Highly Specialised Technology

Sebelipase alfa for treating Wolman disease [ID3995]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Sebelipase alfa for treating Wolman disease [ID3995]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission Summary** from Alexion
   a. Full submission
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2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Children's Liver Disease Foundation
   b. The MPS Society
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4. **External Assessment Report** prepared by prepared by Newcastle NIHR TAR Team

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6. **Technical engagement response from Alexion**

7. **Technical engagement responses and statements from experts:**
   a. Sophie Thomas – Patient expert, nominated by MPS Society
   b. Simon Jones – clinical expert, nominated by MPS Society and Company
   c. Lee-Ann Lorimer – Patient Expert nominated by MPS society

8. **External Assessment Group critique of company response to technical engagement** prepared by Newcastle NIHR TAR Team

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

Highly specialised technology evaluation

Sebelipase alfa for treating Wolman disease (rapidly progressive LAL-D) [ID3995]

Document B

Company evidence submission

November 2022

File name	Version	Contains confidential information	Date
ID3995 Sebelipase alfa_HST_Doc B_ACIC_2NOV22 CiC+AiC REDACTED	**1.0**	**No**	**2 November 2022**

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Abbreviations

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATU	Autorisation temporaire d'utilisation (temporary use authorization)
BSC	Best supportive care
CESD	Cholesterol ester storage diseases
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DSR	Dietary substrate reduction
ERT	Enzyme replacement therapy
FAS	Full analysis set
GATM	Global Access to Medicines programme
GGT	Gamma glutamyltransferase
HDL-C	High-density lipoprotein-cholesterol
HRQL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
IAR	Infusion-associated reactions
IV	Intravenous
LAL	Lysosomal acid lipase
LAL-D	Lysosomal acid lipase deficiency
LDL-C	Low-density lipoprotein-cholesterol
LIPA	Lipase A lysosomal acid
LLN	Lower limit of normal
MRI	Magnetic resonance imaging
NASH	Non-alcoholic steatohepatitis
NHS	National Health Service
PES	Primary efficacy set
QOW	Every other week
QW	Once a week
RCT	Randomized controlled trial
rhLAL	Recombinant human lysosomal acid lipase
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TFHN	Transfusion-free haemoglobin normalization

Abbreviation	Definition
WHO	World Health Organization

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

B.1.1. Decision problem

Sebelipase alfa (Kanuma®) is indicated for 'long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D)'.[1] Following the previous cost-effectiveness assessments conducted by NICE in ID737, the decision has been made to focus this appraisal on part of the technology's marketing authorization, specifically, patients with rapidly progressive LAL-D (historically referred to as Wolman Disease). This population is in line with the target patient population defined within the NICE scope. The decision to target only the population with rapidly progressive LAL-D in this appraisal has been justified based on the particularly high unmet need in this population and the high potential for accrual of health benefits over patients' lifetimes.

The decision problem addressed in this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with Wolman disease	Patients with rapidly progressive LAL-D	The patient population of focus for this submission is patients with rapidly progressive LAL-D, which has historically been referred to as 'Wolman disease' or the 'Wolman phenotype'. LAL-D can present across the lifespan, from the rapidly progressive infantile-onset form where symptom onset is usually up to 6 months of age, to the less-severe later-onset forms, which were historically and collectively known as CESDs. UK clinical experience has shown that, rarely, patients can also present with the rapidly progressive and advanced form of LAL-D between 6 and 24 months of age. The terminology 'rapidly progressive LAL-D' is therefore seen as a more current and clinically accurate description of the target population.
Intervention	Sebelipase alfa	As per final scope	N/A
Comparator(s)	Established clinical practice without sebelipase alfa	As per final scope	N/A. However, the budget impact analysis considers the real-world situation in which sebelipase alfa is already established but access is provided under the Alexion Global Access to Medicines (GATM)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			programme. I.e., where sebelipase alfa is not acquired by the NHS in England.
Outcomes	The outcome measures to be considered include: • Mortality • Body weight and nutritional parameters (including growth) • Haematological parameters (including serum ferritin, need for blood transfusions) • Lipid parameters (including total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides) • Liver function (including transaminase level) • Liver disease progression (including hepatomegaly) • Adrenal gland function (for example, need for adrenal hormone supplementation) • Neurological development parameters • Cardiovascular events • Anti-drug antibodies • Adverse effects of treatment (including infusion-associated reactions)	The outcome measures to be considered include: • Mortality • Body weight and nutritional parameters (including growth) • Haematological parameters (including serum ferritin, need for blood transfusions) • Liver function (including transaminase level) • Liver disease progression (including hepatomegaly) • Neurological development parameters • Anti-drug antibodies • Adverse effects of treatment (including infusion-associated reactions) • Health-related quality of life for patients and carers/family While the following parameters suggested in the final scope are not directly relevant for the rapidly progressive LAL-D population, they may provide valuable information for the long-term follow-up of treated patients who	No adrenal gland function evidence was captured in any of the sebelipase alfa clinical trials, so we will not be able to include this outcome as requested in the pre-invitation scope. Clinicians have noted adrenal failure has not been a reported finding, even in long-term follow-up of affected infants receiving treatment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Health-related quality of life (for patients and carers)	survive beyond infancy and will be discussed in the clinical sections only: • Lipid parameters (including total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides) • Cardiovascular events • Need for liver transplant	
Economic analysis	We plan to provide a full cost–utility analysis comparing sebelipase alfa to the current standard of care without sebelipase alfa	As per final scope	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People who have received haematopoietic stem cell transplant • People who have not received HSCT	No subgroup analyses are to be presented.	Due to the rarity of the condition and the limited patient numbers, no subgroup analyses were planned or conducted for the LAL-CL08 or LAL-CL03 trials. Although no subgroup analyses of the pivotal trials were performed, the efficacy of sebelipase alfa and HSCT as a multimodal therapy in the UK has been explored in a recently published case series (Potter et al. 2021[2]; n = 5). Results for these five patients with rapidly progressive LAL-D have therefore been provided as part of the evidence base presented in this submission.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Impact of the technology beyond direct health benefits, and on the delivery of the specialized service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialized service • Staffing and infrastructure requirements, including training and planning for expertise	As per final scope All points raised in the final scope will be addressed in the company submission. Of note, Alexion has made sebelipase alfa available over the last 6 years for patients with rapidly progressive LAL-D in the UK. The staffing and infrastructure requirements for the administration of sebelipase alfa are therefore already in place, and patients with rapidly progressive LAL-D are already under the care of experienced UK clinicians.	N/A
Special considerations including issues related to equity or equality	N/A – no special considerations, including issues related to equity or equality, were stated within the final scope	As per final scope The aim of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between all is aligned with Alexion's principles on Diversity, Inclusion and Belonging[3] The decision has been made to focus this appraisal only on the treatment of patients with the most severe form of LAL-D which manifests in very young children, known as rapidly progressive LAL-D. The decision to target this specific population in this appraisal has been justified based on	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		the higher potential for accrual of health benefits over the patients' lifetimes, which results in better cost-effectiveness in this population. However, older children, adolescents and adults with LAL-D may be negatively impacted by not having access to treatment with sebelipase alfa, despite evidence of proven clinical efficacy in these groups. As age is a protected characteristic in UK law, it is possible that excluding these patients from this appraisal could result in equality issues. Later-onset LAL-D (cholesterol ester storage disease) is still being considered within the NICE evaluation of sebelipase alfa for treating LAL-D (ID737). It has been paused while this evaluation for treating rapidly progressive LAL-D is undertaken. We have not identified any other foreseeable exclusions, limitations or adverse effects on protected individuals based on disability, gender reassignment, relationship status, pregnancy and maternity, race, religion or belief, sex, and/or sexual orientation.	
Key: HSCT, haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency; NHS, National Health Service.			

B.1.2. Description of technology being evaluated

Table 2 presents a description of sebelipase alfa. The Summary of Product Characteristics (SmPC) is presented in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Sebelipase alfa (Kanuma®)
Mechanism of action	Sebelipase alfa is an rhLAL that acts as an enzyme replacement for LAL.[1] Please refer to Figure 1 for further details.
Marketing authorisation/CE mark status	The European Commission granted market authorization of sebelipase alfa on 28 August 2015.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Sebelipase alfa is indicated for long-term ERT in patients of all ages with LAL-D.
Method of administration and dosage	Sebelipase alfa is for IV use only. The total volume of the infusion should be administered over approximately 2 hours. A 1-hour infusion may be considered after patient tolerability is established. The infusion period may be extended in the event of dose escalation. Sebelipase alfa should be administered through a 0.2 µm filter. <u>Patients with rapidly progressive LAL-D presenting within the first 6 months of life:</u> The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL-D is either 1 mg/kg or 3 mg/kg administered as an intravenous infusion once weekly, depending on the clinical status of the patient.[1] A higher starting dose of 3 mg/kg should be considered based on the severity of the disease and rapid disease progression. Dose escalations should be considered based on suboptimal response to clinical and biochemical criteria, including, e.g. poor growth (especially mid-upper arm circumference, MUAC), deteriorating biochemical markers (e.g. liver transaminases, ferritin, C-reactive Protein, and coagulation parameters), persistent or worsening organomegaly, increased frequency of intercurrent infections, and persistent worsening of other symptoms (e.g. gastrointestinal symptoms):[1] • a dose escalation to 3 mg/kg should be considered in case of suboptimal clinical response;

	• a further dose escalation up to 5 mg/kg should be considered in case of persistent suboptimal clinical response. Further dose adjustments, as a reduction of the dose or an extension of the dose interval, can be made on an individual basis based on achievement and maintenance of therapeutic goals. Clinical studies evaluated doses ranging from 0.35 to 5 mg/kg once weekly. <u>Paediatric and adult patients with LAL-D:</u> The recommended dose in paediatrics and adults who do not present with rapidly progressive LAL-D before 6 months of age is 1 mg/kg administered as an intravenous infusion once every other week. Dose escalation to 3 mg/kg once every other week should be considered based on suboptimal response to clinical biochemical criteria, including: poor growth; persistent or deteriorating biochemical markers (e.g. parameters of liver injury [ALT, AST], parameters of lipid metabolism [TC, LDL-C, HDL-C, TG]; persistent or worsening organomegaly; and persistent worsening of other symptoms [e.g. gastrointestinal symptoms]).
Additional tests or investigations	No additional tests or investigations are needed.
List price and average cost of a course of treatment	The list price of sebelipase alfa is £6,286 per 20 mg vial and the average monthly cost of a course of treatment is [redacted]
Patient access scheme (if applicable)	A simple discount of [redacted]
Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERT, enzyme replacement therapy; HDL-C, high-density lipoprotein-cholesterol; IV, intravenous; LAL-D, lysosomal acid lipase deficiency; LDL-C, low-density lipoprotein-cholesterol; NHS, National Health Service; rhLAL, recombinant human lysosomal acid lipase; TC, total cholesterol; TG, triglycerides.	

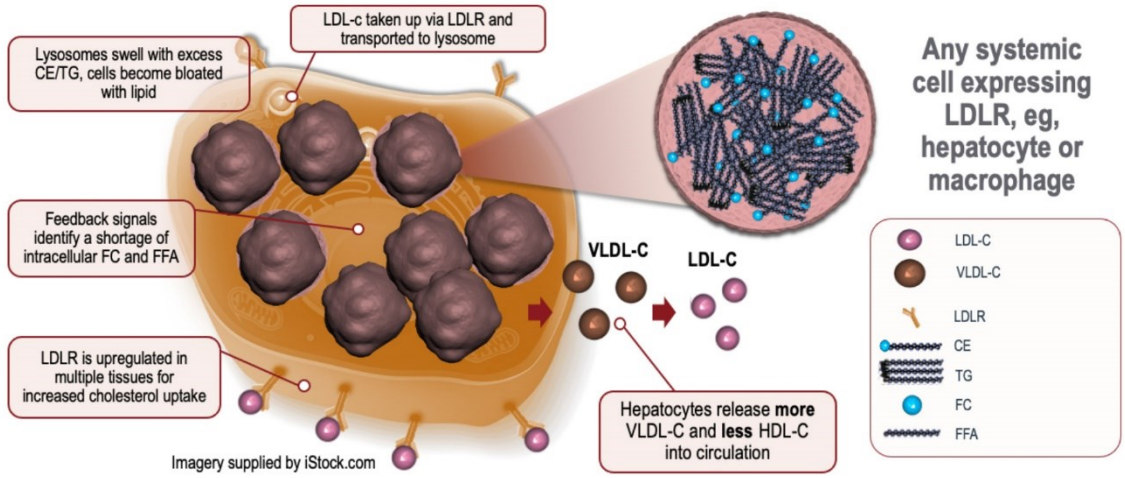
Sebelipase alfa, sold under the brand name Kanuma®, is an innovative, first-in-class treatment option for patients with LAL-D and remains the only effective treatment option for this otherwise fatal disease.

Figure 1 presents the manifestations of LAL-D in patients without treatment with sebelipase alfa, followed by Figure 2 which presents a diagram of how sebelipase alfa acts on these underlying causes of LAL-D.

Sebelipase alfa is a recombinant form of LAL (rhLAL) that binds to cell surface receptors via glycans expressed on the protein and is subsequently internalised into lysosomes.[1] Within the lysosomes, sebelipase alfa catalyses the lysosomal

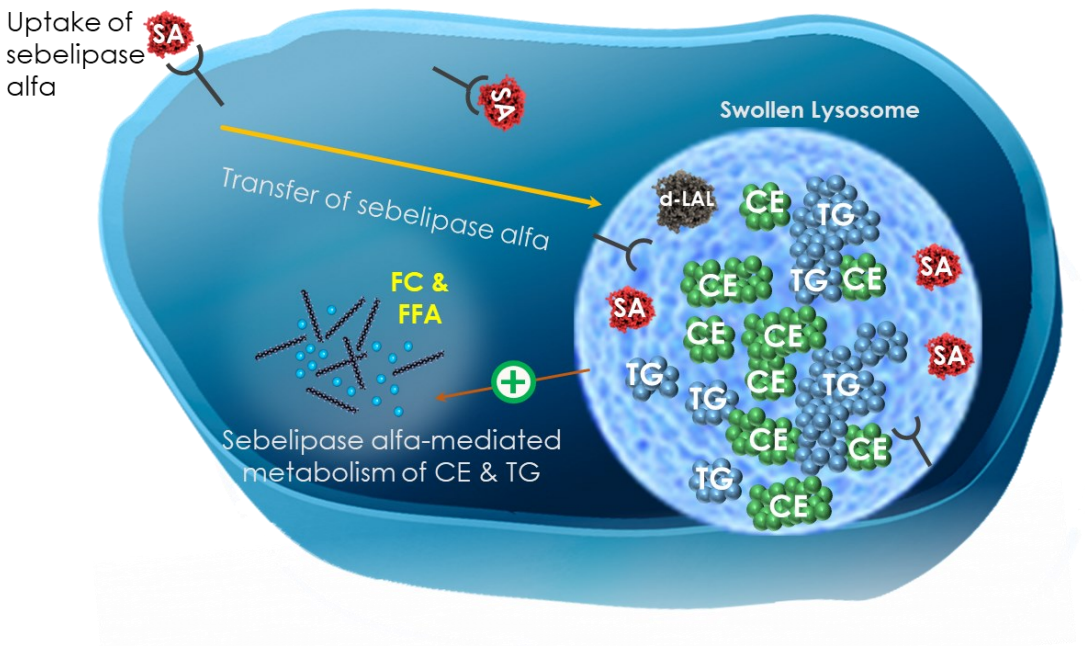
hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. The replacement of LAL enzyme activity enables metabolism of cholesteryl esters and triglycerides in the lysosome and leads to a reduction in liver fat content and serum transaminases, as well as reductions in low-density lipoprotein-cholesterol (LDL-C) and non-high-density lipoprotein-cholesterol (non-HDL-C), triglycerides, and increases in HDL-C.[1] Patients begin to experience improvements in growth, facilitated by a multitude of factors including a better use of calories supplied as lipids, reduced inflammatory response, and potentially a reduction of substrate in the intestine..

Figure 1: Manifestations of LAL-D



Key: CE, cholesterol esters; FC, free cholesterol; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein-cholesterol; LDLR, low-density lipoprotein receptor; TG, triglycerides; VLDL-C, very low-density lipoprotein-cholesterol.
Source: Image adapted from Reiner et al. 2014[4] and Grabowski et al. 2012.[5]

Figure 2: Mode of action of sebelipase alfa



Key: CE, cholesterol ester, d-LAL, defective/non-functioning lysosomal acid lipase; FC, free cholesterol; FFA, free fatty acid; SA, sebelipase alfa; TG, triglyceride.
Source: Figure created by Alexion Pharmaceuticals, Inc. for illustrative purposes.

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

Summary of key points:
• Rapidly progressive LAL-D is a life-threatening and ultra-rare metabolic disorder that is associated with significant morbidity and early mortality. Without treatment, patients with rapidly progressive LAL-D have a median survival of just 3.0 months[6] • Patients experience life-threatening symptoms, including marked failure to thrive, severe malabsorption and liver fibrosis and cirrhosis, which distinctly reduce the patients' and caregivers' quality of life[4, 7] • Caregivers of patients with rapidly progressive LAL-D experience a substantial clinical, emotional and financial burden[8] • Other than sebelipase alfa, there are no other disease-specific treatments available that treat the underlying cause of LAL-D or that are able to prevent the rapid disease progression • Supportive therapies used in the absence of sebelipase alfa do not address the underlying cause of disease and are unable to alter the prognosis of death[6]

B.1.3.1. Disease background

LAL-D is a life-threatening, progressive, ultra-rare metabolic disorder that is associated with significant morbidity and early mortality. It is caused by a genetic mutation that leads to a marked decrease or loss in activity of the LAL enzyme.[9] The genetic mutation is found in the lipase A lysosomal acid (*LIPA*) gene, which is located on chromosome 10q23.2-q23.3.[9] The lack of the LAL enzyme results in a marked accumulation of cholesterol esters and triglycerides in vital organs, particularly the liver and the intestine, as well as in blood vessels and other tissues. The deficiency in LAL results in extremely severe complications such as malabsorption, systemic inflammation, liver failure and growth failure, which, if left untreated, can lead to multiple organ failure and death.[4]

LAL-D is inherited in an autosomal recessive manner, which means each biological parent of a patient with LAL-D must carry at least one defective LAL gene.[7] Children of parents with a defective LAL gene have a 25% chance of inheriting LAL-D with

each pregnancy, a 50% chance of being a carrier and a 25% chance of being unaffected by the disease.[7]

The disease can present across the lifespan, from the rapidly progressive infantile-onset form (historically called Wolman disease) where symptom onset is usually within the first 6 months of life, to the later-onset forms, which are collectively known as cholesterol ester storage diseases (CESDs).[6, 7] The clinical experience in the UK has shown that, rarely, patients can present with rapidly progressed and advance LAL-D between 6 and 24 months of age. These patients present with severe impairment of liver function (advance fibrosis) and require treatment intervention with ERT. There have been [redacted] cases of such presentation in the UK over the last 7 years.[data on file]

Rapidly progressive LAL-D represents a medical emergency and is typically fatal in a matter of months.[10] Without treatment, death usually occurs in the first 6 months of life.[6] A natural history study of infants with rapidly progressive LAL-D found only four of 35 (11.4%) infants survived beyond 12 months of age and all four infants died by 4 years of age despite some receiving haematopoietic stem cell transplant (HSCT) and/or liver transplant.[6] The median age of death was just 3.7 months.[10] This was even lower in the subgroup of untreated patients (i.e. those that did not receive HSCT and/or liver transplant) who experienced early growth failure; the median age of death in this population was just 3.0 months.[10]

B.1.3.2. Epidemiology

Rapidly progressive LAL-D is classed as an ultra-rare disease, commonly defined as a disease that affects fewer than 1 in 50,000 individuals.[11] Similar to other ultra-rare diseases, there is a lack of published information on the incidence and prevalence of rapidly progressive LAL-D. The exact incidence and prevalence of rapidly progressive LAL-D is also very difficult to determine due to the potential for misdiagnosis and underdiagnosis of the disease (further discussed in Section B.1.3.4.1), as well as the early mortality that is common in this patient population.

As sebelipase alfa is currently licensed for use in the UK, and no other treatments are available for rapidly progressive LAL-D, Alexion has been providing and funding access to sebelipase alfa in the UK under a compassionate-use Global Access to Medicines (GATM) programme.[12] There are [redacted] patients in the UK with rapidly

progressive LAL-D who are currently receiving sebelipase alfa via the GATM programme.

When assessing rapidly progressive LAL-D epidemiology in the literature, the estimated incidence rate for rapidly progressive LAL-D is approximately 1 in 350,000 births.[9, 13] Based on clinical experience in England, it is estimated that on [redacted] might present with rapidly progressive LAL-D.[data on file]

B.1.3.3. Burden of disease

B.1.3.3.1. Disease progression and mortality

When an infant presents with symptoms of rapidly progressive LAL-D, it is deemed as a medical emergency. If not treated, death usually occurs in the first 6 months of life. A natural history study of 35 patients with rapidly progressive LAL-D reported that only four (11.4%) patients survived beyond 12 months of age, with all four of these patients dying before the age of 4 despite receiving HSCT and/or a liver transplant.[6, 14] Among the 21 patients with rapidly progressive LAL-D who were untreated and experienced early growth failure (as defined in Appendix D.1.4.1), the median age of death was just 3.0 months.[6] According to clinician advice on HSCT and liver transplant, these patients more accurately represent what would be current standard of care if sebelipase alfa was not available. Moreover, these patients had an estimated probability of survival past 1 year of age of 0%.[6]

The key contributing factors associated with premature mortality in patients with rapidly progressive LAL-D include severe malabsorption, systemic inflammation, undernourishment and failure to thrive (i.e. insufficient growth as determined through anthropometric data such as the weight and length of the child[15]), which subsequently leads to starvation, liver failure, and death.[6, 16-18]

B.1.3.3.2. Clinical manifestation of disease

Rapidly progressive LAL-D patients experience sudden and unpredictable clinical complications, usually within the first months of life: the median age of symptom onset in patients with rapidly progressive LAL-D is 1 month.[6, 16]

Clinical manifestations of rapidly progressive LAL-D may present as early as the first day of life; symptoms may include vomiting, diarrhoea, abdominal distention and steatorrhea.[4, 7, 19]

Other rapidly progressive LAL-D patients may not come to medical attention until weeks or a few months after birth. Patients may present with a marked failure to thrive, defined by the WHO as > 2 standard deviations (SDs) below normal weight and height measurements for age.[15] Patients experience vomiting and diarrhoea as a result of the accumulation of lipid substrates, leading to severe malabsorption. The natural history study of 35 patients with rapidly progressive LAL-D demonstrated that the percentage of underweight patients increased over time, from 20% at first patient record, to 66% at death.[6] Patients with early growth failure had an earlier median age of diagnosis compared with patients without early growth failure (2.5 versus 5.0 months, respectively).[6]

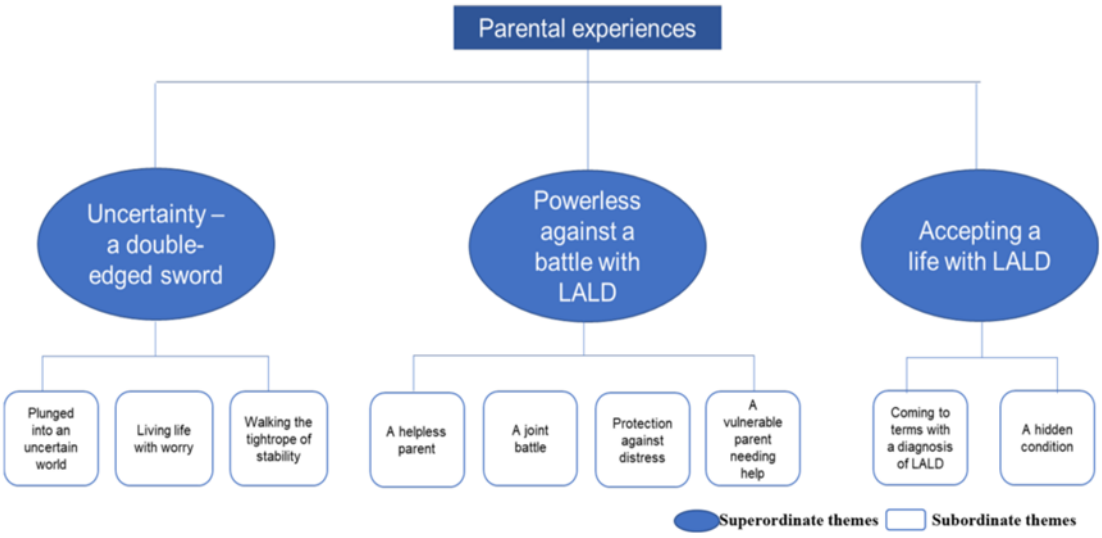
Patients with rapidly progressive LAL-D may also present with hepatomegaly and hepatic injury, along with increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[4] These infants quickly develop liver fibrosis and cirrhosis due to the large accumulation of cholesteryl esters and triglycerides in the liver. An increase in lipid deposition along the gastrointestinal (GI) tract also leads to thickening bowel walls, resulting in malnutrition and wasting.[7]

Furthermore, approximately 50% of infants also have adrenal calcification, a manifestation that allows clinicians to distinguish rapidly progressive LAL-D from other diseases with similar symptoms (i.e. Niemann–Pick Type C).[4, 16]

B.1.3.3.3. Caregiver burden

A recently published qualitative study reported on the lived experiences of parents of children with LAL-D.[8] Figure 3 presents the key themes identified in the eight parents interviewed. These themes capture the parental vulnerability and the importance of retaining a sense of a normal life.

