rationale was given for this exclusion criterion.

The company provided basic details of the 17 non-data extracted studies in Table 5 in Appendix B of the company's response to technical engagement. They additionally provided details of the studies not data extracted for the other reasons (reporting only humanistic outcomes or not reported SF-36 or EQ-5D). The studies were conducted mainly in Europe (Italy, France, Germany etc) as well as the US, China and Taiwan.

The company's technical engagement response states that studies which did not undergo data extraction were those that "provided only data on ALGLU or natural history (rather than AVAL) and data from large registries were already available". The ERG agrees with the company's decision not to include ALGLU or natural history studies since these are not within the decision problem. However, the ERG is unable to follow the meaning of the final part of the quoted sentence (registry data). We therefore cannot fully comment on the validity of the company's assumptions.

The company also states that the reason for excluding studies done outside the UK and the Netherlands was so that "only data most generalisable to the UK were extracted". However, they do not elaborate on characteristics of studies which increase or decrease their generalisability to the UK. For example, factors that make studies done in other European countries less relevant.

2.4 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

The only available *comparative evidence* for the clinical effectiveness of AVAL in the IOPD population is the phase 2 mini-COMET trial (Cohort 3), with a small sample size (n=11 participants). [NB. The ERG acknowledges that the total sample includes 22 participants, but only 11 of these were included in the comparative cohort randomised to AVAL or ALGLU. Data from the remaining 11 participants does not inform cost-effectiveness modelling.]

The ERG considers it unclear whether the effects of AVAL would necessarily be similar to ALGLU when extrapolated over a 50-year time horizon, as assumed by the company. The ERG's scenario analyses showed that ICERs are significantly higher if a survival benefit for AVAL is assumed (due to longer time on treatment and therefore higher treatment costs). 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.

In response to technical engagement the company updated their PAS discount did not change any of their modelling assumptions.

2.5 Issue 5 – The duration of the AVAL treatment effect is very uncertain in the LOPD population

The company assumed that improvements in [redacted].

The ERG considers that this assumption is uncertain and in our base case we assumed the same duration of treatment effect for AVAL and ALGLU: [redacted]. To address this uncertainty we proposed the collection of longer-term follow-up data in people treated with AVAL.

In their response to technical engagement the company states that the evidence from the NEO-EXT study supports the halting of disease progression for a period of at least five years following the initial improvement at one year for AVAL. They also state that this "does not lead to a significant amount of decision uncertainty" but do not provide an explicit justification to support this statement. We would like to reiterate that the extension phase of NEO-EXT is currently ongoing and only a proportion of the 19 enrolled participants have results available at four to six years of receiving treatment.

The company provides a scenario analysis using the ERG's assumption of the duration of the treatment effect, the results of which show that AVAL remains dominant.

We note the response to this issue from the Association of British Neurologists who state: *"It is uncertain but there would be no reason to assume any different duration than in ALGLU treatment and potentially could be better. Data on this can still be prospectively gathered."* Based on this response and on the very uncertain results of the NEO-EXT trial, we maintain our view that the duration of the treatment effect for AVAL and ALGLU should be considered the same until such time that longer term evidence becomes available.

2.6 Issue 6 – The lifetime incremental survival advantage for AVAL is likely to be underestimated in the LOPD population

As insufficient data about the long-term survival is available for AVAL, the company's base case assume that overall survival is equivalent between patients taking AVAL and ALGLU. The ERG considers 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).

In response to technical engagement, the company agrees with the ERG that the model is likely to underestimate the survival gains of AVAL expected in the LOPD population. Accordingly, the company's updated base case aligns with the ERG base case, assuming an overall survival HR of 0.85 for AVAL versus ALGLU.

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

The company's calculation of drug acquisition costs assumes vial sharing of leftover medication. The ERG considers this is unrealistic as the estimate of the number of vials would not always be a whole number and therefore the number of vials needs to be rounded in some way. There is therefore potentially an underestimate of the cost of ERT.

In response, the company submitted results of a survey of eight treatment centres within the UK. The clinical experts stated that to avoid vial wastage, they would round to the nearest vial. In instances where the patient is half-way between vials then alternate dosing would be used. The company, therefore revised their base case for the LOPD population so that doses can be rounded up or down to the nearest vial. They made no change to the modelling of the vials required in the IOPD model. They justify this by stating that as this is a cohort model variation in patient and weight and therefore the number of vials is not required

and when the number of vials can be rounded up or down an average number of vials is more appropriate.

The ERG agrees with the company's approach to vial wastage for LOPD, i.e., rounding to the nearest vial, as supported by the survey of clinical experts. We also consider this approach should also be taken for IOPD. In order to show the variation in the model, we also provide sensitivity analysis varying the starting weight of the cohort.

2.8 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)

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.

The company's response to this is to reiterate their original position in the company submission, i.e. that there is no clinical evidence or established practice to support the initial higher dose of AVAL.

The company stated that there is no clinical evidence or established practice to support the initial higher dose of AVAL. We would counter that this uncertainty applies equally to their assumptions on dosing. Nonetheless, the company included a scenario analysis including increased dosing frequency for AVAL where AVAL remained dominant.

We note the response to this issue from the Association of British Neurologists who state: "The higher dose of ALGLU is used in those with poor response or worse disease burden. It appears there is the same intention to increase the dose of AVAL in such situations which would reduce the cost difference between ALGLU and AVAL in IOPD." Based on this response and from the advice from our clinical experts, we maintain our view that the dosing frequency should be the same for ALGLU and AVAL.

2.9 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 in the IOPD population.