Figure 3: Common themes identified in the experiences of parents of infants with LAL-D



Key: LAL-D, lysosomal acid lipase deficiency
Source: Hassall et al, 2022[8]

During the study, parents reflected on how the diagnosis of an incurable and rare condition was unexpected and extremely challenging.[8] The parents struggled with uncertainty, and how it felt not having many other children with LAL-D to compare their child to, which negatively impacted how they were able to make sense of the diagnosis. Parents also expressed a sense of helplessness and powerlessness as they were unable to care for their child in the way that they once did. They described their experience as a battle which was embroiled with loss, from the imagined loss of their child and visions of a healthy baby, and the cumulative losses associated with living in a hospital environment for a substantial period of time, such as the loss of their support network and their temporary or permanent loss of employment.[8] Furthermore, the death of a child has a long-term effect on bereaved parents; when assessing their quality of life, bereaved parents present with a significantly worse quality of life following child death compared to parents who did not experience the death of a child.[20]

B.1.3.4. Clinical care pathway and proposed positioning of the technology

B.1.3.4.1. UK guidelines and proposed positioning of sebelipase alfa

Due to the rapidly progressive nature of LAL-D in infants and the high rates of early mortality, a quick diagnosis is of high importance. Unfortunately, rapidly progressive

LAL-D is an under-recognised condition, likely due to the ultra-rare nature of the disease and limited disease awareness. A diagnosis of LAL-D may also be initially overlooked due to the non-specific symptomatology at initial presentation. More commonly diagnosed conditions that present with a partially similar clinical manifestation to rapidly progressive LAL-D include hemophagocytic lymphohistiocytosis (HLH), heterozygous familial hypercholesterolemia, or, more rarely, leukaemia.[21] A significant delay in the diagnosis of LAL-D results in a subsequent delay in patient access to potentially life-saving treatments (i.e. sebelipase alfa). The treatment aims for patients with rapidly progressive LAL-D are to improve survival, improve growth and nutritional status, prevent the progression of liver disease, and to see improvements in quality of life.

There are no relevant published guidelines for the management of rapidly progressive LAL-D and besides sebelipase alfa, there are no other disease-specific treatments available that treat the underlying causes of LAL-D or that are able to prevent the rapid disease progression. Due to the extreme severity of the condition, in the absence of any alternative treatment options, Alexion has been providing and funding access to sebelipase alfa in the UK for the past 10 years – first through clinical trials and more recently under its compassionate-use GATM programme.[12] The aim of the GATM programme is to:

- Support patients following their participation in clinical trials
- Provide access to therapies such as sebelipase alfa in countries where regulatory approval and/or reimbursement is not yet established, but where Alexion plans to pursue approval and reimbursement following marketing authorisation
- Enable patients who cannot participate in clinical trials to gain access to investigational therapies

Without access to sebelipase alfa, existing approaches focus on supportive therapies that aim to reduce the existing substantial burden of disease complications but are unable to prevent disease progression and ultimately death. Prior to the advent of sebelipase alfa, liver transplants and HSCT were occasionally used as a last resort in patients with rapid disease progression but were not able to change the prognosis of death.[19] The safety and efficacy of these supportive therapies in rapidly progressive LAL-D has not been evaluated in clinical trials or received any regulatory approval.

Compared with HSCT alone, HSCT following the use of sebelipase alfa may result in improved median survival outcomes in patients with rapidly progressive LAL-D in a subpopulation of patients who cannot continue with sebelipase alfa treatment long-term. Expert clinicians in the UK are at the forefront of evolution of the treatment pathway for rapidly progressive LAL-D, and in recent years, clinicians have introduced the use of multimodal therapy which includes the use of sebelipase alfa plus nutritional support, followed by HSCT in certain patient populations. This multimodal therapy was initially used in patients whose response to treatment diminished over time due to the development of anti-drug antibodies (ADAs), but also has the potential for use when patients can no longer tolerate weekly infusions or in whom venous access becomes an issue.[22, 23] This was further confirmed by UK clinicians, who stated that HSCT has been considered if the patient has been deteriorating due to reduced response to sebelipase alfa over time.[19] [redacted]

[data on file]

A recently published case series explored the efficacy of sebelipase alfa and HSCT as a multimodal therapy in five patients with rapidly progressive LAL-D based in the Royal Manchester Children's Hospital, a specialised centre for the diagnosis and treatment of inherited metabolic disorders.[2] Four of the five patients were alive at least 10 months after HSCT. At the time of writing, Potter et al. 2021 reported that all four surviving patients remain on treatment with sebelipase alfa, with three patients able to decrease their dosage and frequency.[2] One patient died 5 months post-HSCT due to an ongoing inflammatory process and subsequent sepsis development.[2] [redacted] At the point of HSCT, patients receiving HSCT survived to a greater age than they would have if sebelipase alfa was not available, and, due to treatment with sebelipase alfa, their liver function and nutritional status was better than at presentation. The procedure-related mortality associated with

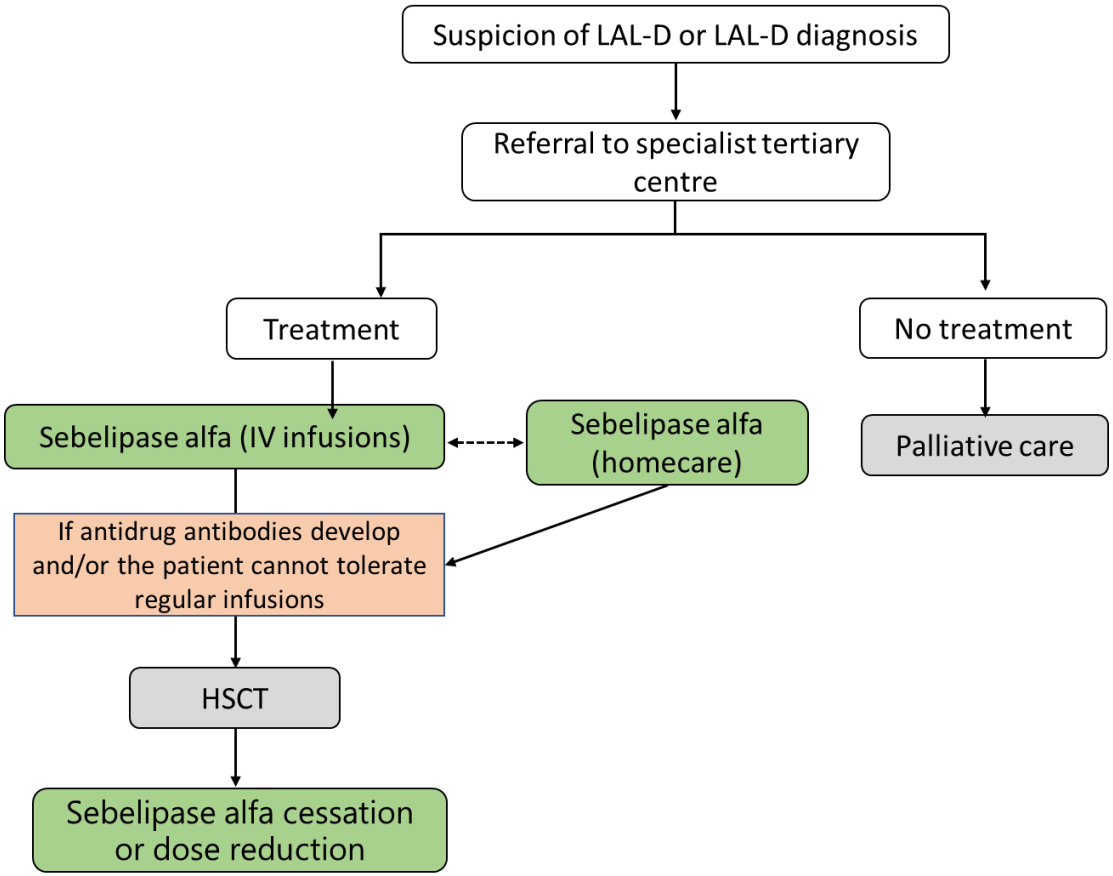
HSCT was therefore reduced. Collectively, these results suggest the potential benefit of the multimodal therapy of sebelipase alfa followed by HSCT.

As part of the lysosomal storage disorder (LSD) service commissioned by NHS England, there are currently three national centres of excellence located at Great Ormond Street Hospital, Manchester Children's Hospital and Birmingham Children's Hospital for the diagnosis and management of LAL-D in infants and children. Although all three centres have extensive experience with ERTs, Birmingham and Manchester are currently treating the vast majority of patients with rapidly progressive LAL-D and were also the designated clinical trial centres for the sebelipase alfa clinical development program. These centres have dedicated inpatient and outpatient facilities that are committed to the management of patients with rapidly progressive LAL-D. Figure 4 presents the clinical pathway of care for patients with rapidly progressive LAL-D and the proposed positioning of sebelipase alfa.

As patients with rapidly progressive LAL-D are severely ill, extensive support is required from multidisciplinary teams from diagnosis and throughout their treatment, regardless of whether or not the patient receives treatment with sebelipase alfa. Alexion is currently funding homecare support service for patients receiving sebelipase alfa through the GATM programme, with plans to continue funding this service if sebelipase alfa is to be reimbursed. This homecare support service includes drug delivery and administration of the infusion at home or other nurse approved locations (e.g. in schools) by a trained nurse.

As the majority of patients with rapidly progressive LAL-D present with malnutrition and wasting, the early involvement of an expert in nutrition and the addition of nutritional intervention, including total parenteral nutrition for the duration of their initial hospitalisation post-diagnosis, is fundamental to the management of the disease. Parenteral nutrition strategies may include a low-fat/high-protein/high-glucose feed or formula, increased calorie/concentrate formula, or feeds of decreased volume and increased frequency.[2, 24] In addition, when adrenal insufficiency is present, patients may also require corticosteroid and mineralocorticoid replacement.[7]

Figure 4: Pathway of care for patients with rapidly progressive LAL-D in LSD services in England, and proposed positioning of sebelipase alfa



Key: ADAs, anti-drug antibodies; HSCT, haematopoietic stem cell transplantation; IV, intravenous; LSD, lysosomal storage disorder.
Notes: Patients who develop ADAs tend to receive treatment with either bortezomib or rituximab[25].

B.1.3.4.2. Unmet clinical need

There is an extremely high unmet need for the treatment of patients with rapidly progressive LAL-D, demonstrated by the high rate of early mortality. In the absence of sebelipase alfa, there are no alternative treatments for patients with rapidly progressive LAL-D that are able to address the pathophysiology of disease and ultimately achieve an effective clinical response; these patients therefore die at an early age.

Prior to the approval of sebelipase alfa, treatments for rapidly progressive LAL-D were largely limited to supportive measures, including lipid-lowering therapies, HSCT and liver transplantation.[6] These supportive therapies do not address the underlying cause of disease, or the impact the disease has on multiple organ systems and are unable to alter the prognosis of death. The median age of survival in these untreated patients who experienced early growth failure was just 3.0 months.[6] Further, these therapies place a substantial burden on the healthcare system, especially considering their expense.

Due to the extreme severity of disease and the lack of any effective alternative treatment option, Alexion has been providing the support and funding required to give UK patients with rapidly progressive LAL-D access to sebelipase alfa for the past 6 years.

Sebelipase alfa is the first and only targeted ERT that is able to act on the underlying enzyme deficiency present in patients with rapidly progressive LAL-D. Since the EU approval of sebelipase alfa in 2015, over 13 years of experience has been collated from a combination of clinical trials and subsequent real-world use. The most recent trial to demonstrate the effectiveness of sebelipase alfa in patients with rapidly progressive LAL-D is LAL-CL08, in which treatment with sebelipase alfa improved prolonged survival, where 90% of patients survived to 12 months of age.[26, 27] Comparatively, none (0%) of the 21 untreated patients who experienced early growth failure enrolled in the natural history study (LAL-1-NH01) survived beyond 12 months of age; symptom onset to death typically occurred over a period of only a few weeks, with a median age at symptom onset of 1.1 months and a median age at death of 3.0 months.[6, 14] LAL-CL08 also demonstrated patients receiving sebelipase alfa had normal psychomotor development, improved growth, haematological parameters,

and liver parameters, and the drug was generally well-tolerated, with an acceptable safety profile.[26, 27] Further evidence from the LAL-CL08 trial is provided in Section B.2.6.1 and Section B.2.10.1 of this submission.

Sebelipase alfa is also expected to have wider benefits. If treated with sebelipase alfa, it is more likely that affected infants will live to be able to attend school and may go on to lead normal and productive lives. The experience from patients treated for rapidly progressive LAL-D in the UK shows that infants, as treatment progresses, are able to grow, develop and lead a life similar to their healthy peers.

B.1.4. Equality considerations

Following the previous appraisal conducted by NICE for sebelipase alfa (ID737), the decision was made to focus this appraisal solely on the treatment of patients with rapidly progressive LAL-D, the most severe form of LAL-D that manifests in infants. This decision was justified based on the higher potential for accrual of health benefits over the patients' lifetimes, which results in better cost-effectiveness in this population. However, older children, adolescents and adults with LAL-D may be negatively impacted by not having access to treatment with sebelipase alfa, despite evidence of proven clinical efficacy in these groups. As age is a protected characteristic in UK law, it is possible that excluding patients with LAL-D from this appraisal on the basis of age could result in equality issues.

We have not identified any other foreseeable exclusions, limitations or adverse effects on protected individuals based on disability, gender reassignment, relationship status, pregnancy and maternity, race, religion or belief, sex and/or sexual orientation.

B.2. Clinical effectiveness

Summary of key points:

Study identification

- LAL-CL08 and LAL-CL03 are part of Alexion's clinical development programme for sebelipase alfa, which were conducted to evaluate the safety and efficacy of sebelipase alfa in patients with rapidly progressive LAL-D[27]
  - LAL-CL08 is a Phase 2, open-label, multicentre trial conducted to assess the efficacy of sebelipase alfa as a first-line therapy for patients with rapidly progressive LAL-D.[26, 27] Final results were reported in Vijay et al. 2021[27], when patients had a maximum follow-up of 3 years
  - LAL-CL03 is a supportive trial to further demonstrate the efficacy of sebelipase alfa as a therapy for rapidly progressive LAL-D, specifically in patients with early-onset growth failure[28, 29] Final results were reported in Vijay et al. 2021[27], when patients had a maximum follow-up of 5 years
- Comparative evidence is provided through the LAL-1-NH01 trial, a natural history study conducted to explore the clinical presentation and progression of LAL-D in patients diagnosed in the first 2 years of life who did not have access to sebelipase alfa[6, 14]
  - Patients who received a clinical diagnosis of rapidly progressive LAL-D from 1985 to 2012 were enrolled and followed up until death (maximum follow-up: 48 months of age). Although the protocol allowed for enrolment of living patients, all patients in the overall population were deceased at enrolment
- Further supportive evidence includes:
  - Potter et al. 2021, a case series of five patients with rapidly progressive LAL-D undergoing a multimodal treatment of sebelipase alfa followed by HSCT[2]
  - Cohen et al. 2019, a chart review of two patients with rapidly progressive LAL-D receiving treatment with sebelipase alfa that presents clinical outcomes and the importance of dietary interventions and systemic clinical care[30]
  - Demaret et al. 2021, a retrospective study of five patients with rapidly progressive LAL-D who received long-term treatment with sebelipase alfa in France[31]
  - Cossette et al. 2022, a case report of a Canadian patient diagnosed with rapidly progressive LAL-D at three months of age that takes into account clinical aspects and patient management, including a semi-structured interview with the main family caregiver[32]

- Real-world evidence is also provided through the GATM programme[12, 33] and the global LAL-D registry[34]

Efficacy

- Patients with rapidly progressive LAL-D who received treatment with sebelipase alfa demonstrated a clinically meaningful improvement in survival[27]
  - In LAL-CL08, the proportion of patients surviving to 12, 18, 24 and 36 months of age was 90%, 80%, 80% and 75%, respectively[27]
  - In LAL-CL03, six of the nine (67%) patients survived beyond 12 months of age, and five (56%) patients surviving beyond 18 months of age.[27] All five of these patients survived to the last available assessment at the 60-month follow-up
  - Comparatively, no (0%) untreated patients with early growth failure in the natural history study (LAL-1-NH01) survived beyond 12 months of age[6, 14]
  - High overall survival rates in sebelipase alfa treated patients were also demonstrated in a global LAL-D registry; the registry presents a median long-term follow-up of [redacted] years, with the oldest patient still alive at [redacted] years[34]
- Patients experienced improvements in weight gain following treatment with sebelipase alfa; median weight-for-age and length-for-age Z-scores and percentiles increased from baseline to end of trial in both LAL-CL08 and LAL-CL03.[27]
  - The median weight-for-age Z-score increased above the threshold for underweight at approximately Week 8 and Week 30 in LAL-CL08 and LAL-CL03, respectively, and remained above this threshold through to the last trial assessments[27]
  - Comparatively, the median weight-for-age percentiles in the natural history study (LAL-1-NH01) were low before diagnosis and worsened as the disease progressed[6, 14]
- Treatment with sebelipase alfa led to a reduction in liver injury, as demonstrated by improvements in serum AST and ALT levels in both LAL-CL08 and LAL-CL03[27]
  - Comparatively, untreated patients in the natural history study (LAL-1-NH01) experienced a substantial increase in median ALT and AST levels from baseline to last recorded follow-up (Week 32)[6, 14]

Safety

- Sebelipase alfa was generally well-tolerated and had an acceptable safety

profile in both LAL-CL08 and LAL-CL03[27]

- All (100%) patients in LAL-CL08 and LAL-CL03 experienced treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs); however, the majority of these adverse events (AEs) related to comorbidities and complications expected in patients with rapidly progressive LAL-D, with the exception of infusion-associated reactions (IARs)[14, 26, 27]

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant evidence of clinical effectiveness for patients with rapidly progressive LAL-D. Of the 561 potentially relevant records identified, eight unique trials were considered to be relevant to the decision problem. Full details of the process and methods used to identify and select relevant evidence are presented in Appendix D.1.

B.2.2. List of relevant clinical effectiveness evidence

Table 3 presents a summary of the evidence presented in this submission to support the use of sebelipase alfa in patients with rapidly progressive LAL-D.

The SLR identified two unique clinical trials: LAL-CL08 and LAL-CL03. These trials are part of the clinical development programme for sebelipase alfa which were conducted to evaluate the safety and efficacy of sebelipase alfa in patients with rapidly progressive LAL-D. The results of the LAL-CL08 and LAL-CL03 trials are presented side-by-side in the publication by Vijay et al. 2021.[27] As there is no comparator arm in the LAL-CL03 and LAL-CL08 trials, data from the natural history study (LAL-1-NH01) has been used to provide historical control data for this submission.[6, 14] LAL-1-NH01 was conducted prior to the availability of sebelipase alfa to characterize the clinical presentation and progression of LAL-D in patients diagnosed in the first 2 years of life. Data were collected through retrospective chart reviews. A summary of the LAL-1-NH01 trial methodology is presented in Appendix D.1.4.1.

In addition to LAL-CL08 and LAL-CL03, further supportive evidence is available through the following publications:

- Potter et al. 2021 – a case series of five patients with rapidly progressive LAL-D undergoing a multimodal treatment of sebelipase alfa followed by HSCT[2]
- Cohen et al. 2019 - a chart review of two patients with rapidly progressive LAL-D that highlights how weekly treatment with sebelipase alfa resulted in a marked improvement in clinical outcomes and the importance of dietary interventions and systemic clinical care.[30] A summary of results for this study are presented in Appendix L.5.
- Demaret et al. 2021 - a nationwide, retrospective study of five rapidly progressive LAL-D patients who received long-term treatment with sebelipase alfa in France.[31] A summary of results for this study are presented in Appendix L.6.

The SLR identified a further two studies; one presented evidence for treatment with HSCT in the absence of sebelipase alfa[35], and one reported on clinician experience of nutritional management in patients with rapidly progressive LAL-D[24]. These studies are not directly relevant to the decision problem and have therefore not been considered relevant for inclusion in this dossier.

Since the SLR was conducted, one further publication has been identified which presents a case report of a Canadian patient diagnosed with rapidly progressive LAL-D at three months of age.[32] This study takes into account clinical aspects and patient management, including a semi-structured interview with the main family caregiver. Further information on this study is presented in Appendix L.7.

Further supportive evidence has also been collated in the form of real-world evidence from the Alexion-supported GATM programme and the global LAL-D registry (ALX-LALD-501). The GATM programme presents clinician-supported narratives of patients with rapidly progressive LAL-D during treatment with sebelipase alfa.[33] As the GATM programme has no formal data collection requirements, the data collected provide limited evidence on the efficacy of sebelipase alfa. There is also a large patient overlap with the LAL-CL08 and LAL-CL03 trials, therefore, to avoid duplication of trial data, limited evidence from the GATM programme has been used to support the efficacy of sebelipase alfa in this submission (Section B.2.6.3.1).

The LAL-D registry (ALX-LALD-501), is an observational, multicentre, global registry designed to collect longitudinal data in patients with a confirmed diagnosis of LAL-

D.[36] The LAL-D registry collates efficacy and safety data for a broad patient population, including patients with rapidly progressive LAL-D. Similar to the GATM programme, the UK patient population of the LAL-D registry overlaps with that of the LAL-CL08 and LAL-CL03 trials; this therefore must be considered when assessing data from the registry.

Table 3: Summary of evidence used in the submission

Evidence	Source(s)	Primary clinical evidence	Supportive clinical evidence	Economic model base case	Justification for inclusion	Corresponding sections in the dossier
Published evidence on sebelipase alfa						
LAL-CL08	LAL-CL08 clinical study report[26] Jones et al. 2017 (Conference abstract) Vijay et al. 2021[27]	✓	×	✓	Most robust source of evidence to align with the decision problem	Methodology: Section B.2.3 Efficacy results: Section B.2.6.1 Adverse events: Section B.2.10.1
LAL-CL03	LAL-CL03 clinical study report[28] Jones et al. 2017[29] Vijay et al. 2021[27]	×	✓	✓	Further supportive evidence to align with the decision problem	Methodology: Section B.2.3 Efficacy results: Section B.2.6.1.6 Adverse events: Section B.2.10.2
Potter et al. 2021	Potter et al. 2021[2]	×	✓	×	Evidence to support the use of sebelipase alfa followed by HSCT	Methodology: Appendix L.4.1 Efficacy results: B.2.6.3.3
Cohen et al. 2019	Cohen et al. 2019[30]	×	✓	×	Chart review of two patients with rapidly progressive LAL-D to support the use of sebelipase alfa	Summary provided in Appendix L.5
Demaret et al. 2021	Demaret et al. 2021[31]	×	✓	×	A supportive retrospective review of five rapidly progressive LAL-D patients who received long-term treatment with sebelipase alfa in France	Summary provided in Appendix L.6
Cossette et	Cossette et al.	×	✓	×	A supportive case report of a female Canadian patient diagnosed with	Summary provided in

al. 2022	2022[32]				rapidly progressive LAL-D at three months of age	Appendix L.7
Real-world evidence for sebelipase alfa						
GATM programme	GATM summary[33]	×	✓	×	Real-world experience of patients currently treated with sebelipase alfa in the UK	Summary provided in Section B.2.6.3.1
ALX-LALD-501	Sixth progress report[36]	×	✓	×	Global registry of patients treated with sebelipase alfa	Methodology and efficacy results: Section B.2.6.3.2 Adverse events: B.2.10.3
Natural history study						
LAL-1-NH01	LAL-1-NH01 clinical study report[14] Jones et al. 2016[6]	×	✓	✓	Most robust source of evidence providing patient outcomes in the absence of sebelipase alfa	Methodology: Appendix D.1.4 Efficacy results: Section B.2.9

Key: GATM, Global Access to Medicines; LAL, lysosomal acid lipase.
Notes: The Vijay et al. 2021[27] publication presents a side-by-side analysis of the final results from LAL-CL08 and LAL-CL03.

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

B.2.3.1. Trial summaries and methods

Table 4 presents a summary of the LAL-CL08 and LAL-CL03 trials and the trial methodology.

Table 4: Summary of LAL-CL08 and LAL-CL03 trials and trial methodology

Trial name	LAL-CL08	LAL-CL03
Trial title	A Phase 2, Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Sebelipase Alfa in Infants with Rapidly Progressive Lysosomal Acid Lipase Deficiency	An Open-Label, Multicentre, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of SBC-102 in Lysosomal Acid Lipase Deficiency
Trial design	Open-label, multicentre, repeat-dose, Phase II trial	Open-label, repeat-dose, intra-subject dose escalation Phase II/III study
Location	Finland, Italy, the US, and the UK	UK, US, France, Italy, Egypt and Turkey
Population	• Infant patients with a confirmed diagnosis of LAL-D • Patients are < 8 months of age at the time of first dosing	• Patients presenting with LAL-D in infancy with evidence of rapidly progressive disease based on documented growth failure within the first 6 months of life.
Intervention(s)	Repeat IV infusions of sebelipase alfa. Dosing schedule as reported in Section B.2.3.1.1.	Repeat IV infusions of sebelipase alfa. Dosing schedule as reported in Section B.2.3.1.2.
Comparator(s)	N/A	N/A
Indicate if trial supports application for marketing authorization	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes
Rationale if trial not used in model	N/A	N/A
Reported outcomes specified in the decision problem	• **Survival** – Proportion of patients surviving at 12, 18, 24 and 36 months of age • **Body weight** and nutritional parameters (including growth) – Z-scores and percentiles for weight-for-age, length-for-age, weight-for-length, arm	• **Survival** – Proportion of patients surviving at 12, 18 24, 36, 48 and 60 months of age • **Body weight** and nutritional parameters (including growth) – Z-scores and percentiles for weight-for-age, length-for-age, weight-for-length, arm

Trial name	LAL-CL08	LAL-CL03
	circumference-for-age, head circumference-for-age, and BMI-for-age – Proportion of patients meeting the criteria for underweight, wasting and stunting • Liver parameters – Transaminase levels (i.e. ALT, AST) • Haematological parameters – Transfusion-free haemoglobin normalization • Effect on developmental milestones (Denver II) • **Adverse effects of treatment** • Anti-drug antibodies	circumference-for-age, head circumference-for-age and BMI-for-age – Proportion of patients meeting the criteria for underweight, wasting and stunting • Liver parameters – Transaminase levels (i.e. ALT, AST) • Haematological parameters – Transfusion-free haemoglobin normalization • Effect on developmental milestones (Denver II) • **Adverse effects of treatment** • Anti-drug antibodies
All other reported outcomes	N/A	N/A
Key eligibility criteria for patients	A patient was required to meet all of the following criteria to be eligible to participate in this trial: 1. Patient's parent or legal guardian (if applicable) consented to participation in the trial 2. Confirmation of documented decreased LAL activity relative to the normal range of the lab performing the assay, or a documented result of molecular genetic testing confirming a diagnosis of LAL-D 3. Substantial clinical concerns, in the opinion of Investigator and Sponsor, of rapid disease progression requiring urgent medical intervention that included, but were not restricted to, the following: a. Marked abdominal distension and	A patient was required to meet all of the following criteria to be eligible to participate in this trial: 1. Patient's parent or legal guardian understood the full nature and purpose of the trial, including possible risks and side effects, and provided written informed consent/permission prior to any trial procedures being performed 2. Male or female child with a documented decreased LAL activity relative to the normal range of the laboratory performing the assay, or a documented result of molecular genetic testing (2 mutations) confirming a diagnosis of LAL-D 3. Growth failure with onset before 6 months of age, as defined by: a. Weight decreasing across at least 2 of the 11 major centiles on a standard WHO

	hepatomegaly b. Failure to thrive as evidenced by: i. Weight for height is 2 or more SD below the mean for gender and age ii. Weight curve had crossed downward by more than 2 major percentile lines on the WHO growth curves (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th) after having previously achieved a stable pattern of growth c. Disturbance of coagulation (e.g. requirement for fresh frozen plasma; 2 values of prothrombin time > 15 sec, or partial thromboplastin time > 40 sec) d. Severe anaemia (e.g. requirement for blood transfusion or haemoglobin < 8 g/dL) e. Sibling with rapidly progressive course of LAL-D A patient who met any of the following criteria was ineligible to participate in the trial: 1. Clinically important concurrent disease or co-morbidities which, in the opinion of the Investigator and Sponsor, would interfere with trial participation, that included, but were not restricted to: a. Additional severe congenital abnormality b. Presence of severe infection that required treatment with parenteral anti-infective treatment in the past 14 days c. Previous history of circulatory collapse requiring inotropic support for more than 48	weight-for-age chart OR b. Body weight in kg below the 10th centile on a standard WHO weight-for-age chart AND no weight gain for the 2 weeks before screening OR c. Loss of 5% of birth weight in a child who is older than 2 weeks of age A patient who met any of the following criteria was ineligible to participate in the trial: 1. Clinically important concurrent disease or comorbidities which, in the opinion of the Investigator and Sponsor, would interfere with trial participation, including, but not restricted to: congestive heart failure; ongoing circulatory collapse requiring inotropic support; acute or chronic renal failure; additional severe congenital abnormality; or other extenuating circumstances such as life-threatening undernutrition or rapidly progressive liver disease 2. Patient was > 24 months of age. (Note: patients > 8 months of age on the date of first infusion were not eligible for the primary efficacy analysis) 3. Had received an investigational medicinal product other than sebelipase alfa in the 14 days preceding the first dose of sebelipase alfa in this trial 4. Myeloablative preparation, or other systemic pre-transplant conditioning, for haematopoietic stem cell or liver transplantation 5. Previous HSCT or liver transplant

Trial name	LAL-CL08	LAL-CL03
	hours d. Congestive heart failure e. Acute or chronic renal failure f. Other extenuating circumstances such as life-threatening under nutrition or rapidly progressive liver disease 2. Patient would be > 8 months of age at the time of first dosing 3. Patient had received an investigational medicinal product other than sebelipase alfa in the 14 days before the first dose of sebelipase alfa in this trial 4. Myeloablative preparation, or other systemic pre-transplant conditioning, for haematopoietic stem cell or liver transplantation 5. Previous HSCT or liver transplant 6. Known hypersensitivity to eggs	6. Known hypersensitivity to eggs
Settings and locations where the data were collected	Patients initially received infusions at a primary trial centre. Patients who were medically stable could transfer to a local medical centre for long-term treatment. Scheduled trial assessments could also be performed at a local medical centre with access to the appropriate facilities and expertise.	
Trial drugs	IV infusion of sebelipase alfa. Further information on dosage of sebelipase alfa is provided in Section B.2.3.1.1 (LAL-CL08) and Section B.2.3.1.2 (LAL-CL03).	
Permitted and disallowed concomitant medication	Premedication was not routinely administered before trial infusions but was recommended in patients who had experienced IARs during a previous infusion. Concomitant medications included prescription medications, over-the-counter medications, herbal products, preventative vaccines, vitamins and dietary supplements. Concomitant therapies included diagnostic, palliative or interventional procedures, e.g. parenteral feeds, surgery, or physical therapy.	
Primary efficacy endpoints	N/A	Proportion of patients surviving to 12 months of age

Trial name	LAL-CL08	LAL-CL03
Key secondary efficacy endpoints	• The proportion of patients surviving at 12, 18, 24, and 36 months of age • Median age at death • Changes from baseline in percentiles and Z-scores for weight-for-age, weight-for-length, length-for-age, head circumference-for-age, and arm circumference-for-age • Dichotomous growth status indicators of underweight, wasting and stunting • Changes from baseline in ALT, AST and serum ferritin levels • Normalization of haemoglobin levels without requirement for blood transfusion • Change from baseline in Denver II total and functional area scores	• Proportion of patients surviving at 18 and 24 months of age • Median age at death • Changes from baseline in percentiles and/or Z-scores for weight-for-age, weight-for-length/weight-for-height, length-for-age/height-for-age, head circumference-for-age and arm circumference-for-age • Dichotomous growth status indicators of underweight, wasting and stunting • Changes from baseline in ALT, AST and serum ferritin • Normalization of haemoglobin levels without requirement for blood transfusion
Exploratory efficacy endpoints	Changes and percentage changes from baseline in: • Liver and spleen volume as measured by ultrasound or MRI • Alkaline phosphatase • GGT • Albumin • Bilirubin (direct [conjugated], indirect [unconjugated], and total) • Platelet levels • Serum lipid levels (total cholesterol, triglycerides HDL-C, LDL-C)	• Changes and/or percent changes from baseline in: – Liver and spleen size/volume as measured by ultrasound or MRI – Alkaline phosphatase – GGT – Albumin – Bilirubin (direct [conjugated], indirect [unconjugated], and total) – Hepatomegaly and/or splenomegaly by physical examination – Platelet levels and serum lipid levels (total cholesterol, triglycerides, HDL-C, LDL-C)

Trial name	LAL-CL08	LAL-CL03
		• Dietary changes, including discontinuation of a low-fat/low-cholesterol diet and/or introduction of an unrestricted age-appropriate diet • Denver II developmental screening test: four functional area scores (fine motor-adaptive, gross motor, personal-social and language skills) • The impact of ADAs on efficacy endpoints
Safety endpoints	• Incidence of TEAEs, SAEs and IARs • Changes from baseline in clinical laboratory tests • Changes in vital signs during post-infusion, relative to pre-infusion values • Physical examination findings • Use of concomitant medications/therapies • Characterisation of ADAs, including ADA positivity rate, time to ADA positivity, median and peak ADA titre and time to peak ADA titre	• Incidence of TEAEs, including SAEs and IARs • Clinical laboratory results (chemistry, haematology, urinalysis, and ADAs) • Vital sign measurements • Physical examination findings • Use of concomitant medications/therapies
Pre-planned subgroups	Subgroup analyses were not planned or conducted.	

Key: ADA, anti-drug antibodies; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; HDL-C, high-density lipoprotein-C; IARs, infusion-associated reactions; IV, intravenous; LAL, lysosomal acid lipase; LAL-D, lysosomal acid lipase deficiency; LDL-C, low-density lipoprotein-C; MRI, magnetic resonance imaging; QOW, every other week; QW, once weekly; SAEs, serious adverse events; SD, standard deviation; TEAEs, treatment-emergent adverse events; WHO, World Health Organization.
Source: LAL-CL08 clinical study report[26]; LAL-CL03 clinical study report[28]; Vijay et al. 2021[27]

B.2.3.1.1. LAL-CL08

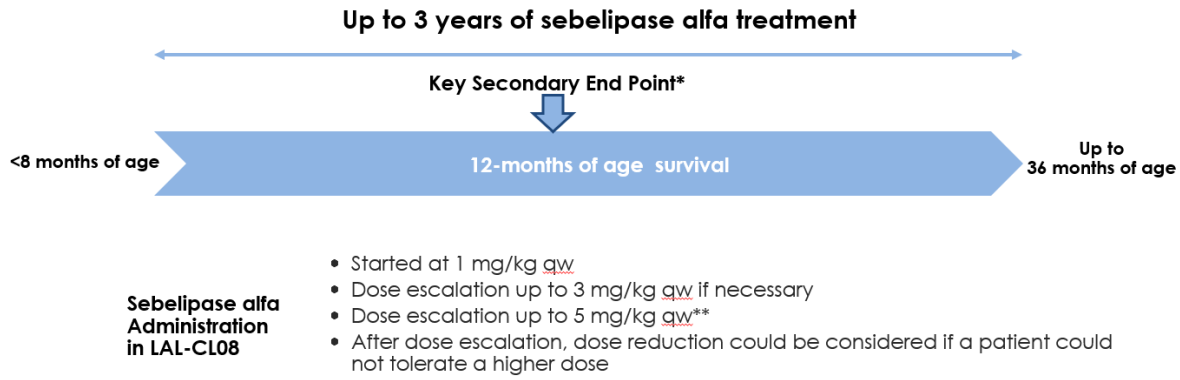
LAL-CL08 is a multicentre, open-label, single-arm Phase 2 trial to evaluate the safety and efficacy of sebelipase alfa in infants with rapidly progressive LAL-D (Wolman disease).[27] An open-label design was adopted as it would not have been ethical to include a control group in such a progressive and life-threatening disease.

LAL-CL08 provides information on 10 patients with rapidly progressive LAL-D. Each patient's treatment was expected to last for at least 18 months, and patients could continue to receive sebelipase alfa in the trial for up to 3 years.[26, 27] The overall duration of a patient's participation in the trial, inclusive of screening and follow-up, could therefore be up to 3 years and 7 weeks (156 weeks).

LAL-CL08 enrolled patients from June 2014 to May 2016 at five sites across four countries: the US, Finland, UK and Italy.[27] One patient who initiated treatment in the UK was subsequently transferred to a site in Italy to receive treatment.[27]

Figure 5 presents the LAL-CL08 trial design schematic.

Figure 5: LAL-CL08 trial design schematic



Key: qw, every week.
Notes: *, Safety was the primary endpoint in CL08.
Source: Vijay et al. 2021[27]; Sebelipase alfa SmPC.[1]

All patients in LAL-CL08 were initiated on once weekly (QW) IV infusions of sebelipase alfa at a dose of 1 mg/kg.[26, 27] Patients who met protocol-defined dose escalation criteria (Appendix L.1.1) could be considered for dose escalation to 3 mg/kg QW. Patients were considered for further dose escalation after four infusions

of 3 mg/kg QW if they continued to meet the dose escalation criteria. Further information regarding dosage of sebelipase alfa used in the registry is presented in Section B.2.10.3.1.

B.2.3.1.2. LAL-CL03

LAL-CL03 is a multicentre, open-label, single-arm, Phase 2/3 trial to evaluate the safety and efficacy of sebelipase alfa in patients with rapidly progressive LAL-D with early-onset growth failure (i.e. growth failure within the first 6 months of life).[27-29] Like LAL-CL08, an open-label design was adopted as it would not have been ethical to include a control group in such a progressive and life-threatening disease.

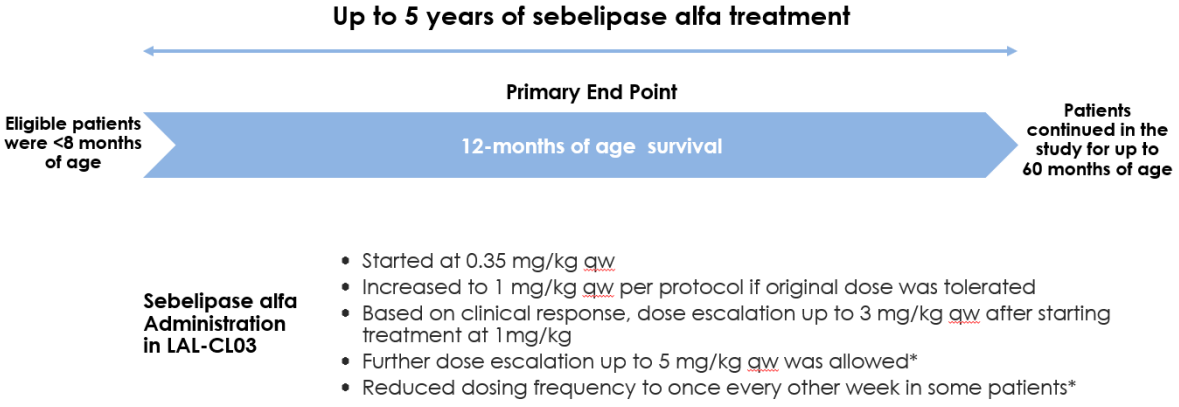
LAL-CL03 provides information on nine patients who are relevant to the decision problem, consisting of a screening period of up to 3 weeks, a treatment period of up to 5 years, and a follow-up visit of at least 30 days after the last dose of sebelipase alfa.[27]

LAL-CL03 was restricted to patients with rapidly progressive LAL-D with early-onset growth failure (i.e. growth failure within the first 6 months of life) as this has been shown to be a reliable predictor for the most rapidly progressive presentation of LAL-D, which allowed for differentiation by disease severity.[27]

Patients were treated at eight sites across six countries (UK, US, France, Ireland, Egypt and Turkey).[27]

Figure 6 presents the LAL-CL03 trial design schematic.

Figure 6: LAL-CL03 trial design schematic



Key: qw, every week.

Notes: *, Based on clinical response and investigator discretion in consultation with the sponsor.
Source: Vijay et al. 2021[27]; Sebelipase alfa SmPC.[1]

Patients initiating treatment with sebelipase alfa received a starting dose of 0.35 mg/kg and were considered for a dose escalation to 1 mg/kg after receiving at least two doses of sebelipase alfa.[27] Dose escalations to 3 mg/kg QW were permitted for patients who met the protocol-defined dose escalation criteria (Appendix L.1.2).[28] The protocol was amended to include an option for dose escalation to 5 mg/kg QW if a patient continued to have progressive disease in association with the presence of neutralizing antibodies, although the latter requirement was removed in a subsequent amendment to allow dose escalation to 5 mg/kg QW in the absence of neutralizing antibodies to optimize efficacy. Dose escalation to 5 mg/kg QW was permitted in patients who met the protocol-defined dose escalation criteria.[28]

B.2.3.2. Baseline demographics and disease characteristics

Table 5 presents the baseline demographics and disease characteristics for the LAL-CL08 and LAL-CL03 trials. Patient disposition data for LAL-CL08 and LAL-CL03 are presented in Appendix D.2.1 and Appendix D.2.2, respectively, alongside a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow for each trial.

Patients in the LAL-CL08 and LAL-CL03 trials were treated across eight different countries worldwide.[27] A large proportion of the enrolled patients were based in the UK and received treatment in UK hospitals (LAL-CL08: n = 8 [80%]; LAL- CL03: n = 3 [33%]).[27]

Table 5: Baseline demographics and disease characteristics

Characteristics	LAL-CL08 (N = 10)	LAL-CL03 (N = 9)
Age at first infusion of sebelipase alfa, months, median (range)[a]	2.8 (0.5, 4.1)	3.0 (1.1, 5.8)
Males, n (%)	5 (50)	5 (56)
Race[b]		
White, n (%)	1 (10)	4 (44)
Black, n (%)	0 (0)	1 (11)
Asian, n (%)	6 (60)	1 (11)
American Indian or Alaska native, n (%)	1 (10)	0 (0)
Other, n (%)	2 (20)	0 (0)

Characteristics	LAL-CL08 (N = 10)	LAL-CL03 (N = 9)
Birth weight, kg, median (range)	[redacted]	[redacted]
Weight-for-age percentile		
n	10	8
Mean (SD)	12.51 (25.27)	12.74 (26.23)
Median (range)	1.06 ([redacted])	3.08 ([redacted])
Patients classified as underweight, n/N (%)[c]	[redacted]	[redacted]
Length-for-age percentile		
n	9	8
Mean (SD)	22.20 (27.3)	20.30 (31.95)
Median (range)	2.87 ([redacted])	1.80 ([redacted])
Patients with stunting, n/N (%)[d]	[redacted]	[redacted]
Weight-for-length percentile		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Patients with wasting, n/N (%)[e]	[redacted]	[redacted]
Baseline liver dysfunction		
ALT, U/L, median (range)	37.0 (28, 248)	145.0 (16, 297)
AST, U/L, median (range)	99.5 (56, 441)	125.0 (71, 716)
GGT, U/L, median (range)	95.0 (42, 484)	46.5 (14, 1000)
Total bilirubin, µmol/L, median (range)	12.0 (4.0, 52.0)	29.0 (3, 464)
Albumin, g/L, median (range)	20.0 (18, 29)	29.0 (13, 40)
Baseline LLM use, n (%)[f]	1 (10)	3 (33)
Adrenal calcification at treatment initiation, n (%)	5 (50)	9 (100)

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; LLM, lipid-lowering medication; LAL, lysosomal acid lipase; SD, standard deviation.
Notes: Three patients initiated treatment with sebelipase alfa through the GATM programme and subsequently transitioned to treatment in the LAL-CL08 trial. Informed consent was obtained for each patient prior to their participation in both the compassionate-use programme and in LAL-CL08, and age at informed consent for LAL-CL08 was used for the data presented in this table.
[a], Calculated based on the age at informed consent for the LAL-CL08 trial.
[b], In LAL-CL03 race and ethnicity were not reported for three patients who were treated in France, in compliance with local regulation.
[c], Underweight is defined as a measurement at least 2 SD below the median for weight-for-age of a reference population.
[d], Stunting is defined as a measurement at least 2 SD below the median for length-for-age/height-for-age of a reference population.
[e], Wasting is defined as a measurement at least 2 SD below the median for weight-for-length/weight-for-height of a reference population.
[f], Two other patients received transient courses of treatment with lipid-modifying agents, either a 13-day course of atorvastatin for intestinal malabsorption or several brief courses of cholestyramine.
Source: LAL-CL08 clinical study report[26], LAL-CL03 clinical study report[28], LAL-CL03 tables and figures[37] and Vijay et al, 2021[27].

B.2.3.2.1. LAL-CL08

All 10 patients in LAL-CL08 had evidence of rapidly progressive LAL-D at the point of trial entry, as reported by the investigator and based on protocol-defined criteria that included marked abdominal distension, failure to thrive, disturbance of coagulation, severe anaemia and/or a sibling with rapidly progressive LAL-D.[26]

The weight-for-age percentile at baseline was low for most patients (median: 1.1%).[27] [redacted] ([redacted]%) patients were underweight, and [redacted] patients had a baseline weight-for-age percentile above the 10th percentile.[26] [redacted] patients were reported by the investigator to have evidence of failure to thrive (based on a decrease in weight-for-age across two major centile lines on the World Health Organization [WHO] growth curve), and a pronounced deceleration in weight between birth and the baseline assessment was observed for [redacted] patients in the trial. At baseline examination, [redacted] ([redacted]%) patients who underwent a liver assessment had a palpable liver.[26]

When assessing the patients' medical history, the most frequently reported findings included vomiting (n = [redacted], [redacted]%), anaemia (n = [redacted], [redacted]%), hepatomegaly (n = [redacted], [redacted]%), hepatosplenomegaly (n = [redacted], [redacted]%) and/or splenomegaly (n = [redacted], [redacted]%), failure to thrive (n = 5, 50%), and adrenal calcification (n = 5, 50%).[26, 27] [redacted] ([redacted]%) patients had a sibling or cousin with LAL-D.[26]

The mean duration between diagnosis with LAL-D and the first sebelipase infusion was [redacted] days (range: [redacted]–[redacted] days).[26] Concomitant medications were administered in all [redacted] ([redacted]%) patients and included analgesics, drugs for acid-related disorders, systemic anti-bacterials, and blood substitutes and perfusion solutions.[26]

B.2.3.2.2. LAL-CL03

A total of nine patients were enrolled in LAL-CL03. Age of symptom onset ranged from [redacted] months of age, and age at diagnosis ranged [redacted] months of age.[28]

All [redacted] ([redacted]%) patients had a medical history of GI conditions, with most patients (n = [redacted], [redacted]%) continuing to have one or more ongoing GI conditions at baseline.[28] GI conditions include abdominal distension, vomiting and diarrhoea. Other frequently reported ongoing medical findings include hepatobiliary disorders (n = [redacted], [redacted]%),

metabolism and nutrition disorders (n = [redacted], [redacted]%) and blood and lymphatic disorders (n = [redacted], [redacted]%). Frequently reported medical history findings include hepatomegaly (n = 9, 100%), splenomegaly (n = 9, 100%), adrenal calcification (n = 9, 100%), failure to thrive (n = 9, 100%) and anaemia (n = [redacted], [redacted]%).[28]

[redacted] ([redacted]%) patients were confirmed to have growth failure in the first 6 months of life, of which [redacted] ([redacted]%) had a demonstrated decrease in weight across at least 2 of the 11 major centiles from birth, and [redacted] had a birth weight that was already so low as to preclude a decrease of 2 major centiles.[28] [redacted] ([redacted]%) [redacted] who did not meet the criteria for confirmed growth failure in the first 6 months of life was enrolled based on evidence of rapidly progressive disease requiring urgent medical intervention.[28]

[redacted] ([redacted]%) patients with baseline weight data experienced growth deceleration between birth and at the point of baseline assessment.[28] [redacted] ([redacted]%) patients were deemed underweight, defined as 2 SDs below the median weight-for-age. The median weight-for-age percentile decreased from [redacted]% at birth to [redacted]% at baseline in approximately 6 months or less.[28]

The percentile scores for other anthropometric parameters were also low at baseline, with a median percentile of 1.80% for length-for-age, [redacted]% for head circumference-for-age and 0.01% for arm circumference-for-age.[28]

Marked abnormalities in liver biochemical parameters were observed at baseline, with AST levels elevated in [redacted] ([redacted]%) patients, and ALT levels elevated in [redacted] ([redacted]%) patients.[28]

Concomitant medications were administered in [redacted] ([redacted]%) patients, and included paracetamol (n = [redacted], [redacted]%) and amoxicillin (n = [redacted], [redacted]%).[28] All [redacted] ([redacted]%) patients were receiving nutritional supplements prior to treatment with sebelipase alfa, including specialised formula. All patients continued to receive nutritional supplements during the trial.[28] [27]

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

B.2.4.1. LAL-CL08

No formal sample size calculations were performed.[27] The planned enrolment of up to 10 patients was based on feasibility, considering the rarity of the disease. No formal inferential statistical testing was planned or performed.[26] All results from the LAL-CL08 trial were presented using by-patient listings, and selected data were presented using graphs and/or descriptive summaries.

Efficacy analyses included the proportion of patients surviving at 12, 18, 24 and 36 months, along with an exact 95% confidence interval (CI) based on the Clopper–Pearson method.[27] Kaplan–Meier estimates and exact 95% CIs for median survival and median time to short-term transfusion-free haemoglobin normalization (TFHN) were also determined.

Two analysis sets were defined for LAL-CL08[26]:

- Full analysis set (FAS, N = 10): this analysis set includes all patients who received any amount of sebelipase alfa
- Pharmacokinetic analysis set: this analysis set includes patients who received at least one complete infusion of sebelipase alfa. The pharmacokinetic analyses are not presented in this submission

B.2.4.2. LAL-CL03

The planned enrolment was approximately 10 patients, including eight patients who were ≤ 8 months of age at the time of their first sebelipase alfa infusion.[28] The remaining patients could be up to 24 months of age provided they fulfilled all the eligibility criteria. Supportive sample size calculations have demonstrated that, for the primary efficacy analysis, if six of the 10 planned patients survived to 12 months of age, the exact 95% CI for 12-month survival would be 34.91% to 96.81%.[28]

All results from the LAL-CL03 trial were presented using by-patient listings, and selected data were presented using graphs and/or descriptive summaries.[28] Unless otherwise noted, continuous parameters were presented as the number of patients with non-missing values (n), i.e. mean, SD, minimum, first quartile, median, third

quartile, and maximum; and categorical parameters were summarized as frequencies and/or using shift tables.[28]

Two analysis sets were defined for LAL-CL03:

- FAS: this analysis set includes all patients who received any amount of sebelipase alfa (N = 9)
- Primary efficacy set (PES): this analysis set included all patients in the FAS who were ≤ 8 months of age on the date of their first sebelipase alfa infusion (N = 9)

Efficacy was analysed for the PES. Efficacy analyses were not repeated for the FAS, as the FAS was identical to the PES (i.e. all patients in the FAS were ≤ 8 months of age on the date of their first infusion of sebelipase alfa).[28]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

LAL-CL08 and LAL-CL03 have been critically appraised using the standard Downs and Black checklist. A detailed table of results for this assessment are presented in Appendix D.3.

B.2.6. Clinical effectiveness results of the relevant studies

B.2.6.1. LAL-CL08

B.2.6.1.1. Survival

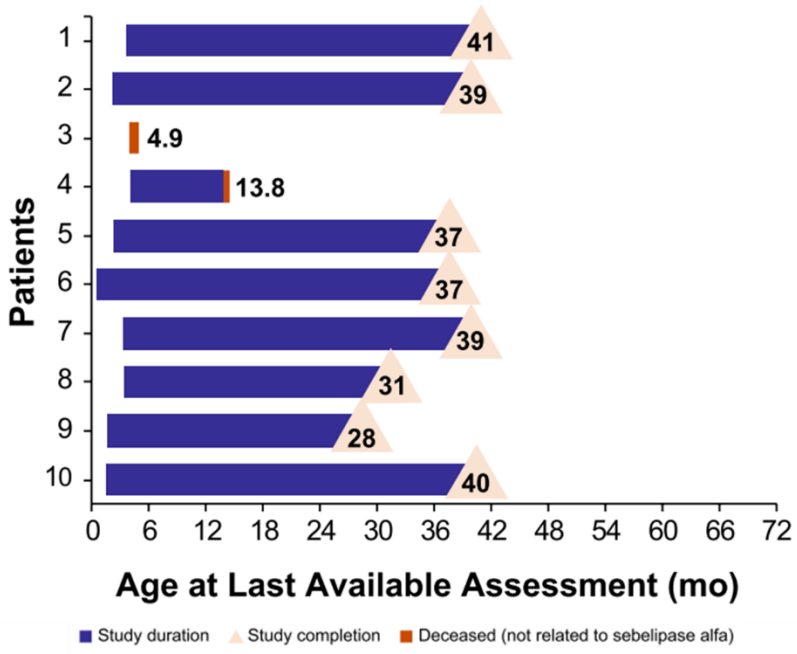
B.2.6.1.1.1. Proportion of patients surviving to 12, 18, 24 and 36 months of age

Figure 7 presents the patient survival over the 3-year follow-up period, and the age of each patient at their last available assessment. Please note that two patients were < 36 months of age at the time of study completion and were excluded from the analysis for survival to 36 months.