According to the company's response to technical engagement there is no information currently available on how dose escalation may occur in clinical practice. They maintain that

"it is not possible" to model any informative scenarios around dose escalation. The ERG, however, considers it is possible to model exploratory scenarios when data are scarce. On reflection the company agrees that a similar dosing approach to that of ALGLU is likely to be applicable. However, they do not model any scenarios or change their base case accordingly.

2.10 Additional issue 1 – Outcomes from probabilistic sensitivity analysis (PSA)

The company identified an error in the model that affect the total QALYs calculation in the 'PSA Results' sheet. The total QALYs did not include the caregiver disutility in cells I42 and I43.

The ERG agrees with the company's correction in the total QALYs calculation, and this is corrected in the revised PSA results in Table 4 and Table 7.

3. Updated cost-effectiveness results - ERG summary and critique

3.1 Company's revised base case cost-effectiveness results

The results of the company's changes to their original base case are shown in Table 2 and Table 3 below for IOPD and LOPD respectively.

Table 2 Company's changes to their original base case (IOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
Company original base case	[redacted]	[redacted]	Dominant
ERG corrections to base case for drug administration and CPRD disease related costs	[redacted]	[redacted]	Dominant
New PAS discount for AVAL	[redacted]	[redacted]	Dominant
Company revised base case	[redacted]	[redacted]	Dominant

Abbreviations: Clinical Practice Research Datalink (CPRD); ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year.

Table 3 Company's changes to their original base case (LOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
Company original base case	[redacted]	[redacted]	Dominant
New PAS discount for AVAL	[redacted]	[redacted]	Dominant
OS AVAL vs. ALGLU HR = 1	[redacted]	[redacted]	£92,183
Vial sharing: round up or down to the nearest number of vials	[redacted]	[redacted]	Dominant
Rate of progression of 6MWT with BSC: [redacted]	[redacted]	[redacted]	Dominant
Disutility of caregivers: 0 072 and 0.102	[redacted]	[redacted]	Dominant
Company revised base case	[redacted]	[redacted]	Dominant

Abbreviations: (BSC) Best supportive care; ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year.

The ERG ran the PSA with the company's revised base and the results are shown in Table 4.

Table 4 Company's revised PSA results (LOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
Company revised base case	[redacted]	[redacted]	Dominant
Company PSA results	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; OS, overall survival; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

3.2 ERG's revised preferred assumptions

In response to the company's survey of clinical experts on vial wastage, we revised our assumption related to vial sharing (Issue 7). We agree with the clinical experts that dosing should be estimated by rounding to the nearest vial, rather than rounding **up** to a whole number of vials.

3.3 Cost-effectiveness results based on ERG preferred model assumptions

The cumulative effect of the ERG's preferred model assumptions is shown in Table 5 and Table 6 for IOPD and LOPD respectively.

Table 5 Cumulative results for the ERG's preferred model assumptions (IOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
Company revised base case	[redacted]	[redacted]	Dominant
Double dosing for AVAL in the first 12 weeks	[redacted]	[redacted]	Dominant
Dosing estimated by rounding to nearest vial	[redacted]	[redacted]	Dominant
Exponential distribution used to model OS	[redacted]	[redacted]	Dominant
ERG utility estimates	[redacted]	[redacted]	Dominant
Age adjusted utility not included	[redacted]	[redacted]	Dominant
ERG's preferred assumptions	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year.

Table 6 Cumulative results for the ERG's preferred model assumptions (LOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
Company revised base case	[redacted]	[redacted]	Dominant
AVAL plateau period equal to the ALGLU plateau period	[redacted]	[redacted]	Dominant
ERG's preferred assumptions	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year.

The ERG ran the PSA with the ERG's revised base and the results are shown in Table 7.

Table 7 ERG revised PSA results (LOPD)

Scenario	Incremental QALYs	Incremental costs	ICER
ERG revised base case	[redacted]	[redacted]	Dominant
ERG PSA results	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; OS, overall survival; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

3.4 Scenario analyses conducted on the ERG's revised preferred assumptions

We explored the effect of increasing the starting age of the modelled patient cohort as well as reducing the relative treatment benefit for AVAL vs ALGLU in the IOPD population (Table 8). Changing the starting age has only a minimal effect on model results whilst the results are largely affected by changes to the assumption for the treatment effect on OS, with a small increase in OS for AVAL associated with large incremental costs.

Table 8 Scenario analysis results for the ERG's preferred model assumptions (IOPD)

Scenario	Incremental QALYs	Incremental costs	ICER (£/QALY)
ERG's preferred assumptions	[redacted]	[redacted]	Dominant
Starting age, 1 year	[redacted]	[redacted]	Dominant
Starting age, 2 years	[redacted]	[redacted]	Dominant
OS AVAL vs ALGLU, HR = 0.95	[redacted]	[redacted]	£348,428
OS AVAL vs ALGLU, HR = 0.85	[redacted]	[redacted]	£591,310

Abbreviations: ICER, incremental cost-effectiveness ratio; IOPD, infantile-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year.

The ERG also explores the effect of varying the overall survival treatment benefit to assume that AVAL has better survival rates than ALGLU (in the LOPD population) (Table 9). Although there is a change in incremental QALYs and incremental costs, AVAL still dominates ALGLU.

Table 9 Scenario analysis results for the ERG's preferred model assumptions (LOPD)

Scenario	Incremental QALYs	Incremental costs	ICER (£/QALY)
ERG's preferred assumptions	[redacted]	[redacted]	Dominant
OS AVAL vs ALGLU, HR = 1	[redacted]	[redacted]	Dominant
OS AVAL vs ALGLU, HR = 0.7	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LOPD, late-onset Pompe disease; OS, overall survival; QALY, quality-adjusted life year.