The proportion of patients surviving to 12, 18, 24 and 36 months of age was 90%, 80%, 80% and 75%, respectively.[27] At the last follow-up, the surviving eight patients were 27.8, 30.7, 36.8, 37.3, 39.1, 39.4, 40.1 and 40.6 months old.[26]

Two (20%) patients died during the trial; both deaths were related to complications of disease progression.[26] One patient received four infusions of sebelipase alfa at a dose of 1 mg/kg QW prior to death due to pericardial effusion at 4.9 months of age. The second patient received 41 infusions (1 to 5 mg/kg QW) prior to death at 13.8 months of age due to sepsis. The median age at death was [redacted] months.[26]

Figure 7: Patient survival and age at last available assessment



Key: mo, months.
Source: Vijay et al. 2021.[27]

Figure 8 presents the Kaplan–Meier plot of survival from birth, and Figure 9 presents the Kaplan–Meier plot of survival from the first dose of sebelipase alfa. Based on Kaplan–Meier curves, survival at 12 months of age was 90%.[26] The survival data from LAL-CL08 are consistent with those reported in LAL-CL03, in which the proportion of the nine patients surviving to 12 months of age was 67% (95% CI: 29.93%, 92.51%).[27] The slightly greater proportion of patients surviving to 12 months of age in LAL-CL08 (90%) versus LAL-CL03 (67%) could be attributed in part to the difference in patient populations, or to the higher starting dose used in the current study.[27]

Figure 8: Kaplan–Meier plot of survival from birth

Source: LAL-CL08 clinical study report[26]

Figure 9: Kaplan–Meier plot of survival from first dose of sebelipase alfa

Source: LAL-CL08 clinical study report[26]

B.2.6.1.2. Growth and nutritional parameters

Growth is profoundly impaired in patients with rapidly progressive LAL-D and is likely secondary to GI complications and malabsorption of nutrients from the diet. It is

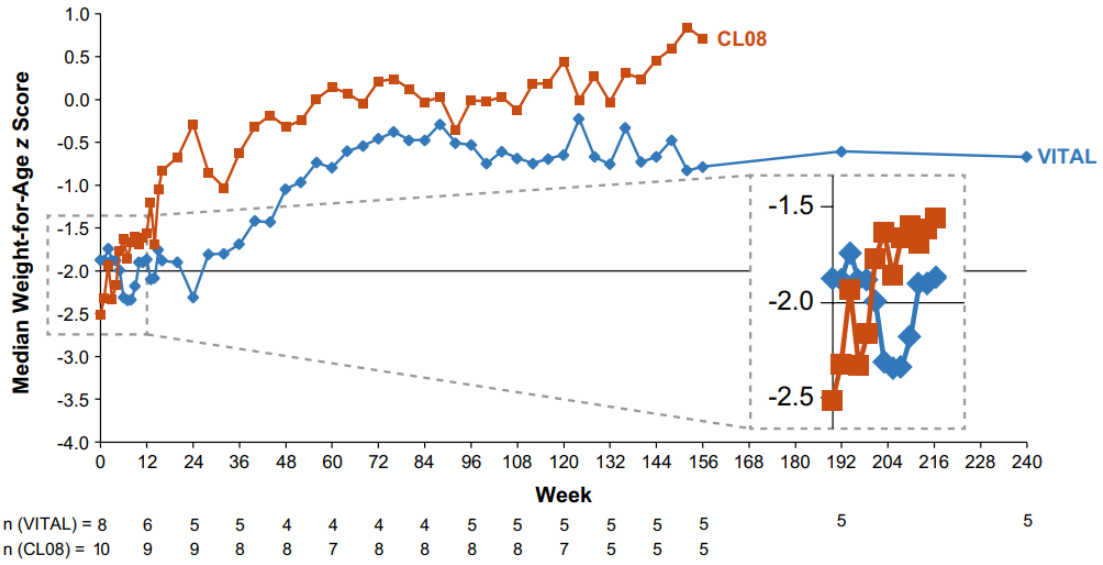
expected that patient that respond to treatment may show improvements in the growth parameters as a result of improvement of the GI complications of LAL-D. Therefore, assessments of weight and length/height were performed frequently. All growth parameters were standardised to age- and gender-norms based on WHO child growth charts (or CDC growth charts for patients > 2 years of age) to support an analysis of the attainment of developmentally appropriate growth.[26]

B.2.6.1.2.1. Changes from baseline for weight-for-age and length-for-age

When assessing weight-for-age by Z-scores and percentiles, key parameters of growth evaluation in infants, sebelipase alfa led to clinically meaningful improvements in weight gain that were sustained over time.[27]

Figure 10 presents the median weight-for-age Z-scores for LAL-CL08, alongside data collected in LAL-CL03 (labelled as VITAL), and a reference line at−2 standard deviations that indicates the threshold for underweight children, as established by the United Nations Children's Fund. In LAL-CL08, the median Z-score increased from −2.52 (range: −4.45, 0.84; n = 10) at baseline to 0.711 (range: −0.51, 1.08; n = 5) at week 156.[27] The median weight-for-age Z-score increased above the threshold for underweight at approximately Week 8, and remained above this threshold through to the last assessment at Week 156.[27] The observed weight-for-age and length-for-age by Z-score are presented in Appendix L.2.2.

Figure 10: Median weight-for-age Z-scores in LAL-CL08 and LAL-CL03 (VITAL)



Notes: Data reported weekly through week 16, then every 4 weeks through week 156 in both studies, then at Week 192 (Month 48) and Week 240 (Month 60) in LAL-CL03 (VITAL) only. The horizontal line indicates the threshold for underweight, as established by the United Nations Children's Fund.
Source: Vijay et al. 2021[27]

When assessing weight-for-age by percentile, sebelipase alfa treatment led to clinically meaningful improvements in growth from baseline through last assessment in [redacted] patients who had a low baseline weight-for-age percentile and survived beyond Week 4.[26]

The effect of treatment was apparent by Week 24 (Month 6), with a median change from baseline in weight-for-age percentile of [redacted] (range: [redacted]).[26] At Week 48 (Month 12), all patients with available data (n = [redacted]) had an increase in weight-for-age percentile, in which the median change from baseline was [redacted] (range: [redacted]). At the last available assessment for each patient, the median change from baseline in weight-for-age percentile was [redacted] (range: [redacted]).[26]

These improvements in growth with sebelipase alfa are also clinically meaningful when compared with the marked decrease in weight-for-age percentile observed for [redacted] patients between birth and the baseline assessment.[26]

Treatment with sebelipase alfa also resulted in an increase in length-for-age percentile. There was a notable improvement in length-for-age by Week 12, where the median increase in length-for-age percentile from baseline was [redacted] (range: [redacted], [redacted]).[26] At the last available assessment for each patient, the median change from baseline in length-for-age percentile was [redacted] (range: [redacted]).[26]

A table of the observed weight-for-age and length-for-age percentiles and change from baseline at Weeks 2, 4, 12, 24, 48, 96, 144 and at the patient's last assessment is presented in Appendix L.2.1.

Intermittent periods of slower growth were observed in some patients.[26] Dietary changes and comorbidities and complications of LAL-D (e.g. intercurrent infection, feeding difficulties related to the persistence of diarrhoea and/or vomiting, and alterations in fluid balance due to hypoalbuminemia) may also have been contributing factors. Three patients had periods of poor growth in association with high ADA titers.[26]

The change from baseline in percentiles for weight-for-length, head circumference-for-age and arm circumference-for-age have been presented in Appendix L.2.3. The results presented for these endpoints support the trends observed for weight-for-age.

B.2.6.1.2.2. Nutritional parameters

Table 6 presents the proportion of patients who met any of the three indicators of undernutrition at Weeks 2, 4, 24, 48, 96, 144 and at the patient's last assessment.

During the period where patients were treated with sebelipase alfa, there was a decrease in the proportion of patients who met the criteria for stunting, underweight or wasting.[26] By Week 48, [redacted] of the surviving patients (n = [redacted]) met the criteria for stunting, underweight or wasting; these improvements were maintained at most assessments through to the end of the trial.[26]

Of the [redacted] patients who died before Week 48 of treatment, there was an improvement in the indicators of undernutrition during the period they were treated with sebelipase alfa.[26]

Table 6: Summary of indicators of undernutrition (FAS)

	Patients defined as meeting the definition, n/N (%)		
	Stunting[a]	**Wasting[b]**	**Underweight[c]**
Baseline	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]
Week 4 (Month 1)	[redacted]	[redacted]	[redacted]
Week 12 (Month 3)	[redacted]	[redacted]	[redacted]
Week 24 (Month 6)	[redacted]	[redacted]	[redacted]
Week 48 (Month 12)	[redacted]	[redacted]	[redacted]
Week 60 (Month 15)	[redacted]	[redacted]	[redacted]
Week 96 (Month 24)	[redacted]	[redacted]	[redacted]
Week 144 (Month 36)	[redacted]	[redacted]	[redacted]
Week 156 (Month 39)	[redacted]	[redacted]	[redacted]
Last assessment	[redacted]	[redacted]	[redacted]

Key: FAS, full analysis set.
Notes: [a], Stunting is defined as at least 2 standard deviations below the median for length-for-age/height-for-age.
[b], Wasting is defined as wasting at least 2 standard deviations below the median for weight-for-length/weight-for-height.
[c], Underweight is defined as at least 2 standard deviations below the median for weight-for-age.
Source: LAL-CL08 clinical study report[26]

B.2.6.1.3. Liver parameters

Elevated transaminase levels (ALT and AST) are markers of liver cell injury and commonly noted among patients with rapidly progressive LAL-D.

B.2.6.1.3.1. Observed value and changes from baseline in ALT and AST

Treatment with sebelipase alfa leads to a reduction in liver injury, as demonstrated by improvements in serum transaminase levels, including normalization.[27] The effect was consistently maintained over long-term treatment.[27]

Table 7 presents the change from baseline in ALT and AST throughout the trial follow-up period.

Figure 11 presents a plot of ALT levels in individual patients over the trial period. A consistent treatment effect was not observed because median increases and decreases in ALT were observed over the trial period.[26] Among patients with abnormal baseline levels and follow-up data, normalization of AST was observed for [redacted]% of patients, and the patients in whom levels did not normalise, or only did so infrequently, often showed an improvement on treatment.[26] A total of three patients had elevated ALT levels at baseline; all three patients achieved normal ALT levels during their course of treatment.[26, 27] Six patients had normal baseline ALT levels, and [redacted] of these patients experienced an increase in ALT from baseline to their last assessment (Week 3).[26] The remaining [redacted] patients who survived to the end of the trial had fluctuating levels of ALT.

Figure 12 presents a plot of AST levels in individual patients over the trial period. During treatment with sebelipase alfa, patients experienced a decrease in median AST, which was apparent from Week 1 and sustained throughout the trial.[26] [redacted] patients had elevated AST levels at baseline, and [redacted] of these patients achieved normal AST levels during treatment with sebelipase alfa, although abnormalities continued to be reported. The remaining [redacted] patients had elevated AST levels throughout the trial, including [redacted] who died, [redacted] who had a rapid and marked decrease in AST following initiation of therapy but continued to have a high AST level at the last assessment, and [redacted] who had fluctuating levels through the treatment period.[26]

Of note, [redacted] patients had an overall treatment response in the liver from baseline through last assessment, but showed a more variable clinical course that included transient marked abnormalities in ALT and AST.[26] [redacted] patients developed high ADA titers during the trial that were associated with diminished clinical efficacy.[26]

Table 7: Observed values and change from baseline in ALT and AST levels (FAS)

	Observed value, U/L		Change from baseline, U/L	
	n	**Median (range)**	**n**	**Median (range)**
Alanine aminotransferase				
Baseline	9	37.0 (28, 248)	N/A	N/A
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4 (Month 1)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (Month 3)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 (Month 6)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]
Week 60 (Month 15)	[redacted]	[redacted]	[redacted]	[redacted]
Week 96 (Month 24)	[redacted]	[redacted]	[redacted]	[redacted]
Week 144 (Month 36)	[redacted]	[redacted]	[redacted]	[redacted]
Week 156 (Month 39)	5	29.0 (22, 106)	[redacted]	[redacted]
Last assessment	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase				
Baseline	8	99.5 (56, 441)	N/A	N/A
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4 (Month 1)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (Month 3)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 (Month 6)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]
Week 60 (Month 15)	[redacted]	[redacted]	[redacted]	[redacted]
Week 96 (Month 24)	[redacted]	[redacted]	[redacted]	[redacted]
Week 144 (Month 36)	[redacted]	[redacted]	[redacted]	[redacted]
Week 156 (Month 39)	5	44.0 (38, 110)	[redacted]	[redacted]
Last assessment	[redacted]	[redacted]	[redacted]	[redacted]

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FAS, full analysis set; N/A,

not applicable; U/L, units per litre.
Notes: Baseline is defined as the last available assessment prior to the start of the first infusion of sebelipase alfa.
Source: LAL-CL08 clinical study report[26] and Vijay et al. 2021[27]

Figure 11: Plot of ALT levels in individual patients over time (FAS)

Key: ALT, alanine aminotransferase.
Source: LAL-CL08 clinical study report[26]

Figure 12: Plot of AST levels in individual patients over time (FAS)

Key: AST, aspartate aminotransferase.
Source: LAL-CL08 clinical study report[26]

B.2.6.1.3.2. Liver and spleen volume

Treatment with sebelipase alfa was also associated with an improvement in liver and spleen volume on abdominal ultrasound, with decreases from baseline observed for [redacted]% patients and [redacted]% of patients with available valid data, respectively.[26] From baseline assessment to last assessment, the median spleen volume decreased from 5.8 MN (n = 8) to 4.0 MN (n = 2), and median liver volume decreased from 3.2 MN (n = 7) to 1.9 MN (n = 2).[27]

B.2.6.1.4. Haematological parameters

Haematological abnormalities such as anaemia are frequently observed in infants with LAL-D, and are likely multifactorial, resulting from a combination of malabsorption secondary to gastrointestinal complications, a disease-associated inflammatory environment secondary to macrophage activation syndrome, and hypersplenism due to splenomegaly that is commonly observed in these patients.[26]

Prior to approval of sebelipase alfa for the treatment of LAL-D, there were no effective therapies for this life-threatening disease, and the above-mentioned conditions were managed with supportive measures such as transfusions (often frequent) of whole blood, red blood cells, fresh frozen plasma and/or other components.[26]

B.2.6.1.4.1. Transfusion-free haemoglobin normalisation

The proportion of patients achieving TFHN of ≥ 4 weeks at any time during the trial (hereafter referred to as short-term TFHN) were summarised.[27] To achieve short-term THFN, patients were required to have haemoglobin levels that were consistently above the age-adjusted lower-limit of normal (LLN) over a minimum period of 4 weeks, with no transfusions during this period or for 2 weeks prior to the first haemoglobin measurements in the period.[27] The proportion of patients achieving TFHN maintenance (also referred to as sustained early TFHN) was also summarised, which was defined as patients who were transfusion-free at Week 6 and had no haemoglobin levels below the age-adjusted LLN beginning at Week 8 and continuing for at least 13 weeks.[26]

Sebelipase alfa reduces the need for invasive therapies such as blood transfusions. In total, seven (70%) patients achieved short-term TFHN.[27] [redacted] of the [redacted] patients died after the Week 3 infusion and was not evaluable for TFHN. [27]

Based on Kaplan–Meier estimates, the median time to achieve TFHN was 5.5 months (95% CI: 3.7, 19.6 months).[26, 27]

[redacted] patients who underwent HSCT at [redacted] would have required haemoglobin transfusions for iatrogenic reasons during their transplant; [redacted] of these [redacted] patients achieved TFHN.[26]

Most of the seven patients maintained TFHN for at least 13 weeks.[27] Although the need for transfusion was reduced, no patient met the formal criterion for TFHN maintenance because TFHN was not attained until after Week 8.[26]

B.2.6.1.5. Neurological development parameters

In order to better understand the development of surviving infants with LAL-D treated with sebelipase alfa, LAL-CL08 evaluated developmental milestones using the Denver II, which was designed to compare a given child's performance on various age-appropriate tasks with the performance of other children of the same age.[26] This assessment provides an organised clinical impression of a child's overall development and while it is not predictor of later development, it may alert to potential developmental difficulties.

Denver II was administered for [redacted] ([redacted]%) patients who were at least 1 month of age at the date of the assessment and were deemed sufficiently responsive to be tested for each skill area.[26]

[redacted] patients tested as normal in all four skill areas at baseline, and thereafter alternated between testing normal or suspect in all four skill areas.[26]

[redacted] patients tested as suspect in all four skill areas at baseline, and [redacted] of these patients continued to test as suspect in all four skill areas at all or most assessments during treatment.[26] The [redacted] showed an apparent sustained improvement, testing normal in all four skill areas beginning at Week 48 and continuing through the last on-treatment assessment at Week 120.

[redacted] was reported as untestable at baseline, and [redacted] died before the next scheduled Denver II assessment.[26]

Due to the limited data available, it was not possible to draw any firm conclusions about developmental milestones in patients treated with sebelipase alfa.[26]

B.2.6.1.6. Serum lipids

The majority of patients with LAL-D present with elevated total cholesterol and LDL-C and reduced HDL-C levels.[4] The effect of sebelipase alfa on serum lipid levels (i.e. LDL-C and HDL-C and triglycerides) in LAL-CL08 is presented in Appendix L.2.4.

B.2.6.2. LAL-CL03

B.2.6.2.1. Survival

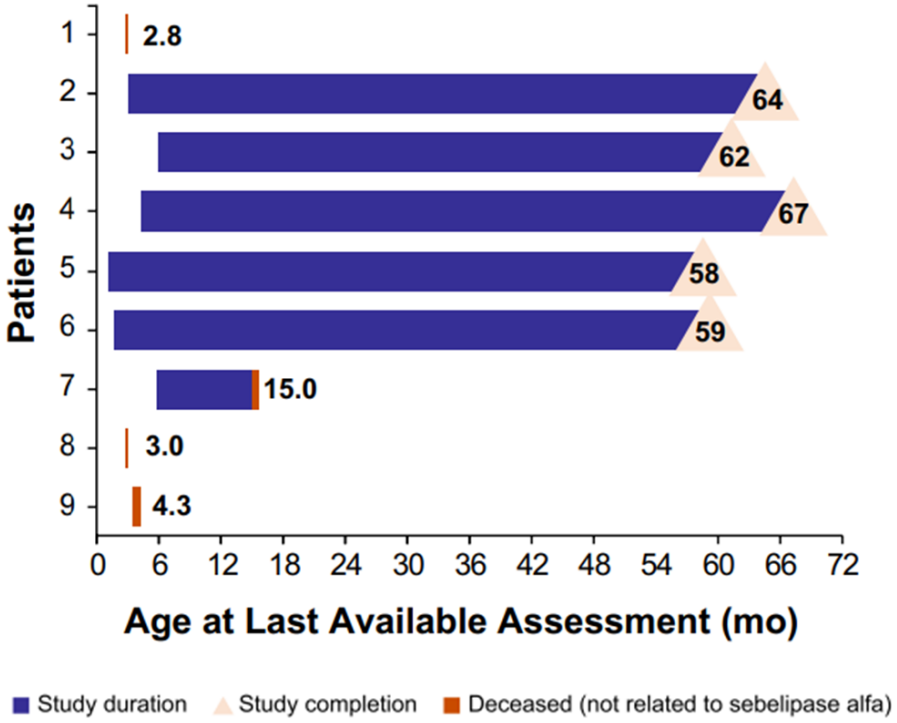
The primary objective of the study was to evaluate the effect of sebelipase alfa therapy on survival at 12 months of age in patients with growth failure due to LAL-D.[27] Survival beyond 12 months was also evaluated as part of the secondary endpoints of the study.

B.2.6.2.1.1. Proportion of patients surviving to 12, 18, 24, 36, 48 and 60 months of age

Figure 13 presents the patient survival over the 5-year follow-up period, and the age of each patient at their last available assessment.

Treatment with sebelipase alfa provides a clinically meaningful improvement in survival in patients with rapidly progressive LAL-D. Six of the nine (67%) patients survived beyond 12 months of age, and five (56%) patients survived beyond 18 months of age.[27] All five of these patients survived to the last available assessment at the 60-month follow-up. The five patients alive at the end of the trial were 67.0, 63.7, 62.4, 58.5 and 58.1 months of age at their last assessment.[27] The remaining four patients died at 15.0, 4.3, 3.0 and 2.8 months of age; median age at death in these 4 patients was [redacted] months.[28] Cause of death was hepatic failure, sudden cardiac death, peritoneal haemorrhage, or cardiac arrest and was assessed as unrelated or unlikely related to study drug.[27]

Figure 13: Patient survival and age at last available assessment



Key: mo, months
Source: Vijay et al. 2021.[27]

Figure 14 presents the Kaplan–Meier plot of survival from birth, and Figure 15 presents the Kaplan–Meier plot of survival from the first dose of sebelipase alfa for the PES. Based on Kaplan–Meier curves, survival at 12 months of age was 67%.[28].

These survival results demonstrate the clinical benefit of treatment with sebelipase alfa in a group of patients with a life-threatening condition where historical attempts at treatment, as seen in the natural history study LAL-1-NH01 (presented in section B.2.9) have met with very limited success, as evident by the paucity of long-term survivors.[6, 27]

The slightly higher survival rates observed in LAL-CL08 may be related to an evolution in the understanding of disease management, leading to better nutritional management and earlier initiation, using a higher starting dose, and faster dose escalation of sebelipase alfa compared to LAL-CL03.

Figure 14: Kaplan–Meier plot of survival from birth (PES)

Key: PES, primary efficacy set.
Source: LAL-CL03 clinical study report[28]

Figure 15: Kaplan–Meier plot of survival from first dose of sebelipase alfa (PES)

Key: PES, primary efficacy set.
Source: LAL-CL03 clinical study report[28]

B.2.6.2.2. Growth and nutritional parameters

B.2.6.2.2.1. Observed values and change from baseline in weight-for-age and length-for-age

When assessing weight-for-age by Z-scores and percentiles, sebelipase alfa led to clinically meaningful improvements in weight gain that were sustained over time.[27]

Figure 10 presents the median weight-for-age Z-scores for LAL-CL03 (labelled as VITAL), alongside data collected in LAL-CL08 and a reference line at−2 standard deviations that indicates the threshold for underweight children, as established by the United Nations Children's Fund. The median Z-score increased from −1.88 (−4.79 to 0.74; n = 8) at baseline to −0.67 (−1.41 to 1.87; n = 5) at Week 240 (Month 60; last visit with data available for > 4 patients).[27] The observed weight-for-age and length-for-age by Z-score are presented in Appendix L.3.2.

Growth deceleration from birth was observed for all [redacted] ([redacted]%) patients with available weight data, with a decrease in median weight-for-age percentile from [redacted]% at birth to [redacted]% at the baseline assessment approximately 1 to 6 months later.[28]

When assessing weight-for-age by percentile, sebelipase alfa treatment led to clinically meaningful improvements in growth from baseline through to last assessment in [redacted] patients of the PES that survived to 12 months of age.[28] The effect of treatment was apparent by Week 60 (Month 15), with a median change from baseline in weight-for-age percentile of [redacted] (range: [redacted], [redacted]), and remained relatively stable through to the end of the trial.[28] At the last available assessment for each patient, the median change from baseline in weight-for-age percentile was [redacted] (range: [redacted], [redacted]).[28]

Results for the observed length-for-age percentile were generally consistent with those seen for weight-for-age. The median change from baseline in length-for-age percentile was [redacted] (range: [redacted], [redacted]) at Week 60 (Month 15), and remained relatively stable through to Week 240 ([redacted]; range:[redacted], [redacted]; n = [redacted]), which was the last assessment.[28]

A table of the observed weight-for-age and length-for-age percentiles and change from baseline at selected timepoints is presented in Appendix L.3.1.

While intermittent periods of slower growth were observed for [redacted] patients, this typically occurred in association with comorbidities and complications such as intercurrent infection, IARs, and feeding difficulties related to the persistence of diarrhea and/or vomiting.[28] Dietary changes involving total parenteral nutrition, enteral supplements and/or introduction of oral fat-restricted diets were also a

contributing factor. Alterations in fluid balance due to hypoalbuminemia and other factors may be a confounding factor in the assessment of weight for some patients. For example, [redacted] who presented with ascites from baseline showed a further decrease in weight-for-age during the initial weeks of treatment, which may potentially have been related to the improvement in ascites and discontinuation of diuretic at Week 7.[28]

The change from baseline in arm circumference-for-age, head circumference-for-age, BMI-for-age and weight-for-length are presented in Appendix L.3.3.

B.2.6.2.2.2. Nutritional parameters

Table 8 presents the proportion of patients who met any of the three indicators of undernutrition at selected timepoints.

During the period where patients were treated with sebelipase alfa, there was a decrease in the proportion of patients who met the criteria for stunting, underweight or wasting.[28] By Week 144, [redacted] ([redacted]%) of [redacted] patients evaluated met the criteria for stunting, underweight or wasting.[28] These improvements were maintained during continued treatment with sebelipase alfa.

Table 8: Summary of anthropometric indicators of undernutrition (PES)

	Patients defined as meeting the definition, n/N (%)			
	Stunting[a]	**Wasting[b]**	**Underweight[c]**	**No stunting, wasting or underweight[d]**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4 (Month 1)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (Month 3)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 (Month 6)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]
Week 60 (Month 15)	[redacted]	[redacted]	[redacted]	[redacted]
Week 96 (Month 24)	[redacted]	[redacted]	[redacted]	[redacted]
Week 144 (Month 36)	[redacted]	[redacted]	[redacted]	[redacted]
Week 192 (Month 48)	[redacted]	[redacted]	[redacted]	[redacted]

Week 240 (Month 60)	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up/early withdrawal	[redacted]	[redacted]	[redacted]	[redacted]

Key: PES, primary efficacy set.
Notes: [a], Stunting is defined as at least 2 standard deviations below the median for length-for-age/height-for-age.
[b], Wasting is defined as wasting at least 2 standard deviations below the median for weight-for-length/weight-for-height.
[c], Underweight is defined as at least 2 standard deviations below the median for weight-for-age.
[d], Patients who did not meet any of the above criteria. Percentages are calculated based on the number of patients with available data for each parameter (length-for-age/height-for-age, weight-for-length/weight-for-height, and weight-for-age) at the given timepoint.
Source: LAL-CL03 clinical study report.[28]

B.2.6.2.3. Liver parameters

B.2.6.2.3.1. Changes from baseline in ALT and AST levels

Treatment with sebelipase alfa leads to a reduction in liver injury, as demonstrated by reductions in serum transaminase levels ALT and AST over long-term follow-up.[27] The temporal course of the reductions in serum transaminases was rapid, with evidence of improvement by Week 1, at low doses (≤ 0.35 mg/kg), and further decreases by Week 4 (1 mg/kg), with levels remaining fairly stable thereafter.[28]

Table 9 presents the change from baseline in ALT and AST throughout the trial follow-up period, and Figure 16 and Figure 17 present plots of ALT and AST levels, respectively, for each individual patient during the trial.

ALT levels decreased rapidly following initiation of treatment with sebelipase alfa.[28] The median reduction from baseline in ALT was evident from Week 1 [redacted] U/L), in which all patients were receiving a dose of ≤ 0.35 mg/kg.[28] At Week 4, when most patients were escalated to a dose of 1 mg/kg QW, the median reduction in ALT from baseline was [redacted] U/L. Median percentage changes from baseline at Week 1 and Week 4 were [redacted] % and [redacted] %, respectively.[28] ALT levels remained relatively stable from Week 4 through to Week 240, indicating rapid (Week 4) and sustained (through to Week 240) reduction with sebelipase alfa treatment. Normalisation of ALT levels was achieved in [redacted] patients with elevated baseline ALT, with normal levels achieved in these patients between Week 1 and Week 6.[28]

When assessing AST levels, patients experienced a rapid decrease following initiation of treatment with sebelipase alfa.[28] Like ALT levels, AST reductions were apparent from Week 1, with a median reduction from baseline of [redacted] U/L. At Week

4, when most patients were escalated to a dose of 1 mg/kg QW, the median reduction in AST from baseline was [redacted] U/L.[28] AST levels remained relatively stable from Week 4 through to Week 240, the last assessment for which data were available for more than one patient, with a few patients having fluctuations in AST over time as described below. These results indicate rapid (Week 4) and sustained (through to Week 240) reduction with sebelipase alfa treatment.[28] Normalisation of AST levels was achieved for [redacted] of the [redacted] patients with elevated AST levels at baseline.[28]

Of note, [redacted] patients had transient elevations in serum transaminases that were temporally associated with a switch from a QW to QOW dosing regimen or were noted in association with a viral infection, or a study ultrasound that was positive for gallstones.[28]

Table 9: Observed values and change from baseline in ALT and AST levels (PES)

	Observed value, U/L		Change from baseline, U/L	
	n	Median (range)	n	Median (range)
Alanine aminotransferase				
Baseline	9	145.0 (16.0, 297.0)	NA	NA
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4 (Month 1)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (Month 3)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 (Month 6)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]
Week 60 (Month 15)	[redacted]	[redacted]	[redacted]	[redacted]
Week 96 (Month 24)	[redacted]	[redacted]	[redacted]	[redacted]
Week 144 (Month 36)	[redacted]	[redacted]	[redacted]	[redacted]
Week 192 (Month 48)	[redacted]	[redacted]	[redacted]	[redacted]
Week 240 (Month 60)	4	26.5 (18.0, 38.0)	[redacted]	[redacted]
Follow-up/early withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase				
Baseline	9	125.0 (71.0, 716.0)	NA	NA
Week 2	[redacted]	[redacted]	[redacted]	[redacted]

	Observed value, U/L		Change from baseline, U/L	
	n	Median (range)	n	Median (range)
Week 4 (Month 1)	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (Month 3)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 (Month 6)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 (Month 12)	[redacted]	[redacted]	[redacted]	[redacted]
Week 60 (Month 15)	[redacted]	[redacted]	[redacted]	[redacted]
Week 96 (Month 24)	[redacted]	[redacted]	[redacted]	[redacted]
Week 144 (Month 36)	[redacted]	[redacted]	[redacted]	[redacted]
Week 192 (Month 48)	[redacted]	[redacted]	[redacted]	[redacted]
Week 240 (Month 60)	4	44.5 (41.0, 54.0)	[redacted]	[redacted]
Follow-up/early withdrawal	[redacted]	[redacted]	[redacted]	[redacted]

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PES, primary efficacy set.
Notes: Baseline is defined as the last available assessment before the first infusion of sebelipase alfa.
Source: LAL-CL03 clinical study report[28] and Vijay et al. 2021.[27]

Figure 16: Plot of ALT levels in individual patients over time (PES)

[redacted]

Key: ALT, alanine aminotransferase; PES, primary efficacy set.
Source: LAL-CL03 clinical study report.[28]

Figure 17: Plot of AST levels in individual patients over time (PES)

Key: AST, aspartate aminotransferase; PES, primary efficacy set.
Source: LAL-CL03 clinical study report.[28]

B.2.6.2.3.2. Liver and spleen volume

Treatment with sebelipase alfa was associated with an improvement in liver and spleen volume on abdominal ultrasound in the subset of patients with available valid data.[28] From baseline assessment to last assessment, median spleen volume decreased from 7.0 MN (n = 2) to 2.6 MN (n = 3), and median liver volume decreased from 3.4 MN (n = 3) to 1.6 MN (n = 3).[27]

B.2.6.2.4. Haematological parameters

B.2.6.2.4.1. Transfusion-free haemoglobin normalization

The proportion of patients achieving short-term TFHN and maintenance TFHN were summarised, as defined in Section B.2.6.1.4.1.

Sebelipase alfa reduces the need for invasive therapies such as blood transfusions, as demonstrated through the high rate of TFHN. In total, six patients achieved short-term TFHN, defined as haemoglobin levels that were consistently above the age-adjusted LLN over a minimum period of 4 weeks, with no transfusions during this period or for 2 weeks before the first haemoglobin measurement in the period.[27, 28] These six patients represented 66.7% of the nine patients in the PES, and 100% of

patients in the PES who received sebelipase alfa treatment for at least 4 weeks, and who could therefore be assessed for short-term TFHN.[27, 28]

Based on Kaplan–Meier estimates, the median time to achieve TFHN was 4 months (95% CI: 0.3, 16.6 months).[27, 28]

Two patients achieved TFHN maintenance, which was defined as patients who were transfusion-free at Week 6 and had no haemoglobin levels below the age-adjusted LLN beginning at Week 8 and continuing for at least 13 weeks.[27, 28] These two patients represented 22.2% of the nine patients in the PES, and 33.3% of patients in the PES who received sebelipase alfa treatment for at least 21 weeks, and who could therefore be assessed for maintenance TFHN.[27, 28]

B.2.6.2.5. Neurological parameters

Denver II**,** a measure of developmental problems in young children, was administered for patients who were at least 1 month of age at the date of the assessment and who were deemed sufficiently responsive to be tested for each skill area.[28] Overall, development milestones were primarily normal for those infants who were on treatment with sebelipase alfa for 24 weeks or longer.[28] None of the surviving patients were untestable on a post-dose assessment, and no patient treated for at least 24 weeks tested as “abnormal” in any skill area at any time point.[27]

[redacted] patients were administered the Denver II tests at screening[28]:

- [redacted] tested normal for language and fine motor-adaptive skills but was untestable for gross motor function and personal-social skills. Post-dose data were not available because [redacted] died
- [redacted] tested normal in all four skill areas, and continued to test normal in the vast majority of assessments through to Week 216
- [redacted] tested as suspect in all four skill areas and continued to test as suspect through to their last assessment at Week 24

[redacted] patients were administered the Denver II tests at post-baseline assessments only[28]:

- [redacted] tested normal in all four skill areas at their first assessment, and continued to test normal in most assessments through to Week 216

- [redacted] tested normal in all four skill areas at their first assessment at Week 40 through to Week 216, with the exception of Weeks 51 through 120 where [redacted] tested as suspect for gross motor function, and in Week 168 where [redacted] tested as suspect for gross motor function and personal-social skills
- [redacted] tested normal in all four skill areas at their first assessment (Week 24) through to their last assessment (Week 72), with the exception of the first assessment where they tested as suspect for gross motor function

[redacted] been attending school without any reported difficulties compared with his peers.[28]

B.2.6.2.6. Serum lipids

The effect of sebelipase alfa on serum lipid levels (i.e. LDL-C and HDL-C and triglycerides) in LAL-CL03 is presented in Appendix L.3.4.

B.2.6.3. Real-world evidence

B.2.6.3.1. Global Access to Medicines programme

As previously mentioned, Alexion has been providing access to sebelipase alfa via the GATM programme for patients with rapidly progressive LAL-D who were either previously enrolled in a clinical trial or have been born with rapidly progressive LAL-D since the EU approval of sebelipase alfa in 2015.[12] As there was no formal data collection requirements for the GATM, all information, with the exception of the number of patients enrolled, is commentary provided by clinicians.

Since [redacted], [redacted] with rapidly progressive LAL-D have participated in the GATM programme across seven different hospitals in the UK.[33] [redacted]

[redacted].[33]

[redacted]

[redacted]

B.2.6.3.2. ALX-LALD-501

Alexion has also funded a global registry of patients diagnosed with LAL-D. This registry includes UK patients with rapidly progressive LAL-D that were treated via the GATM programme, as well as patients from France, Israel, Italy, Japan, Netherlands, Saudi Arabia, Spain and the US.[36] Patients of any sex and age, living or deceased, with a diagnosis of LAL-D, irrespective of treatment status or treatment choice, are eligible for registry participation.[36] As well as providing information on the long-term effectiveness and safety of sebelipase alfa, this registry aims to provide further understand the disease, its progression and any associated complications.[36]

The registry plans to collect data until June 2026, with the final registry results anticipated to be reported in January 2027.[36] The global registry evaluates the long-term effectiveness and safety of sebelipase alfa. Unlike the GATM, this registry collates data through a formal data collection process to provide evidence on a large range of outcomes. The UK patient population enrolled in the LAL-D registry largely overlaps with that of the GATM programme and the LAL-CL08 and LAL-CL03 trials. In some cases, longer patient follow-up is available; patients previously enrolled in LAL-CL08 and LAL-CL03 trials may continue to be monitored within the registry.

An August 2020 data-cut from the registry has provided data for [redacted] patients with rapidly progressive LAL-D who initiated treatment with sebelipase alfa prior to 2 years of age, as to align with the decision problem presented in this submission.[34] [redacted] died prior to enrolment, and [redacted] was enrolled with unconfirmed LAL-D but went on to receive treatment when LAL-D was subsequently confirmed.

Two analysis sets were formed from the registry:[34]

- Safety population (N = [redacted]) – all patients enrolled in the registry who initiated treatment with sebelipase alfa prior to 2 years of age
- Study population (N = [redacted]) – all patients with confirmed rapidly progressive LAL-D who were alive at enrolment with valid enrolment date, date of birth, sex, known sebelipase alfa status and start date if ever treated

Of the [redacted] patients forming the study population, [redacted] were based in the UK. Following enrolment in the registry, patients in the overall population were followed up for a median of [redacted] ([redacted]) years.[34] UK patients had a slightly longer follow-up after enrolment of [redacted] ([redacted]) years.[34]

The survival data presented for the registry in Section B.2.6.3.2.2 utilises the safety population, and therefore includes mortality data for all patients enrolled in the registry with rapidly progressive LAL-D. All other efficacy data are reported using the study population. AE data and sebelipase alfa exposure data focuses on the safety population.

B.2.6.3.2.1. Baseline characteristics

Table 10 presents the baseline demographics and disease characteristics of patients enrolled in the registry.

Although all patients reported below initiated treatment with sebelipase alfa prior to 2 years of age, approximately half of the patients at the time of enrolment in the registry were between 2 and 5 years of age (n = [redacted], [redacted]%).[34] This is because patients may have participated in clinical trials prior to registry enrolment. The median age at the last follow-up was [redacted] ([redacted]) years in the overall population and [redacted] ([redacted]) in the UK population.[34]

Baseline characteristics were consistent between UK and non-UK patients.[34] These patients were also relatively consistent with those presented in Table 5 for LAL-CL08 and LAL-CL03. Compared to the trials, the registry included a slightly [redacted] proportion of males in the overall population, and patients presented with a [redacted] median weight-for-age in the UK population.

Table 10: Baseline demographics and disease characteristics of the ALX-LALD-501 registry (study population)

Characteristics	UK patients (n = [redacted])	Non-UK patients (n = [redacted])	All patients (N = [redacted])
Age at registry enrolment, years, median (range)	[redacted]	[redacted]	[redacted]
Age at diagnosis, years, median (range)	[redacted]	[redacted]	[redacted]
Age at symptom onset, years, median (range)	[redacted]	[redacted]	[redacted]

Patient demographics			
Male, n (%)	[redacted]	[redacted]	[redacted]
Race, n (%)			
American Indian or Alaskan Native	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African-American	[redacted]	[redacted]	[redacted]
White/Caucasian	[redacted]	[redacted]	[redacted]
Other/Multiple	[redacted]	[redacted]	[redacted]
Unknown or Missing	[redacted]	[redacted]	[redacted]
Manifestations that raised suspicion of LAL Deficiency, n (%)			
Hepatomegaly	[redacted]	[redacted]	[redacted]
Splenomegaly	[redacted]	[redacted]	[redacted]
Elevated AST	[redacted]	[redacted]	[redacted]
Elevated ALT	[redacted]	[redacted]	[redacted]
Adrenal calcification	[redacted]	[redacted]	[redacted]
Growth failure	[redacted]	[redacted]	[redacted]
Family history	[redacted]	[redacted]	[redacted]
Baseline liver dysfunction			
ALT, U/L, median (range)	[redacted]	[redacted]	[redacted]
AST, U/L, median (range)	[redacted]	[redacted]	[redacted]
GGT, U/L, median (range)	[redacted]	[redacted]	[redacted]
Total bilirubin, µmol/L, median (range)	[redacted]	[redacted]	[redacted]
Albumin, g/L, median (range)	[redacted]	[redacted]	[redacted]
Weight-for-age percentile			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Length-for-age percentile			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; LAL, lysosomal acid lipase; SD, standard deviation.
Notes: [a], [redacted] had a negative age at diagnosis due to being diagnosed in-utero.
Source: ALX-LALD-501 registry data[34]

B.2.6.3.2.2. Clinical effectiveness data

Patients at sebelipase alfa treatment initiation (n = [redacted]) had a median age of [redacted] years. ranging from [redacted] to [redacted] years.[34] Median age at last sebelipase alfa treatment (n

= [redacted]) was [redacted] years (range: [redacted] to [redacted] years), demonstrating a substantial extension of life when treated with sebelipase alfa.[34]

Survival

Figure 18 presents the Kaplan-Meier of overall survival for the safety population. The registry presents a median long-term follow-up of [redacted] years, with the oldest patient still alive at [redacted] years.[34]

A total of [redacted] patients died, of which [redacted] died prior to registry enrolment, and [redacted] who died approximately [redacted] years from sebelipase alfa treatment initiation due to liver failure/cirrhosis.[34]

Figure 18: Kaplan-Meier of overall survival (safety population)

Key: NA, not applicable.
Notes: Overall survival is time from treatment initiation to patient's death of any reason in years. For patients alive at time of analysis censoring at their last known follow-up date is applied. *represents censored observations.
Source: ALX-LALD-501 registry data[34]

Growth parameters

Table 11 presents the observed weight-for-age and length-for-age percentiles and change from baseline at the last reported value for the study population.

When assessing the weight-for-age and length-for-age percentiles, key parameters of growth evaluation in infants, sebelipase alfa treatment led to improvements in growth from baseline through last assessment.

Median weight-for-age percentiles at baseline were higher in the registry than reported in LAL-CL08 and LAL-CL03, possibly due to the treatment of patients with sebelipase alfa prior to enrolment in the registry.[34]

The median weight-for-age percentiles improved from baseline for the overall population by [redacted] and in the UK population by [redacted].[34] The median length-for-age percentiles improved from baseline for the overall population by [redacted] and in the UK population by [redacted].[34]

Table 11: Observed values and change from baseline for weight-for-age and length-for-age percentiles (study population)

	Observed value			Change from baseline		
	UK patients (n = [redacted])	**Non-UK Patients (n = [redacted])**	**All patients (N = [redacted])**	**UK patients (n = [redacted])**	**Non-UK Patients (n = [redacted])**	**All patients (N = [redacted])**
Weight-for-age percentiles						
Baseline[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last reported value						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Length-for-age percentiles						
Baseline[a]						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last reported value						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: ALX-LALD-501 registry data[34]						

B.2.6.3.3. Multi-modality therapy (sebelipase alfa and HSCT)

As previously introduced, Potter et al. 2021 is a recently published case series that explored the efficacy of sebelipase alfa and HSCT as a multi-modality therapy therapy.[2] The UK is at the forefront of evolution of the treatment pathway for rapidly progressive LAL-D; UK clinicians have introduced the use of multi-modal therapy in patients whose response to treatment has diminished over time due to the development of ADAs, but also has a potential for use when patients can no longer tolerate weekly infusions or in whom venous access becomes an issue.[22, 23]

Of 15 patients treated for rapidly progressive LAL-D at the Royal Manchester Children's Hospital since 2005, five patients received multi-modal therapy of sebelipase alfa followed by HSCT, according to a clinical expert. Of note, four of the five patients presented in Potter et al. 2021 had previously been enrolled in clinical trials and/or were in the GATM programme. In three of the five patients, an initial response to sebelipase alfa was attenuated by ADAs, with associated clinical and laboratory features of deterioration.[2] One patient developed anaphylaxis to sebelipase alfa, and the other patient died post-HSCT with ongoing hemophagocytic lymphohistiocytosis (HLH).

Four of the five patients were alive at least 10 months after HSCT.[2] At time of reporting, the time since HSCT in each of the four surviving patients was 4 years 6 months, 2 years 9 months, 2 years 1 month and 10 months. All four patients remain on treatment with sebelipase alfa, with three patients able to decrease their dosage and frequency. No evidence of neutralizing ADAs were identified. These four patients also experienced an improvement in GI symptoms that were not seen with sebelipase alfa alone, as confirmed through both improvements in their dietary tolerance and resolution of diarrhoea, and histologically in their biopsies. One patient died 5 months post-HSCT due to an ongoing inflammatory process and subsequent sepsis development.[2] Further results from the Potter et al. 2021 study are presented in Appendix L.4. Since the publication of Potter et al. 2021, clinicians provided an April 2022 update [redacted]

B.2.7. Subgroup analysis

Due to the rarity of the condition and the extremely limited patient numbers, subgroup analyses were not planned or conducted for LAL-CL03 or LAL-CL08.

B.2.8. Meta-analysis

A meta-analysis is not required as LAL-CL08 and LAL-CL03 provide the efficacy and safety data to support the use of sebelipase alfa for the treatment of patients with rapidly progressive LAL-D. Although not presented in the clinical sections of this submission, results from LAL-CL08 and LAL-CL03 have been pooled to provide results for a larger sample of patients to inform the Kaplan-Meier estimates of survival to 12 months and 5 years of age in the economic model .[27] The remaining results were not considered appropriate to be pooled due to differences in trial methodology (e.g. dosing regimens) and baseline patient disease characteristics.

B.2.9. Indirect and mixed treatment comparisons

An SLR was conducted to identify relevant published clinical evidence of pharmacological treatments for rapidly progressive LAL-D, in line with the population presented in LAL-CL08. A total of 21 publications of eight unique trials were identified, including the previously discussed LAL-CL08 and LAL-CL03 trials.[27, 29] Full details of the SLR search strategy, study selection process and results are presented in Appendix D.1.

No head-to-head data are available for sebelipase alfa versus standard of care (i.e. supportive therapies) in patients with rapidly progressive LAL-D. A comparative study was not considered appropriate due to the unethical nature of conducting a comparative study in patients with such a progressive and life-threatening disease.

As previously discussed in Section B.1.3.4, sebelipase alfa is the only treatment currently available in the UK to effectively treat patients with rapidly progressive LAL-D by addressing the underlying cause of the disease. It is therefore believed that an indirect treatment comparison (ITC) would not provide any additional information above what is presented in LAL-CL08 and LAL-CL03.

Only one study was identified to provide evidence for the comparators of relevance (i.e. in the absence of sebelipase alfa), which was a natural history study (LAL-1-

NH01).[6] In summary, LAL-1-NH01 investigated disease progression in patients with rapidly progressive LAL-D prior to the availability of sebelipase alfa. A total of 35 patients who received a clinical diagnosis of rapidly progressive LAL-D between 1985 and 2012 were enrolled in the study. Of these 35 patients, 21 patients were untreated (i.e. did not receive HSCT and/or liver transplant) with early growth failure. Where data are available for these patients, these are the data that have been presented within this submission, to align with the pathway of care in UK clinical practice in the absence of sebelipase alfa, as confirmed by UK clinical experts. Prior to the advent of sebelipase alfa, liver transplants and HSCT were occasionally used as a last resort in patients with rapid disease progression but were not able to change the prognosis of death and were associated with high risk of HSCT-related toxicities, infections and the potential of graft-versus-host disease. Expert clinical opinion therefore confirmed that HSCT and/or liver transplant would not be recommended under their care, without sebelipase alfa, in UK clinical practice and are therefore not considered to be relevant treatment options.[19] Where data aren't available specifically for these patients, we have used data from the untreated population (n = 25), or the overall population (n = 35); this will be clearly stated alongside any evidence presented. Further information on the LAL-1-NH01 trial is presented in Section B.2.9 and Appendix D.1.4. Given the ethical concerns of withholding treatment with sebelipase alfa in this population, LAL-1-NH01 was considered to be the most appropriate source of data to form a historic control arm for comparison to the efficacy data from LAL-CL08 and LAL-CL03.

The baseline characteristics reported in LAL-1-NH01 were generally consistent with those reported in LAL-CL08 and LAL-CL03. Further information on the comparison of baseline characteristics for LAL-CL08, LAL-CL03 and LAL-1-NH01 is presented in Appendix D.1.4.2. A total of [redacted] ([redacted]%) patients enrolled were based in the UK.[14]

B.2.9.1. Survival

B.2.9.1.1. Proportion of patients surviving to 12 months of age and beyond

Survival of patients with rapidly progressive LAL-D treated with sebelipase alfa at 12 months of age was the primary efficacy endpoint in LAL-CL03 and a secondary

endpoint in LAL-CL08.[27] Survival rates beyond 12 months of age were a secondary endpoint in both trials.

Table 12 summarizes the survival rates for patients with rapidly progressive LAL-D enrolled in LAL-CL08, LAL-CL03 and LAL-1-NH01. At 12 months of age, patients with rapidly progressive LAL-D enrolled in LAL-CL08 and LAL-CL03 had a survival rate of 90% and 67%, respectively, compared to no survivors (0%) in the untreated patients with early growth failure (n = 21) in the natural history study.[6, 27]

Table 12: Naïve comparison of survival rates for patients with rapidly progressive LAL-D in LAL-CL08, LAL-CL03 and LAL-1-NH01

Study	LAL-CL08	LAL-CL03	LAL-1-NH01
Population	Patients with rapidly progressive LAL-D	Patients with rapidly progressive LAL-D and early-onset growth failure	Patients with untreated rapidly progressive LAL-D with early-onset growth failure
Survival at 12 months	9/10 (90%) patients	6/9 (67%) patients	0/21 (0%) patents
Survival at 24 months	8/10 (80%) patients	5/9 (56%) patients	0/21 (0%) patents
Survival at 60 months	-	5/9 (56%) patients	0/21 (0%) patents
Key: HSCT, haematopoietic stem cell transplant. **Source :** Vijay et al, 2021[27] and Jones et al. 2016.[6]			

B.2.9.2. Growth failure

Growth failure is a prominent manifestation of rapidly progressive LAL-D. Without treatment with sebelipase alfa, patients experience low weight-for-age scores at first, which worsen as the disease progresses. When treated with sebelipase alfa, patients experience improvements in weight-for-age, as demonstrated in both LAL-CL08 and LAL-CL03.[27]

In LAL-CL08, median weight-for-age percentile at baseline was [redacted] and increased by a median of [redacted] by Week 144.[26] In LAL-CL03, median weight-for-age percentile at baseline was [redacted] and increased by a median of [redacted] by Week 144.[28] In LAL-1-NH01, median weight-for-age percentiles at first chart record (which may represent birth weight) for the untreated population (n = 25) were [redacted].[38] The median percentile substantially decreased before diagnosis (untreated population: [redacted]) and

continued to worsen post-diagnosis as the disease progressed. The untreated population experienced a median decrease in weight-for-age percentile from first record to death of [redacted].[38]

The percentage of underweight patients in LAL-1-NH01 (defined as ≤ 2 SD below median weight-for-age at birth) increased over time in the overall population (n = 35) from [redacted]% at first record, [redacted]% at diagnosis and [redacted]% at death.[14] In LAL-CL08, [redacted]% of patients were underweight at baseline and by Week 156 [redacted] patients met the criteria for being underweight.[26] Similar results were seen in LAL-CL03, where [redacted]% of patients were underweight at baseline, and although this proportion fluctuated throughout treatment with sebelipase alfa, [redacted] patients ended up as underweight by Week 144 and for the remainder of the trial period.[28]

These contrasting results demonstrate the favourable impact of sebelipase alfa on growth measures.

B.2.9.3. Transaminase levels

Elevated transaminase levels (ALT and AST) are markers of liver cell injury and commonly noted among patients with rapidly progressive LAL-D. The change from baseline in AST and ALT levels are key endpoints in LAL-CL08 and LAL-CL03. Whilst patients treated with sebelipase alfa experienced a reduction in their AST and ALT levels over the course of the trial, patients in the natural history study experienced a substantial increase of AST and ALT level from diagnosis to death. This therefore provides some insight into the relationship between liver dysfunction, as shown through increased levels on AST and ALT, and disease progression in the absence of treatment with sebelipase alfa.

In LAL-CL08, patients undergoing treatment with sebelipase alfa experienced a reduction in median ALT levels from 37.0 U/L at baseline (n = 9) to [redacted] U/L (n = [redacted]) at Week 144 , and a reduction in median AST levels from 99.5 U/L (n = 8) at baseline to [redacted] U/L (n = [redacted]) at Week 144.[26, 27]

In LAL-CL03, patients undergoing treatment with sebelipase alfa experienced a reduction in median ALT levels from 145.0 U/L at baseline (n = 9) to [redacted] U/L (n = [redacted]) at Week 144 , and a reduction in median AST levels from 125.0 U/L (n = 9) at baseline to [redacted] U/L (n = [redacted]) at Week 144.[27, 28]

These results are in contrast to what was observed in the overall population (n = 35) of the natural history study, where worsening of median serum transaminase levels from diagnosis to death was observed. At diagnosis, median ALT and AST levels were 56.5 U/L (n = 24) and 151 U/L (n = 19), respectively.[6] Median ALT and AST levels at death (last follow-up recorded at Week 32) were substantially increased, 110.5 U/L and 238 U/L, respectively.[6]

B.2.10. Adverse reactions

B.2.10.1. LAL-CL08

B.2.10.1.1. Extent of exposure

Table 13 presents the sebelipase alfa exposure by dose. A total of 1,193 infusions were administered in LAL-CL08. The median duration of treatment was [redacted] weeks (range: [redacted] weeks) and the median number of attempted infusions was [redacted] (range: [redacted]).[26]

Of the two patients who died during the trial, [redacted] received four infusions and the other received [redacted] prior to death.[26] Of the eight surviving patients, [redacted] received [redacted] infusions, [redacted] received [redacted] infusions, [redacted] received [redacted] infusions and [redacted] received [redacted] infusions.[26] Most of these infusions were administered in full.

LAL-CL08 is the most recent clinical trial to provide a narrative of the patient and clinician experience of sebelipase alfa in the treatment of rapidly progressive LAL-D as the awareness and knowledge of the condition continues to increase. The LAL-CL08 trial is therefore more reflective of recent clinical practice and the dosages of sebelipase alfa administered.

Table 13: Sebelipase alfa exposure by dose

Parameter	All treated patients up to 5 mg/kg (N = 10)			
	1 mg/kg QW (n = [redacted])	3 mg/kg QW (n = [redacted])	5 mg/kg QW (n = [redacted])	All doses (n = [redacted])
Median number of weeks on treatment (range)	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusions administered	[redacted]	[redacted]	[redacted]	[redacted]

Key: QW, once weekly.
Source: LAL-CL08 clinical study report.[26]

B.2.10.1.2. Summary of adverse events

Table 14 provides an overview of the incidence of TEAEs in LAL-CL08, which are shown for the overall duration of the trial and by time interval.

All ten (100%) patients reported TEAEs and SAEs, with most of the SAEs reportedly associated with the complications and comorbidities of LAL-D.[26] Five (50%) patients experienced SAEs that were related or possibly related to sebelipase alfa, of which most were classified as IARs. Eight (80%) patients reported IARs. There were no clear trends in the frequency of TEAEs or IARs over the duration of the trial. However, the severity of the AEs decreased over time, with severe TEAEs reported in only one patient after 12 months of treatment and in no patients after 24 months of treatment.[26]

Seven (70%) patients received a dose modification during one or more infusions due to a TEAE.[26] No patients received permanent dose reduction or were discontinued from the trial due to TEAEs.[26]

Table 14: Proportion of patients reporting AEs in LAL-CL08

	All treated patients						
	Overall (N = 10)	By time interval					
		0 to 3 months (N = 10)	> 3 to 6 months (N = 9)	> 6 to 12 months (N = 9)	> 12 to 18 months (N = 8)	> 18 to 24 months (N = 8)	> 24 months (N = 8)
Any TEAE	10 (100)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE[a]	8 (80)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any IAR[b]	8 (80)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE	10 (100)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any severe TEAE	7 (70)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose modification due to a TEAE[c]	7 (70)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment withheld or permanently discontinued due to a TEAE[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	2 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; CRF, case report form; IAR, infusion-associated reaction; TEAE, treatment-emergent adverse event.
Notes: TEAEs included events with an onset at or following the start of treatment with the trial drug or events that worsened in severity or relationship at or following the start of treatment and occurring up to 30 days after the last infusion of sebelipase alfa.
[a], Related TEAEs include any event assessed by the Investigator as related or possibly related to the trial drug.
[b], IARs include any event with an onset during the trial drug infusion or within 4 hours after the trial drug infusion, where the event was assessed by the Investigator as related or possibly related to the trial drug.
[c], Dose modifications include dose increased, dose reduced, infusion interrupted, infusion stopped or rate changed per the AE CRF page.
[d], Includes trial drug withheld or trial drug permanently discontinued per the AE CRF page.
Source: Vijay et al. 2021[27] and LAL-CL08 clinical study report.[26]

B.2.10.1.3. Treatment-emergent adverse events

Table 15 presents the TEAEs that were reported by at least four (40%) of patients by system organ class and preferred term.

All 10 (100%) patients experienced at least one TEAE during the trial.[27] The most commonly reported TEAEs included pyrexia (n = [redacted], [redacted]%), diarrhoea (n = [redacted], [redacted]%), vomiting (n = [redacted], [redacted]%), tachycardia (n = [redacted], [redacted]%), gastroenteritis (n = [redacted], [redacted]%) and respiratory distress (n = [redacted], [redacted]%).[26]

Table 15: Summary of TEAEs, regardless of cause, reported by ≥ 4 patients

SOC Preferred term	All treated patients (N = 10)	
	Events, n	Patients, n (%)
Any TEAE	[redacted]	**10 (100)**
Cardiac disorders	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Teething	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Device-related infection	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Device-related sepsis	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Rhinovirus infection	[redacted]	[redacted]
Parainfluenza virus infection	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Respiratory rate increased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]

SOC Preferred term	All treated patients (N = 10)	
	Events, n	Patients, n (%)
Product issues	[redacted]	[redacted]
Device occlusion	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Irritability	[redacted]	[redacted]
Agitation	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]
Wheezing	[redacted]	[redacted]
Tachypnoea	[redacted]	[redacted]
Skin and subcutaneous tissue disorder	[redacted]	[redacted]
Dermatitis, diaper	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Key: SOC, system organ class; TEAE, treatment-emergent adverse event.
Note: If a patient experienced > 1 event in a given SOC, that patient was counted once for that SOC. If a patient experienced > 1 event within a given Preferred Term, that patient was counted only once for that Preferred Term. The SOCs were sorted alphabetically, and Preferred Terms were sorted in decreasing order of incidence within the SOC.
Source: Vijay et al. 2021[27] and LAL-CL08 clinical study report.[26]

Table 16 summarizes all treatment-related TEAEs and all IARs reported during the trial.

Ten (100%) patients experienced a total of [redacted] treatment-related TEAEs, in which the most commonly reported were tachycardia (n = [redacted], [redacted]%), pyrexia (n = [redacted], [redacted]%), irritability (n = [redacted], [redacted]%), agitation (n = [redacted], [redacted]%) and urticaria (n = [redacted], [redacted]%).[26]

Most treatment-related TEAEs were classified as IARs. Eight (80%) patients experienced a total of 98 IARs, in which the most commonly reported were tachycardia (n = 7, 70%), pyrexia (n = 6, 60%), irritability (n = 5, 50%), agitation (n = 4, 40%) and urticaria (n = 4, 40%).[27]

Most IARs were successfully managed by infusion interruption/discontinuation, infusion-rate reduction and/or conventional treatment with antihistamines, corticosteroids, analgesics or antipyretics.[26]

Table 16: Summary of treatment-related TEAEs and infusion-associated reactions

SOC Preferred term	All treated patients (N = 10)			
	Treatment-related TEAEs		IARs	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Any TEAE	[redacted]	**10**	**98**	**8**
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	7
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Lip swelling	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal distention	[redacted]	[redacted]	[redacted]	[redacted]
Tongue erythema	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	6
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Drug-specific antibody present	[redacted]	[redacted]	[redacted]	[redacted]
Body temperature increased	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	[redacted]	[redacted]	[redacted]	5
Agitation	[redacted]	[redacted]	[redacted]	4
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nephrotic syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]	[redacted]
Tachypnoea	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorder	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	4
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]

SOC Preferred term	All treated patients (N = 10)			
	Treatment-related TEAEs		IARs	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

Key: IAR, infusion-associated reaction; SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: Treatment-related TEAEs include events assessed by the Investigator as related or possibly related to treatment. If a patient experienced > 1 event in a given SOC, that patient was counted once for that SOC. If a patient experienced > 1 event within a given Preferred Term, that patient was counted only once for that Preferred Term. The SOCs were sorted alphabetically, and Preferred Terms were sorted in decreasing order of incidence within the SOC.
Source: Vijay et al. 2021[27] and LAL-CL08 clinical study report.[26]

B.2.10.1.4. Anti-drug antibodies

Six (60%) patients developed ADAs to sebelipase alfa. Patients were deemed ADA-positive at Week 5 (n = 1), Week 8 (n = 2), Week 12 (n = 1), Week 20 (n = 1) or Week 60 (n = 1).[27] The patients who developed ADAs during or before Week 12 all had high ADA titres compared with those who developed ADAs after Week 12. All 6 ADA-positive patients tested positive for neutralizing antibodies that inhibited both LAL enzyme activity and cellular uptake. [27] Data suggested that neutralizing antibodies had an impact on clinical response in three patients. These three patients higher ADA titers than other patients in the trial (peak titers ranging from 222,070 to 302,963).[26, 28] Very-high titers of ADA were related to whole *LIPA* gene deletions.[26] While the patients experienced some initial improvement on sebelipase alfa, the increase in ADA titer was strongly associated with diminished clinical efficacy, including decreases in weight-for-age percentile.[26] This loss of efficacy prompted sebelipase alfa dose escalation and other clinical measures, including immunomodulatory therapy (e.g, rituximab or bortezomib). Improvement and/or stabilization of clinical response was observed when ADA titers decreased after the introduction of immunomodulation therapy or following successfully engrafted HSCT.[26]

B.2.10.1.5. Deaths

Two (20%) patients died during the trial; both deaths were related to complications of disease progression.[27] One patient received [redacted] infusions of sebelipase alfa at a dose of 1 mg/kg QW prior to death due to pericardial effusion at 4.9 months of age.[26] The second patient received [redacted] infusions (1 to 5 mg/kg QW) prior to death at 13.8 months of age due to sepsis. Both deaths were deemed unrelated to sebelipase alfa.[27]

B.2.10.2. LAL-CL03

B.2.10.2.1. Extent of exposure

Of the nine patients treated in this trial, [redacted] patients initiated treatment with sebelipase alfa at a dose of 0.35 mg/kg QW.[28] This was an investigational dose, and as per the current label, this dose is now off-label.[1] [redacted] patients were subsequently escalated to a dose of 1 mg/kg QW at Week 2 (i.e. third infusion). The remaining [redacted] patients died after receiving a single infusion of sebelipase alfa, although the deaths were considered to be unrelated to treatment with sebelipase alfa.[26]

For [redacted], trial analyses include available data collected during the patient's treatment with sebelipase alfa under a temporary use authorization (Autorisation Temporaire d'Utilisation; ATU). [redacted] was based in France and received a lower initial dose of 0.2 mg/kg, with a more gradual initial dose escalation over 4 weeks.[28] [redacted] began treatment under LAL-CL03 at Week 85 at a dose of 1 mg/kg, and the dose was escalated to 3 mg/kg QW at Week 91.[28] [redacted] patients were administered a dose of 1 mg/kg QW, in which [redacted] patients received a dose escalation to 3 mg/kg based on clinical response to treatment.[28] [redacted] of these [redacted] patients went on to receive 5 mg/kg due to continued disease progression during long-term treatment.[28]

A total of 1,249 infusions of sebelipase alfa were administered.[27] The median duration of exposure to sebelipase alfa was [redacted] weeks per patient (range: [redacted] weeks).[28] The median total number of infusions attempted per patient was [redacted] infusions (range: [redacted]).[28]

[redacted] patients received one or more infusions on an every-other-week (QOW) regimen.[28] [redacted] patients had frequent infusion interruptions, most of which involved changes in infusion rate to manage or prevent IARs.[28]

B.2.10.2.2. Summary of adverse events

Table 17 presents the incidence of TEAEs in LAL-CL03, which are shown for the overall duration of the trial and by time interval.

All nine (100%) patients reported TEAEs and SAEs, with most SAEs reportedly associated with the complications and comorbidities of LAL-D.[27] The frequency of SAEs appeared to decrease over time. Only one patient had an SAE that was deemed related to sebelipase alfa, which was further categorised as an IAR. Overall, IARs were reported in five (56%) patients.[27]

Seven (78%) patients received a dose modification (i.e. a decrease in dose or infusion interruption) during one or more trial infusions due to a TEAE, primarily due to IAR management.[27] While the frequency of IARs was relatively consistent over time, the proportion of patients requiring dose modification to manage IARs decreased over time.

No patients discontinued treatment or were discontinued from the trial due to a TEAE, SAE or IAR.[27]

Table 17: Proportion of patients reporting AEs in LAL-CL03

	All treated patients					
	Overall (N = 9)	By time interval				
		0 to 12 months (N = [redacted])	> 12 to 24 months (N = [redacted])[a]	> 24 to 36 months (N = [redacted])[a]	> 36 to 48 months (N = [redacted])	> 48 months (N = [redacted])
Any TEAE	9 (100)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any related TEAE[b]	6 (67)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any IAR[c]	5 (56)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE	9 (100)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any related serious TEAE[b]	1 (11)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose modification due to a TEAE[d]	7 (78)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to a TEAE[d]	0 (0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	4 (44)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; CRF, case report form; IAR, infusion-associated reaction; TEAE, treatment-emergent adverse event.
Notes: TEAEs included events with an onset at or following the start of treatment with the trial drug, or events that worsened in severity or relationship at or following the start of treatment and occurring up to 30 days after the last infusion of sebelipase alfa.
[a], Non-serious TEAE data were unavailable for one patient from Week 0 to Week 39.
[b], Related TEAEs include any event assessed by the Investigator as related or possibly related to the trial drug.
[c], IARs include any event with an onset during the trial drug infusion or within 4 hours after the trial drug infusion, where the event was assessed by the Investigator as related or possibly related to the trial drug.
[d], Dose modifications include dose decreased, dose interrupted and drug permanently discontinued per the AE electronic CRF page.
Source: Vijay et al. 2021[27] and LAL-CL03 clinical study report.[28]

B.2.10.2.3. Treatment-emergent adverse events

Table 18 presents the TEAEs that were reported by at least four (40%) patients by system organ class and preferred term.

All nine (100%) patients experienced at least one TEAE during the trial.[27] The most commonly reported TEAEs included diarrhoea (n = [redacted], [redacted]%), vomiting (n = [redacted], [redacted]%), cough (n = [redacted], [redacted]%), nasopharyngitis (n = [redacted], [redacted]%), pyrexia (n = [redacted], [redacted]%) and rhinitis (n = [redacted], [redacted]%).[28]

Table 18: Summary of TEAEs, regardless of cause, reported by patients

SOC Preferred term	All treated patients (N = 9)	
	Events, n	Patients, n (%)
Any TEAE	[redacted]	**9 (100)**
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Skin and subcutaneous tissue disorder	[redacted]	[redacted]
Dermatitis, diaper	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Blood and lymphatic system disorder	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

Key: SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: If a patient experienced > 1 event in a given SOC, that patient was counted once for that SOC. If a patient experienced > 1 event within a given Preferred Term, that patient was counted only once for that Preferred Term. The SOCs were sorted alphabetically, and Preferred Terms were sorted in decreasing order of incidence within the SOC. TEAEs included events with an onset at or following the start of treatment with sebelipase alfa, or events that worsened in severity or relationship at or following the start of treatment and occurring up to 30 days after the last infusion of sebelipase alfa.
Source: LAL-CL03 clinical study report.[28]

Table 19 summarizes all IARs reported during the trial.

Five (56%) patients experienced a total of 54 IARs, in which the most frequently reported IARs were pyrexia (n = 3, 33%), vomiting (n = 3, 33%), urticaria (n = 3, 33%), tachycardia (n = 2, 22%) and pallor (n = 2, 22%).[27]

[redacted] patients experienced recurrent IARs at ≥ 2 trial infusions of sebelipase alfa, of which [redacted] patients had recurrent IARs following infusions at both 1 mg/kg and 3 mg/kg, including IARs that were considered moderate or severe.[28]

All IARs were successfully managed by infusion interruption, infusion-rate reduction, and/or conventional treatment with antipyretics (i.e. paracetamol/ibuprofen) and antihistamines.[28] Most IARs were resolved the same day, with all but [redacted] IAR (urticaria) resolved within 2 days.[28]

Table 19: Summary of infusion-associated reactions

SOC Preferred term	All treated patients (N = 9)	
	Events, n	Patients, n (%)
Any IAR	**54**	**5 (56)**
Cardiac disorders	[redacted]	[redacted]
Tachycardia	[redacted]	2 (22)
Gastrointestinal disorders	[redacted]	[redacted]
Vomiting	[redacted]	3 (33)
Diarrhoea	[redacted]	[redacted]
Retching	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	3 (33)
Chills	[redacted]	[redacted]
Hyperthermia	[redacted]	[redacted]
Infusion site extravasation	[redacted]	[redacted]
Infusion site oedema	[redacted]	[redacted]
Irritability	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Body temperature increased	[redacted]	[redacted]
Oxygen saturation decreased	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Hypotonia	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Agitation	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]

SOC Preferred term	All treated patients (N = 9)	
	Events, n	Patients, n (%)
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Urticaria	[redacted]	3 (33)
Pruritus	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Pallor	[redacted]	2 (22)
Hypertension	[redacted]	[redacted]

Key: IAR, infusion-associated reaction; SOC, system organ class; TEAE, treatment-emergent adverse event.
Source: Vijay et a. 2021[27] and LAL-CL03 clinical study report[28]

B.2.10.2.4. Anti-drug antibodies

ADAs were detected during treatment in four (57%) of the seven patients who were tested.[27] ADA positivity was first detected between Week 5 in one patient and Week 8 in two patients, with one further patient becoming ADA-positive at Week 59.

For one patient ADA-positive persisted at the majority of assessments from the initial ADA-positive result at week 5 through the end of the study.[27] ADA positivity persisted in two patients at the majority of assessments for a period of 110 or 208 weeks but then tested ADA-negative for the remainder of the study.[27] One patient had only intermittent low-titer ADAs interspersed with periods during which results were ADA-negative.[27]

All four ADA-positive patients were tested for the presence of neutralising antibodies.[27] Three tested positive for neutralising antibodies that inhibited cellular uptake of LAL, of which two also tested positive for neutralising antibodies that inhibited LAL enzyme activity,[27] While a poor growth response was noted in [redacted] who developed neutralizing antibodies, [redacted] had other medical complications (e.g. infection, feeding difficulties) that could be causal factors.[28]

The presence of ADAs did not appear to have an effect on the safety profile of sebelipase alfa in terms of frequency and severity of drug-related TEAEs, SAEs or IARs.[27]

B.2.10.2.5. Deaths

In total, four patients died due to complications related to disease progression or a non-trial-related procedure.[27] Two patients died at approximately 3 months of age after only receiving a single infusion of sebelipase alfa (0.35 mg/kg) before death. The cause of death was hepatic failure (n = 1) and peritoneal haemorrhage (n = 1).[27]

[redacted] patient received [redacted] infusions of sebelipase alfa (2 x 0.35 mg/kg QW and 2 x 1 mg/kg QW) before death at 4.3 months of age.[28] The cause of death was cardiac arrest, which was thought to occur secondary to a severe brain haemorrhage.[27]

[redacted] patient received [redacted] infusions of sebelipase alfa before death at 15.0 months of age due to sudden cardiac death.[28]

B.2.10.3. ALX-LALD-501 registry

B.2.10.3.1. Exposure to sebelipase alfa

Table 20 presents an overview of treatment with sebelipase alfa in the registry population. The starting dosages administered to UK patients in the registry were 1 mg/kg QW or 3 mg/kg QW aligns with that administered in UK clinical practice, as confirmed by UK clinicians.[34] Half the UK patients with available records (n = [redacted], [redacted]%) reportedly received 1 mg/kg QW or 3 mg/kg QW as their last known dosage, with the remaining [redacted] receiving 5 mg/kg QW.[34]

Table 20: Treatment with sebelipase alfa (study population)

	UK patients (n = [redacted])	**Non-UK patients (n = [redacted])**	**All patients (N = [redacted])**
Current sebelipase alfa treatment status, n (%)			
Previously treated	[redacted]	[redacted]	[redacted]
Currently treated	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Age at treatment initiation, years, median (range)[a]	[redacted]	[redacted]	[redacted]
Sebelipase alfa dose and frequency at treatment initiation, n (%)			
N	[redacted]	[redacted]	[redacted]
< 1 mg/kg	[redacted]	[redacted]	[redacted]
1 mg/kg every other week	[redacted]	[redacted]	[redacted]
1 mg/kg, once weekly	[redacted]	[redacted]	[redacted]
3 mg/kg every other week	[redacted]	[redacted]	[redacted]
3 mg/kg, once weekly	[redacted]	[redacted]	[redacted]
5 mg/kg, once weekly	[redacted]	[redacted]	[redacted]

Other	[redacted]	[redacted]	[redacted]
Last known Sebelipase alfa dose and frequency, n (%)			
N	[redacted]	[redacted]	[redacted]
1 mg/kg every other week	[redacted]	[redacted]	[redacted]
1 mg/kg, once weekly	[redacted]	[redacted]	[redacted]
3 mg/kg every other week	[redacted]	[redacted]	[redacted]
3 mg/kg, once weekly	[redacted]	[redacted]	[redacted]
5 mg/kg, every other week	[redacted]	[redacted]	[redacted]
5 mg/kg, once weekly	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Transplants during follow-up, n (%)			
Patients with data on transplants during follow-up, N	[redacted]	[redacted]	[redacted]
Liver transplant	[redacted]	[redacted]	[redacted]
HSCT	[redacted]	[redacted]	[redacted]

Key: HSCT, hematopoietic stem cell transplant.
Notes: [a], the exact treatment start data is missing for [redacted] and [redacted] is therefore not included in the calculation for age at treatment initiation. [b], [redacted] received a dose between 1 to 3 mg/kg every other week. [C], [redacted] received a dose between 1 to 3 mg/kg once weekly, [redacted] received a dose between 3 to 5 mg/kg every other week, [redacted] received a dose of 2 mg/kg every three weeks and [redacted] received a dose of 5 mg/kg every 1.4 weeks.
Source: ALX-LALD-501 registry data.[34]

B.2.10.3.2. Summary of AEs

Table 21 presents an overview of the incidence of AEs in the registry for the safety population. In the overall population, a total of [redacted] AEs were reported from [redacted] ([redacted]%) patients.[34] Of these, [redacted] events from [redacted] patients were considered related to sebelipase alfa. For the UK patients, a total of [redacted] AEs were reported from [redacted] ([redacted]%) patients, of which [redacted] events from [redacted] ([redacted]%) patients were considered related to sebelipase alfa.[34]

[redacted] patients were tested for ADAs, [redacted] of which were tested due to lack of sebelipase alfa effectiveness. All [redacted] patients were positive for ADAs.[34]

Table 21: Proportion of patients reporting AEs (safety population)

	UK patients (n = [redacted])		**Non-UK patients (n = [redacted])**		**All patients (N = [redacted])**	
	n (%)	**No. of events**	**n (%)**	**No. of events**	**n (%)**	**No. of events**

Any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any related serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any severe AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any related severe AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IARs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; IAR, infusion-associated reaction. **Source:** ALX-LALD-501 registry data.[34]						

B.2.10.3.3. Frequently reported AEs

Table 22 presents the AEs that were reported by at least four patients by system organ class and preferred term.

In total, [redacted] ([redacted]%) patients of the overall population experience an AE.[34] The most commonly reported AEs include pyrexia (n = [redacted], [redacted]%), vomiting (n = [redacted], [redacted]%), diarrhoea (n = [redacted], [redacted]%) and gastroenteritis (n = [redacted], [redacted]%). These AEs align with those reported in LAL-CL08 and LAL-CL08.[34]

Table 22: Summary of AEs, reported by ≥ 4 patients (safety population)

	UK patients (n = [redacted])		Non-UK patients (n = [redacted])		All patients (N = [redacted])	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular device infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event. **Source:** ALX-LALD-501 registry data.[34]						

B.2.10.3.4. Deaths

[redacted] patients in the safety population died, [redacted] of which was a [redacted] who died at enrolment.[34] The remaining [redacted] was based in [redacted], and died at [redacted] years of age. The cause of death was listed as liver cirrhosis/failure.[34]

B.2.11. Ongoing trials

There are no ongoing studies relevant to the decision problem.

B.2.12. Interpretation of clinical effectiveness and safety evidence

As discussed in Section B.1.3.4.2, there is a clear unmet need for an innovative treatment with proven effectiveness for patients with rapidly progressive LAL-D. Due to the rarity of disease, clinical experience is relatively limited. Treatment experience is improving with each patient as the awareness of disease grows, enabling clinicians to diagnose and treat earlier leading to improved outcomes. LAL-CL08 is the most recent clinical trial to provide evidence of the effectiveness of sebelipase alfa in patients with rapidly progressive LAL-D and is deemed most representative of UK clinical practice due to the trial encompassing the greater awareness and clinical knowledge gained by clinicians over recent years. LAL-CL08 is supported by evidence from the LAL-CL03 trial, which presents evidence for the effectiveness of sebelipase alfa in patients with rapidly progressive LAL-D with early-onset growth failure.

The available evidence from clinical trials clearly shows that sebelipase alfa is associated with a clinically meaningful improvement in survival. The proportion of patients surviving to 12, 18, 24 and 36 months of age was 90%, 80%, 80% and 75%, respectively.[27] At the last follow-up, the surviving eight patients were 27.8, 30.7, 36.8, 37.3, 39.1, 39.4, 40.1 and 40.6 months of age.[26] In LAL-CL03, the proportion of patients surviving to 12 months of age was 67% (95% CI: 29.9%, 9.5%).[27, 29] A total of five (56%) patients survived to the longer-term follow-up assessment of 60 months. When compared with the poor outcomes a historical control (LAL-1-NH01), no (0%)untreated patients with early growth failure survived beyond 12 months of age; the median age of survival was just 3.0 months.[6]

High overall survival rates were also demonstrated in the ALX-LALD-501 registry. The registry presents a median long-term follow-up of [redacted] years, with the oldest patient still alive at [redacted] years.[34] [redacted] ([redacted]%) of [redacted] patients died, of which [redacted] died prior to registry enrolment, and [redacted] died approximately 3.5 years from treatment initiation due to liver failure/cirrhosis.[34]

Patients also experienced improvements in weight gain following treatment with sebelipase alfa; in both studies, median weight-for-age and length-for-age percentiles increased from baseline to end of study.[27] Treatment with sebelipase alfa led to a reduction in liver injury, as demonstrated by improvements in serum AST and ALT levels in both LAL-CL08 and LAL-CL03. This effect was consistently maintained over long-term treatment. Sebelipase alfa also reduced the need for invasive therapies such as blood transfusions, and patients remained generally stable in all four skill areas of the Denver II developmental screening test through to the end of the LAL-CL08 and LAL-CL08 trials.[27]

Considering the life-threatening disease presentation of patients with rapidly progressive LAL-D, sebelipase alfa was generally well-tolerated, with an acceptable safety profile in both LAL-CL08 and LAL-CL03.[27] All 10 (100%) patients in LAL-CL08 and all nine (100%) patients in LAL-CL03 experienced TEAEs, including SAEs. The vast majority of the reported TEAEs and SAEs represented comorbidities and complications expected with rapidly progressive LAL-D, with the exception of IARs (refer to Section B.2.10.1.3 and Section B.2.10.2.3 for LAL-CL08 and LAL-CL03, respectively). No treatment-related deaths were reported in either LAL-CL08 or LAL-CL03.[27]

The UK is at the forefront of new pioneering approaches to treatment, including the use of the multimodal therapy of sebelipase alfa followed by HSCT. Prior to the introduction of sebelipase alfa, HSCT was used as a last resort in patients with rapidly disease progression. Patients treated with HSCT reportedly survived longer than untreated patients, but survival was still very poor, with a median age at death of 8.6 months.[6] The median age of death in the untreated population (without HSCT and/or liver transplant) with early growth failure was just 3.0 months.[6] Since the advent of sebelipase alfa, UK practice has evolved to include HSCT as an option in patients whose response to treatment with sebelipase alfa was diminished due to the development of ADAs, but also has a potential for use when patients can no longer

tolerate weekly infusions or in whom venous access becomes an issue. While literature on this multi-modality treatment is limited, Potter et el. 2021 has demonstrated the possible benefit of this treatment in UK clinical practice, in which four of five patients were alive at least 10 months after HSCT.[2] At the time of publication, three of the four patients were able to decrease their dosage and frequency of sebelipase alfa.[2] [redacted]

Clinical practice is expected to evolve further; for example, HSCT may have potential for use in patients who can no longer tolerate weekly infusions or in whom venous access has become an issue.[22, 23] [redacted]

Without access to sebelipase alfa, the existing approaches using supportive therapies are only able to reduce the existing burden of disease complications, rather than prevent disease progression and ultimately premature death. Sebelipase alfa is the only available pharmaceutical treatment option able to alter the underlying cause of rapidly progressive LAL-D, resulting in prolonged survival with normal neurological development, improved growth, haematological parameters, and liver parameters, thereby reducing the clinical, emotional and financial burden on both patients and their caregivers.

B.2.12.1. Strengths and limitations of the evidence base

LAL-CL08 and LAL-CL03 provide the largest dataset available to demonstrate the efficacy of sebelipase alfa in the treatment of patients with rapidly progressive LAL-D.[27] As comparative trials in patients with rapidly progressive LAL-D were not considered appropriate due to the unethical nature of withholding a potentially effective treatment from patients with such a progressive and life-threatening disease, both studies were open-label and lacked a direct comparator. As such, it was necessary to use a historical control from the natural history study LAL-NH01

population as a reference.[6] LAL-1-NH01 is the largest dataset available to provide an account of treatment outcomes of patients with rapidly progressive LAL-D in the absence of sebelipase alfa treatment, thereby forming the most appropriate source of evidence to form a historical comparator arm to LAL-CL08 and LAL-CL03.

LAL-CL08 and LAL-CL03 are good-quality studies and were conducted in accordance with GCP, the Declaration of Helsinki, and the moral, ethical, and scientific principles that justify medical research.[27] LAL-CL08 and LAL-CL03 covered a wide range of endpoints, including a comprehensive battery of clinical, laboratory, and developmental and social outcome measures, to give a thorough analysis of the efficacy and safety of sebelipase alfa in patients with rapidly progressive LAL-D.

Although the LAL-CL08 and LAL-CL03 trials have limitations, they are expected limitations and are consistent with other ultra-rare disease trials. The open-label nature of the trials and the small population size make it difficult to distinguish dose effects and do not allow for any statistical comparisons.

B.2.12.1.1. Study applicability to clinical practice

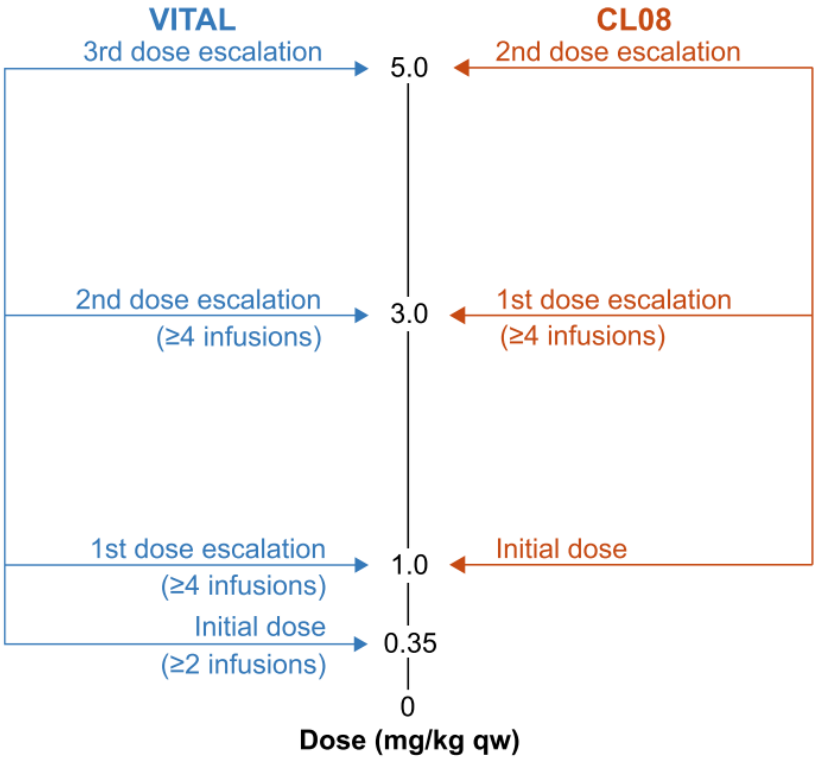
The patient populations in LAL-CL08 and LAL-CL03 are aligned with the population outlined in the decision problem presented in this submission: patients with rapidly progressive LAL-D. It has also been confirmed by UK clinicians that the LAL-CL08 and LAL-CL03 trial populations are representative of the patients seen within UK clinical practice. LAL-CL08 is also the most recent clinical trial to provide a narrative of the patient and clinician experience of sebelipase alfa in the treatment of rapidly progressive LAL-D as the awareness and knowledge of the condition continues to increase. The slightly higher survival rates observed in LAL-CL08 may be due to this evolution of understanding on disease management, leading to better nutritional management and earlier initiation, using a higher starting dose, and faster dose escalation of sebelipase alfa compared to LAL-CL03.

Patients in the LAL-CL08 and LAL-CL03 trials were treated across eight different countries worldwide. A large proportion of the enrolled patients were based in the UK and received treatment in UK hospitals (LAL-CL08: n = 8 [80%]; LAL- CL03: n = 3 [33%]).[27]

Although LAL-CL08 and LAL-CL03 both permitted dose escalations of sebelipase alfa in eligible patients, key differences existed in the initial starting dose. Figure 19

presents the dose escalation process in LAL-CL08 and LAL-CL03. The initial starting dose in LAL-CL03 was 0.35 mg/kg QW with escalation to 1.0 mg/kg, whereas in LAL-CL08, the initial starting dose was 1.0 mg/kg QW.[27] This higher initial starting dose, as well as the faster dose escalation, may have been a contributing factor towards the slightly improved outcomes demonstrated in LAL-CL08 compared with those in LAL-CL03. These results suggest that starting treatment as early as possible may allow for the achievement of better outcomes.

Figure 19: Dose escalation in LAL-CL08 and LAL-CL03 (VITAL)



Key: qw, once weekly.
Source: Vijay et al. 2021.[27]

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

A systematic search of the literature was conducted on 1 June 2015 with the aim of identifying all economic studies for LAL-D that could be used to inform the design and parameterization of the economic model. Details of the searched databases, inclusion and exclusion criteria, and results can be found in Alexion's first HST submission regarding use of sebelipase alfa for the treatment of LAL-D [ID737].[39] No economic studies were found through this search. Alexion Pharma UK is unaware of the publication of any new independent economic evidence since 2015 and believe it highly unlikely that any new economic evidence would be identified in a full systematic review. However, a new targeted search identified a recent systematic review of economic evaluations of ERT in LSDs, including infantile-onset LAL-D (published 19 September 2022).[40] Only one relevant study was found, which was the National Centre of Pharmacoeconomics (NCPE) assessment of sebelipase alfa in 2018.[41] This is the Irish national assessment of the economic analysis of sebelipase alfa for all patients with LAL-D, conducted by Alexion Pharma UK as submitted to NICE in October 2015. Both published reports are based on the liver disease Alexion model of LAL-D but represent the most relevant contextual economic evidence to this re-appraisal.

Table 23: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Alexion company submission NICE HTA ID737	2015	Cost-consequence analysis; SA vs BSC. Markov model of liver disease progression. Population included children and adults with LAL-D.	11 years	BSC, 19.24 SA, 39.73	BSC, £46,748 SA, £18,562,649	£904,097
NCPE (Ireland) using Alexion model	2018	Cost-effectiveness state transition model; SA vs BSC. Lifetime horizon.	Infantile, 1-6 months; paediatric adult, 13 years	NR	NR	€2,813,000 (infantile cohort), €2,701,000 (paediatric adult cohort)

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LAL-D, lysosomal acid lipase deficiency; NR, not reported; QALYs, quality-adjusted life years; SA, sebelipase alfa.
Note: Costs and benefits were discounted at 1.5% per annum.

B.3.2. Economic analysis

The scope of this economic evaluation extends to the evaluation of the incremental cost per quality-adjusted life year (QALY) of sebelipase alfa compared with established clinical practice without sebelipase alfa, referred to hereafter as best supportive care (BSC). The economic model submitted by Alexion Pharma UK in October 2015 was a cost-consequence analysis of the broader LAL-D population (including both children and adults), it was therefore considered to have low generalizability to the decision problem of this evaluation, particularly because non-

alcoholic steatohepatitis (NASH) was the model's structural basis, given a revised (younger, more ill) population with rapidly progressive LAL-D (i.e. Wolman disease). Table 24 presents specific critiques from the second evaluation consultation document (ECD2).[39] Therefore, a de novo health economic model was constructed to address the revised population.

Table 24: Criticisms of economic evaluation from ID737 evaluation consultation supporting change in modelling approach

Issue	Response
4.27: … it was uncertain if sebelipase alfa delayed or stopped progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events or death.	The progress of liver disease is no longer modelled, as directed by Scoping consultation.
4.28: …the ERG considered that the way the company had identified utility values used in its model had not been transparently described.	Utilities are no longer sought for liver-disease health states.

B.3.2.1. Patient population

Sebelipase alfa is indicated for long-term ERT in patients of all ages with LAL-D. The economic evaluation of this submission considers a subgroup of the sebelipase alfa indication: patients with rapidly progressive LAL-D that presents in babies and children under 2 years. This group of patients is described as having Wolman disease. The trials that comprise the evidence of effectiveness in this submission and used in the economic model, align with the scope of this HST, that is 'people with Wolman disease' or as referred to throughout this submission, rapidly progressive LAL-D.

B.3.2.2. Model structure

The model addresses the decision problem using a cost–utility analysis. The analysis is predicated on a memoryless state transition model (Markov model) of six health states and monthly cycles, with an integrated decision tree, facilitating two competing treatment strategies through a lifetime time horizon. In alignment with the NICE reference case, the base case analysis takes the payer perspective of the UK NHS setting, based on the 2022 cost year. Future costs and benefits were discounted at 1.5% annually. This is justified on the basis that treatment with

sebelipase alfa restores people who would otherwise die to full or near full health, and this is sustained over a very long period.

The primary structural basis of the model is overall mortality, a function of the combined risk of disease-related mortality, HSCT-related mortality, and other-cause mortality. The secondary structure considers the nature of clinical resourcing (defining the division of living health states); the dose requirement of sebelipase alfa (mg/kg/wk), which is independently implemented using a decision tree; and patient utility.

B.3.2.2.1. Health states

Health states do not represent exclusive levels of utility (utility is modelled as a function of age) but provide a division in respect to mortality risk and resource consumption (Table 25).

Table 25: Health states of the model

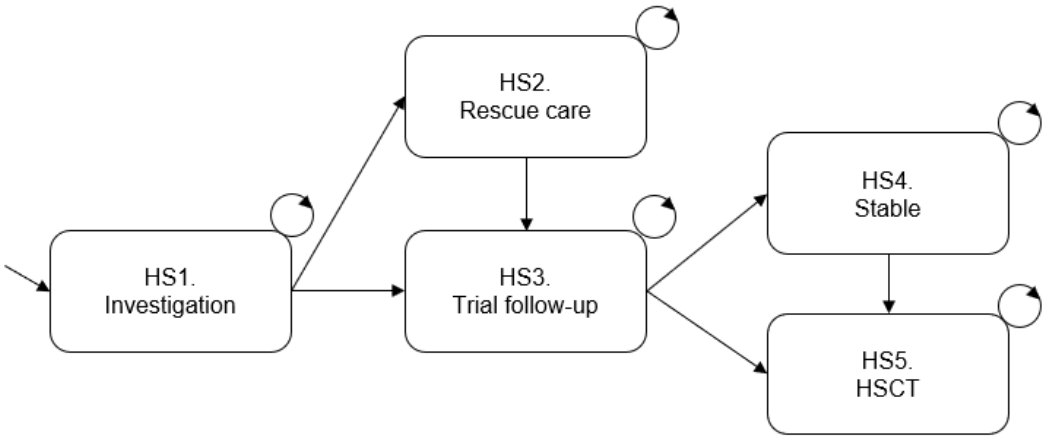
Name	Representation	Use of sebelipase alfa
HS1. Investigation	Hospital based neonatal care including IV parenteral nutrition. Trial based Wolman-related mortality risk.	Sebelipase alfa from birth, infused in the hospital setting.
HS2. Rescue care	1 month of neonatal critical care preceding a LAL-D death. Effective tunnel state.	Sebelipase alfa until death, infused in the hospital setting.
HS3. Trial follow-up	Physician and dietician monitoring for up to 5-years, with LAL-D related mortality risk as observed in trials unless transition to HSCT. Specialist nutrition included.	Sebelipase alfa administered by the Alexion homecare service.
HS4. Stable	Physician and dietician monitoring from 5 years until loss of venous access and consequent transition to HSCT as rescue (late HSCT). No LAL-D related mortality. Specialist nutrition included.	Sebelipase alfa administered by the Alexion funded homecare service.
HS5. HSCT	Period characterised initially by immunomodulation and HSCT and remaining natural life. Entry via early or late HSCT, both carrying mortality risk from the procedure. Physician and dietician monitoring continues post HSCT. Specialist nutrition included.	Sebelipase alfa is discontinued 18 months after HSCT.
HS6. Dead	Mortality from Wolman-related, HSCT-related, or other cause	N/A
Key: ADA, anti-drug antibody; BSC, best supportive care; HS, health state; IV, intravenous; HSCT, haematopoietic stem cell transplant; N/A, not applicable; SA, sebelipase alfa.		

Infants with rapidly progressive LAL-D enter the model at birth (time zero) into Diagnostic investigation (HS1). Diagnostic investigation lasts the average of 3.22 months, when surviving infants may transition from Month 4 to the outpatient setting and the Trial follow-up health state (HS3). However, LAL-D-related mortality is preceded by 1 month in Rescue care (HS2). This transition is allowed from any health state and informed by trial outcomes over a five-year follow-up. All infants in the BSC strategy will transition through Rescue care to LAL-D death within the first

year, some experiencing outpatient management on the way (HS3). Otherwise, after 5 years in HS3, the follow-up period in trials, transition is allowed to the Stable disease health state (HS4), where they may reside for the long-term or transition to the HSCT health state (HS5). There is no LAL-D mortality in the Stable health state.

Patients who require HSCT may transition at one of two timepoints. In the base case early HSCT is at 18 months old, whilst late HSCT is allowed at 30 years old. Early HSCT is a transition from the Trial Follow-up health state, late HSCT is a transition from the Stable health state. In either case there is a one-off risk of HSCT-related mortality.

Figure 20: Health state diagram



Key: HS, health state; HSCT, haematopoietic stem cell transplant.
Note: Rectangles represent living health states. Mortality is a risk from every health state (Other cause mortality from age 5 = HS4 and 5). Straight arrows represent allowable transition and direction between health states, curly arrows indicate residency, unattached arrow shows point of model entry.

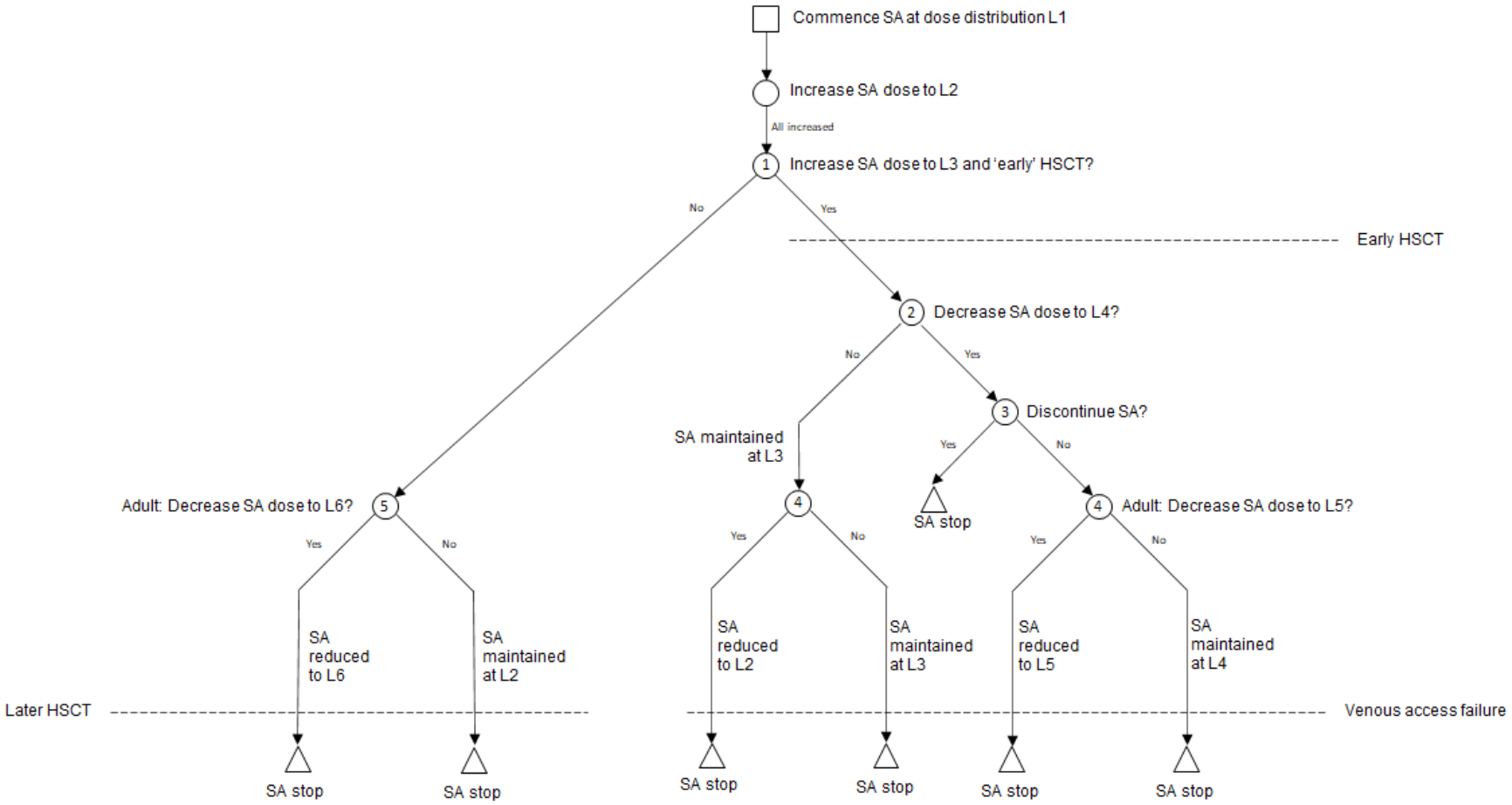
B.3.2.2.2. Decision tree

The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL-D is either 1 mg/kg or 3 mg/kg administered as a once weekly IV infusion, depending on the clinical status of the patient.[1] A higher starting dose of 3 mg/kg should be considered based on the severity of the disease and rapid disease progression. A dose escalation to 3 mg/kg should be considered in case of suboptimal clinical response after a minimum of four infusions. A further dose escalation up to 5 mg/kg should be considered in case of persistent suboptimal

clinical response[1]. Further dose adjustments, as a reduction of the dose or an extension of the dose interval, can be made on an individual basis based on achievement and maintenance of therapeutic goals. Indeed, the dose requirement of sebelipase alfa may decrease as well as increase through a lifetime according to bodyweight, so too the individual per kilogram requirement (as informed in this model by expert clinical opinion).

A decision tree implemented independently of health state occupancy provides the flexibility to incorporate response-dosing reviews at multiple time points (Figure 21). In the model it is the method used to weight proportions of the cohort at alternative doses (mg per kg) and dosing schedules (QW or twice weekly); whilst also accounting for changing needs post-HSCT and changing bodyweight over time. Table 33 and Table 34 detail the doses according to pre-defined treatment milestones, with the proportion of patients (base case) across each dose, and the duration of the respective treatment phases. Table 26 below details the clinical decision to be made at each decision node of the tree.

Figure 21: Decision tree of sebelipase alfa dosing



Key: HSCT, haematopoietic stem cell transplant; SA, sebelipase alfa.
Note: The box is a decision node and represents the decision to use sebelipase alfa or not (BSC). Circles numbered 1 -5 are chance nodes and represent clinical decisions beyond the payer's control. Codes L1-L6 are sebelipase alfa dose distribution 'levels'. Triangles are terminal nodes, representing alternative dosing pathways. Dashed lines are illustrative indications of the time of period when HSCT is possible. Venous access failure is an assured risk and therefore not a represented by a decision node: subsequent late rescue HSCT is allowed only in those without previous early HSCT.

Table 26: Decision tree chance nodes and dose distributions

Node	Clinical question	Dose distribution according to clinical decision	
		Yes	No
-	Commence sebelipase alfa?	L1	
1	Increase sebelipase alfa dose a second time in the face of anti-drug antibodies and diminishing response and commence multi-modal treatment?	L3	L2
2	Decrease sebelipase alfa dose post early HSCT?	L4	L3
3	Discontinue sebelipase post early HSCT?	Nil	L4
4	Decrease sebelipase alfa dose post early HSCT now patient is no longer paediatric?	L5	L4
5	Decrease sebelipase alfa dose now patient is no longer paediatric?	L6	L3
Key: HSCT, haematopoietic stem cell transplant.			

The combined health states and decision tree go beyond the capture of life years (survival) and provide a flexible basis by which to capture resource and treatment costs, with the question of cost-effectiveness being highly sensitive to the latter. The model meets the economic requirement of the decision problem by quantifying competing life years, health-related quality of life (HRQL; a function of age), and the cost of consumed resources.

B.3.2.2.3. Outcome measures

Other included patient outcomes were: requirement for HSCT; bodyweight; treatment-related adverse events (TEAEs); and HRQL. Outcome measures considered but not included were: haematological and lipid parameters; liver disease, function and transplant; adrenal gland function; and cardiovascular events. Whilst the impact of these outcomes on survival is implicitly captured, their impact on health-related quality of life is not included. Measuring this impact is challenging in the infant population of the included trials, and no HRQL evidence relevant to people with rapidly progressive LAL-D exists to inform these states of health without increasing uncertainty.

Table 27: Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	**HST ID737 (LAL-D not restricted to Wolman disease)**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime (not beyond 100 years)	Wolman disease is rapidly progressive but if treated with ERT, mortality is much reduced, with early patients in the UK now 12 years old and living a near-normal life. Expert clinical advice is that survival may persist near normally.
Treatment waning effect	No post-discontinuation waning effect was considered.	No post-discontinuation waning effect is considered.	The experience of clinical experts is that effect is not maintained for any substantial period after discontinuation.
Treatment discontinuation	Discontinuation was included as function of treatment-related adverse events.	Positive discontinuation may follow HSCT	HSCT has been used in clinical practice in infants and children following loss of response to sebelipase alfa due to anti-drug antibodies; because of diminishing venous access for delivery of sebelipase alfa; or because of treatment intolerability; or because of the burden of long-term weekly injections experienced by some patients.
Source of utilities	Age 0–1 years; assumption. Liver outcomes: published NASH study (Mahady 2012).[42]	UK general population (Alava 2022)[43]	Patients with Wolman disease established on ERT live a near-normal life, typically living around regular treatment administration, and in some cases ongoing dietary restriction. The measurement of HRQL in babies, infants and children is highly uncertain; no superior estimates to that of Alava 2022, general population age 16, were identified.
Source of costs	NHS reference costs 2013–14.	For hospital care: National schedule	NICE reference case

	Various published studies of resource use and costs in liver disease.	of NHS reference costs 2020/21. For hospital drugs: MIMs 2022 and eMIT September 2021. For community resources: PSSRU 2021.	
Key: eMIT, electronic Market Information Tool; ERT, enzyme replacement therapy; HRQL, health-related quality of life; LAL-D, lysosomal acid lipase deficiency; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal and Social Services Research Unit.			

B.3.2.3. Intervention technology and comparators

The modelling of sebelipase alfa, the intervention, aligns with the indication within the granted marketing authorization, although as noted in Section B.3.2.1, this evaluation focuses on a narrower patient population, specifically people with rapidly progressive LAL-D (Wolman disease), also the stated population of the decision problem. The comparator(s) listed within the scope for the purposes of the decision problem is established clinical practice without sebelipase alfa, referred to herein as BSC.

The primary evidence sources used for the statistical analysis used in the economic model are the patient-level data from the LAL-CL03 (NCT01371825)[28] and LAL-CL08 (NCT02193867)[26] studies for sebelipase alfa, and the LAL-1-NH01 study (NCT01358370)[38] for untreated patients (Section B.2). The LAL-CL03 (n=9) and LAL-CL08 (n=10) studies are Phase II/III, and Phase II, respectively. The studies are both single-arm dose escalation studies in recruited infant patients with LAL-D. Ten of the 19 patients across both studies were male (52.6%).

In the LAL-CL03 study, estimated survival to 12 months of age was 67%, and survival to 4 years of age was 56%.[44] In LAL-CL08, 1-year survival was 90% and 3-year survival was 80%.[45] When the data from both studies are combined, the resulting 5-year survival was 68%% in all patients.[27]

Matched infant participants from the LAL-1-NH01 natural history study were used as a historical control group of untreated patients.[46] This historical control study included 21 untreated patients with growth failure due to rapidly progressive LAL-D.[47] In this trial, no patient survived to 12 months of age. (Section B.2.9)

Every person diagnosed with rapidly progressive LAL-D in the UK in the past 6 years has been supported with access to sebelipase alfa through the Alexion GATM programme if treatment was requested.

B.3.2.3.1. Multi-modal therapy in rapidly progressive LAL-D

The use of HSCT to treat people with rapidly progressive LAL-D was considered in the modelling of sebelipase alfa in the previous appraisal, ID737. The committee's views were described in the 2017 Final Appraisal Determination.[39] The potential of HSCT to help babies with Wolman disease avoid the lifelong need for regular infusions and increased rates of survival in babies with other conditions after HSCT was acknowledged, but the committee agreed that the effectiveness of HSCT for babies with LAL-D who had been stabilized on sebelipase alfa was unknown. However, more experience of HSCT in patients with Wolman disease has been reported in the intervening time.

The Potter et al. 2021[2] study provides an in-depth look at five of the 15 patients with Wolman disease at the Royal Manchester Children's Hospital that had at the time been treated (since 2005). These five patients were included in the multi-modal group (sebelipase alfa, dietary substrate restriction [DSR], and HSCT) having experienced a clinical deterioration due to high titre sebelipase alfa ADAs. Treatment was an increased dose of ERT and immunotherapy ahead of a subsequent HSCT. At the point when the transplant procedure took place, patients' nutritional status and liver function were better than at presentation, reducing the procedure-related mortality associated with HSCT. Post-HSCT, the four surviving patients all had noticeable improvement in their ability to tolerate normalization of enteral feeds. In three of these patients, oral intake improved, and the reliance of tube feeds decreased over time. The need for sebelipase alfa treatment (dose and/or frequency) also reduced with some patients able to cease treatment altogether.

In this economic analysis the role of HSCT in rapidly progressive LAL-D is therefore considered explicitly, both within the observed age range of current patients (using individual patient data), and in the projection of the future lives of people with this form of the disease (relying on expert clinical opinion). In the model, transition to HSCT is first implemented as an 'early' in life possibility, then as a 'later' in life possibility for those without earlier transplant. More than one HSCT was not modelled.

B.3.3. Clinical parameters and variables

B.3.3.1. Overall survival

The cost-effectiveness model consists of a survival model that traces patient mortality from three causes: the natural/background mortality of all ages, Wolman-related mortality within the first 5 years of life, and HSCT-related mortality the first 5 years post procedure. This approach follows from Vijay et al. 2021[27] and Potter et al. 2021[2] which report overall survival (OS) until 60 months. It should be noted that in both studies, no deaths had occurred in the final 3 years of follow up, which, in combination with expert clinical feedback, supports the assumption that these surviving patients can be considered as long-term survivors.[25] In line with methods described in NICE Technical Support Document 14[48], and the assumption of general population survival after 60 months, parametric survival modelling was performed to interpolate 5-year Kaplan–Meier OS data. These provide alternative transition probabilities for rapidly progressive LAL-D death beyond the direct use of Kaplan–Meier estimates in the base case.

In the base case, baseline curve parameters for each arm were sourced using patient-level data from LAL-CL03, LAL-CL08, LAL-1-NH01, and Potter et al. 2021.[2, 44-46] The OS from Potter et al. 2021 for the five HSCT-treated patients was also included, using the Kaplan–Meier figure to derive pseudo patient-level data. One HSCT-treated patient from Potter et al. 2021 was included in the LAL-CL08 study, and thus was removed from the survival analysis of sebelipase alfa-only patients and included in the HSCT survival analysis. All six standard curves were explored (exponential, Gompertz, Weibull, log-logistic, log-normal, generalized gamma), but the original Kaplan–Meier curves were used in the base case for the first 5 years (as LAL-CL03, LAL-CL08 have 60 month follow-up data), before switching to general UK population mortality thereafter.[49]

The same approach was used for the HSCT-treated patients using the Potter et al. 2021 data. Figure 22 presents the Kaplan–Meier curve alongside Table 28, which presents summary statistics for OS for patients treated with sebelipase alfa and untreated patients. **Error! Reference source not found.** presents the Kaplan–Meier curve for the patients treated with multi-modal therapy. The curve shows that patients treated with sebelipase alfa have consistently longer OS than untreated patients across the observed 60-month study period. This is reflected in the summary statistics, where patients treated with sebelipase alfa had a longer median survival time (in days) than patients who received BSC. (Median,: 93 [95% CI: 86,148]). Patients treated with multi-modal therapy displayed better OS at 60 months: 80% compared with patients treated with sebelipase alfa only, 72.22%.

Ultimately, the decision tree probabilities, described in Section B.3.2.2, determine the split of patients who follow the sebelipase alfa-only survival and those who follow the sebelipase alfa + ‘early’ HSCT survival during the first 5 years.

Figure 22: Overall survival by treatment arm

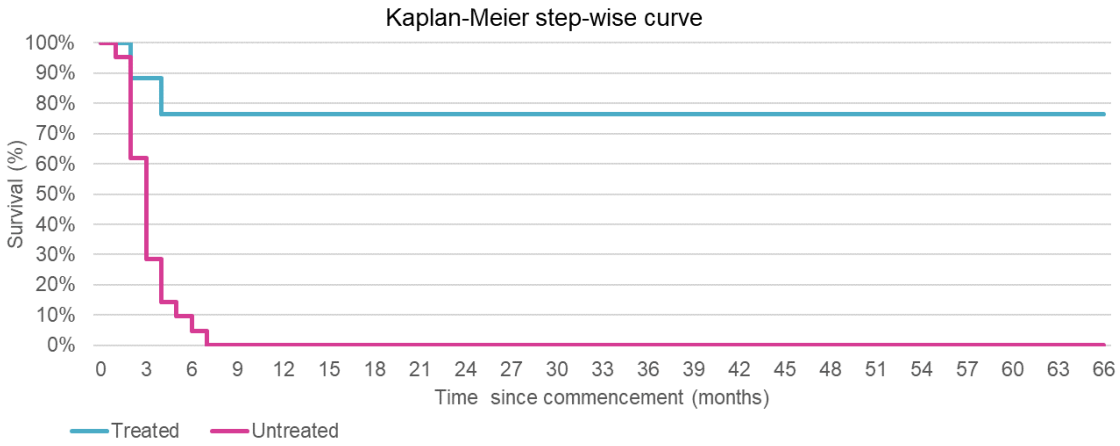


Figure 23: Overall survival of sebelipase alfa + HSCT treated patients

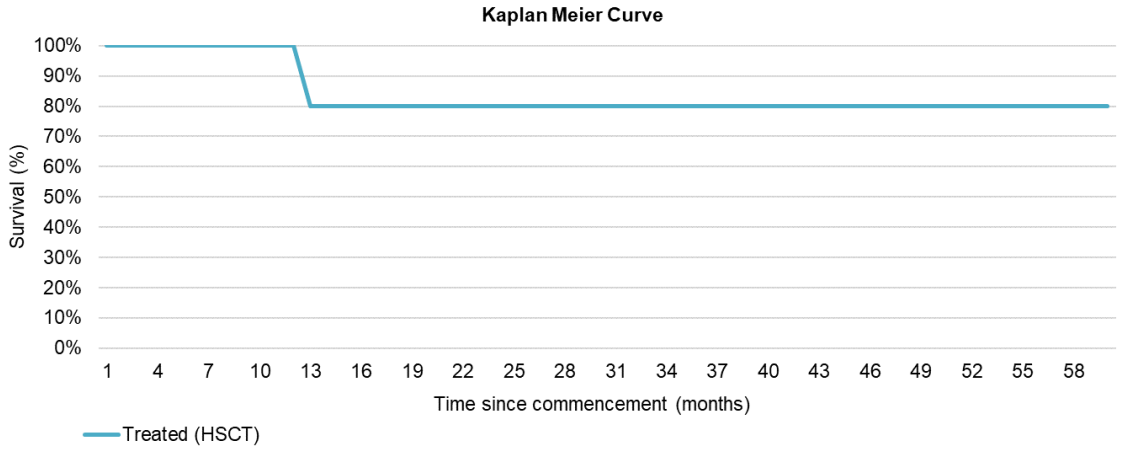


Table 28: Summary statistics for overall survival by treatment arm

Treatment	n	Events	Restricted mean (days)	Restricted mean (SE)	Median	95% CI
Best supportive care (untreated)	21	21	110.86	9.15	93	(86,148)
Sebelipase alfa (treated)	18	5	1522.50	196.68	NR	NR
Key: CI, confidence interval; NR, not reached; SE, standard error.						

Table 29: Summary statistics for overall survival of HSCT-treated patients

Treatment	n	Events	Restricted mean (days)	Restricted mean (SE)	Median	95% CI
Sebelipase alfa + HSCT	5	1	50.52	8.48	NR	NR

Key: CI, confidence interval; HSCT, haematopoietic stem cell transplant; NR, not reached; SE, standard error.

B.3.3.2. Parametric survival models

Parametric distributions were estimated using the flexsurv package in R. To model each treatment, both separate models (models fitted to each treatment arm separately) and treatment effect models (a single model fitted to both or all treatment arms, including a treatment covariate) were considered. Only treatment effect models were included in this economic analysis (under the assumption of proportional hazard). Separately fitted models were not chosen as the small sample size for each arm could result in poor-fitting extrapolations. Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used together with visual inspection to assess the model fit and plausibility. AIC and BIC data provided in Table 30 indicate the gamma distribution is the best statistical fit for the sebelipase alfa-only survival. The difference between the gamma AIC and BIC and the second-best ranked AIC and BIC (Weibull) is less than five, implying there is no meaningful difference between the first- and second-best ranking AIC and BIC. The exponential distribution, on the other hand, is the best fit for the sebelipase alfa + HSCT survival, but again the small difference compared with the second-best ranked AIC and BIC (Gompertz) implies there is no meaningful difference between the top two ranks.

Table 30: AIC and BIC of sebelipase alfa treatment

Distribution	AIC	AIC Rank	BIC	BIC Rank
Exponential	336.2	4	339.5	3
Gamma	327.6	1	334.2	1
Gompertz	335.5	3	340.5	4
Log-logistic	341.1	5	346.1	5
Log-normal	346.1	6	351.1	6
Weibull (AFT)	331.8	2	336.8	2

Key: AFT, accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: Cells are shaded according to their rank, where dark green is best fit, and red is worst fit.

Table 31: AIC and BIC of multi-modal therapy

Distribution	AIC	AIC Rank	BIC	BIC Rank
Exponential	15.1	1	14.7	1
Gamma	16.9	4	15.7	3
Gompertz	16.3	2	15.5	2
Log-logistic	16.9	5	16.1	5
Log-normal	16.7	3	15.9	4
Weibull (AFT)	17.0	6	16.2	6

Key: AFT, accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: Cells are shaded according to their rank, where dark green is best fit, and red is worst fit.

Below are the visual representations of fit when all six parametric curves have been overlaid onto the Kaplan–Meier curve. The model has been split by treatment (treated, with or without HSCT, or untreated) into three figures: Figure 24, Figure 25, and Figure 26.

Figure 24: Parametric curves and Kaplan–Meier data: untreated

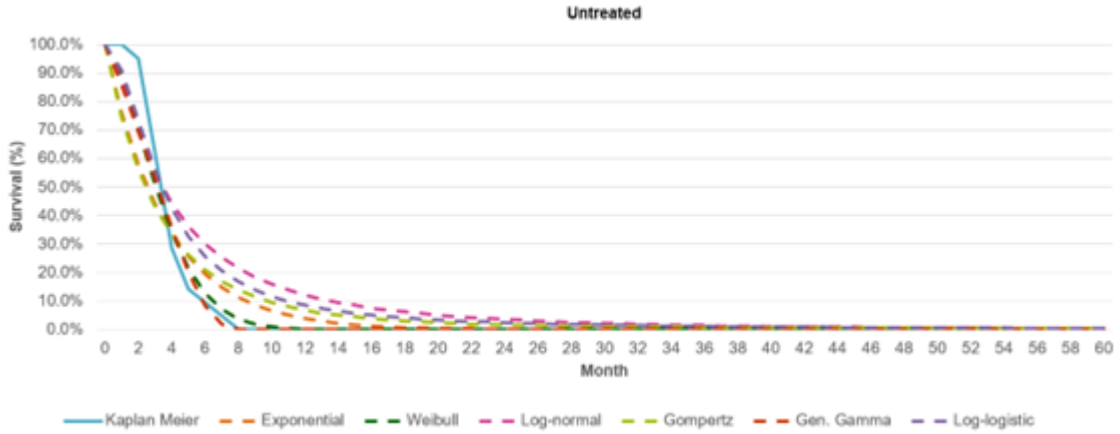
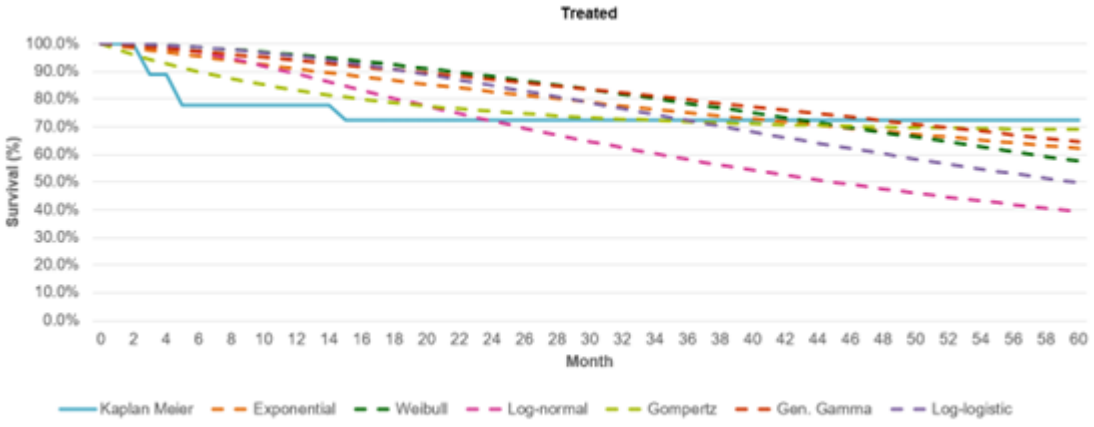
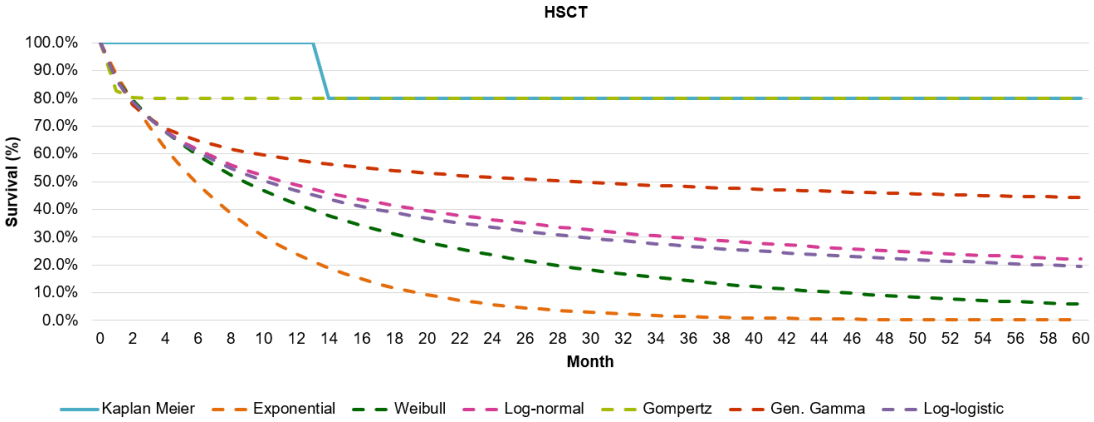


Figure 25: Parametric curves and Kaplan–Meier data: treated



Key: BSC, best supportive care.

Figure 26: Parametric curves and Kaplan–Meier data: sebelipase alfa + HSCT



Key: HSCT, Haematopoietic stem cell transplant.

Visual inspection shows that parametric fits are inconsistent across both treated and untreated arms; therefore, in the context of a 5-year interpolation, direct estimation from the Kaplan–Meier curve was preferred for the base case. However, the exponential, Weibull, Gompertz, and log-normal models were tested in deterministic sensitivity analyses.

B.3.3.3. HSCT

The first allowed transition to the HSCT health state, HS5, is permitted from the Trial follow-up health state, HS3, at 24 months post-entry (effectively 24 months of age). This is 'early in life' HSCT. Twenty-four months was the average time to event according to expert clinical opinion, with the predominant clinical rationale being loss of response. The proportion transitioning to early HSCT in the model was [redacted] of the starting cohort. This proportion is based on the clinician reported experience at the Royal Manchester Children's Hospital (RMCH), a specialist centre for diagnosis and treatment of inherited metabolic disorders including delivery of HSCT. At the RMCH there have been six HSCT cases in a total of 12 candidates on sebelipase alfa. Potter et al report the sebelipase alfa experience at RMCH but is less contemporary in respect of HSCT; excluding the most recent cases as well as a growing confidence in transplant.[2]

The second allowed transition to the HSCT health state is permitted from the Stable [disease] health state, HS4. This is 'later in life' HSCT. Those allowed to transition are characterized as those without prior HSCT who are expected to require

transplant as a means of rescue intervention ahead of imminent venous access failure or those self-determining away from ERT due to administration burden.

No person with rapidly progressive LAL-D has yet survived to adulthood so the long-term viability of venous access cannot be directly informed by trial or real-world evidence. However, discussions with a clinical expert experienced in treating liposomal storage disorders with long term ERT suggested that it is reasonable to expect a point in these patients' lives when maintaining venous access could become an issue. Long-term weekly therapy to age 30 would require more than 1,500 infusions. Diminishing venous access would impact on their ability to receive treatment and result in the need for rescue HSCT, followed by stopping treatment. Loss of venous access in paediatric patients requiring long-term venous access for treatment has been acknowledged in other conditions, such as short-bowel syndrome SBS (NICE TA804, Teduglutide)[21]. Avalglucosidase alfa, indicated for long-term ERT for the treatment of patients with infantile-onset Pompe disease, is analogous insofar as IV treatment is commenced in an infant population, but administration frequency is QOW and therefore half as frequent. Similarly, the prevalent age of patients on treatment remains too young to draw conclusions. The issue of loss of venous access was not included in NICE TA821, avalglusosidase alfa for treating people with Pompe.[22]

It was assumed in the base case that loss of venous access sufficient to prompt HSCT would occur at a mean age of 30 years. However, given the lack of evidence to support this assumption, and the acknowledged uncertainty in this area, scenarios exploring 20 and 40 years are also presented.

Table 32: Probability and timing of HSCT

HSCT event	Age	Probability conditional on being alive	Source
Early	24 months	[redacted]	Manchester Women and Children's hospital case audit and clinical expert opinion
Late	30 years	[redacted]	Clinical expert opinion
Key: HSCT, haematopoietic stem cell transplant.			

B.3.3.4. Dosing

Dose requirement was modelled as a distribution of alternative doses and frequencies applied within the decision tree to phases of treatment following pre-specified treatment milestones. Dose and frequency were initially informed by CL-03 and CL-08, then by expert clinical opinion (Table 33).[27]

Table 33: Treatment milestone and dose distribution

Treatment milestone	Dosing levels	Dose	Proportion of patients	Source/note
Treatment initiation	L1	3 mg/kg QW	100%	Expert clinical opinion
1st dose increase, following initial exploratory dose	L2	3 mg/kg QW	50%	
		5 mg/kg QW	50%	
2nd dose increase and initiation of immunomodulators and HSCT (multi-modal treatment)	L3	5 mg/kg QW	100%	
Dose decrease post early HSCT	L4	3 mg/kg QW	100%	
Dose decrease with adulthood post early HSCT	L5	1 mg/kg QW	50%	
		3 mg/kg QW	50%	
Dose decrease with adulthood (without early HSCT)	L6	3 mg/kg QW	50%	
		5 mg/kg QW	50%	
Key: BIW, twice weekly; HSCT, haematopoietic stem cell transplant; kg, kilogram; mg, milligram; QW, once weekly; Q2W, once every 2 weeks.				

Table 34: Treatment phases

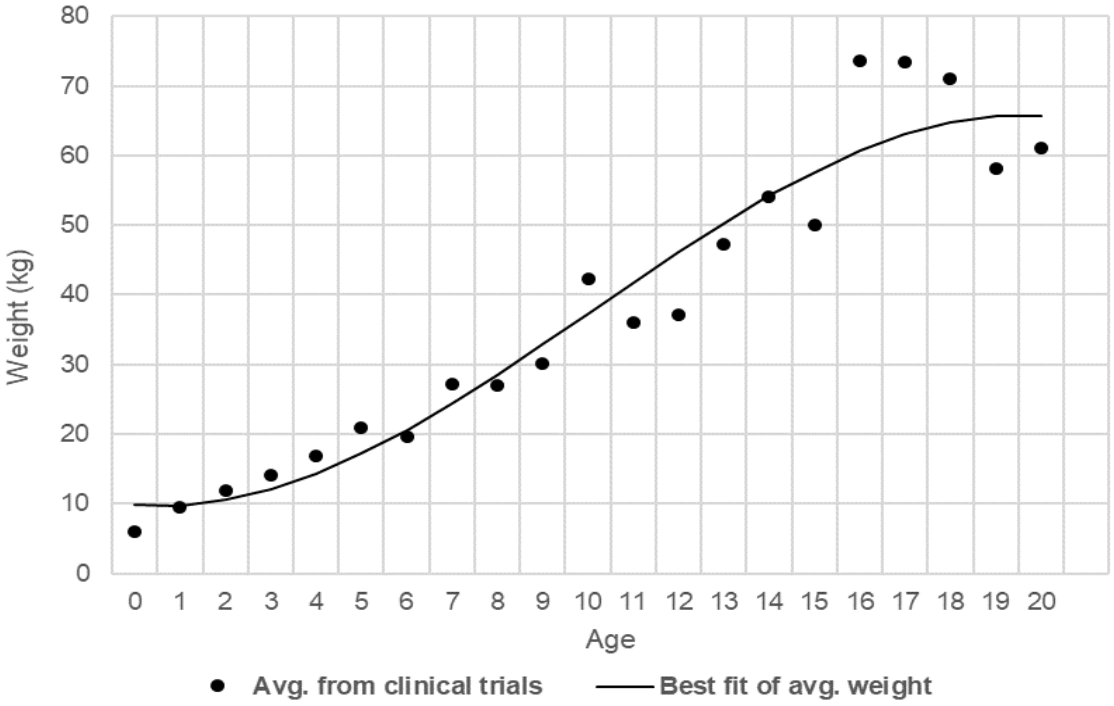
Sequential treatment phase [bounding milestones/nodes]		Length of phase	Source
I	Initial [Initiation to first increase]	Age 0–3 months	Vijay et al. 2021. Table 4.
II	Stable [First increase to second increase]	Age 3–9 months	Clinical expert interview
III	Multi-modal reduction [Second increase, early HSCT reduction]	Age 9–30 months	
IV	Discontinue [Reduction to stop]	Age 30–42 months	
V	To adult [Stop to adult]	Age 42 months to 18 years	
VI	Adult adjusted [Adult to loss of venous access]	Age 18 to 30	

Key: HSCT, haematopoietic stem cell transplant; IM, immuno-modulator therapy.
Notes: Phases may not be sequential. Sebelipase alfa dose is unchanged between phases C1 and C2, but C1 includes adjunct therapy.

B.3.3.5. Patient weight

As sebelipase alfa is a weight-based treatment, patient bodyweights are needed to estimate the drug cost for each age. It is assumed that patients' bodyweight follows the weight-for-age trajectory of the average weight for each age observed in the LAL-CL03[44] and LAL-CL08[45] trials (0–20 years). Because patients of all ages were not observed in the trials, and some age groups had very few patients, a polynomial (of degree 3) best-fit line was estimated as the average weight-for-age trajectory, shown in Figure 27 and Table 35. This best-fit line smooths out any outliers and ensures that patient weight data passes a visual inspection, with the assumption that within the first 20 years, patient weight will increase with age. As trial data is sparse for patients above the age of 20, the UK general population weight norms are used as benchmark values.[50]

Figure 27: Regression-predicted weights by age



Key: Avg., average; kg, kilograms.

Table 35 Regression-predicted wights by age

Age	Regression-predicted - average weight	Trial-average weight
0	9.9	6.0
1	9.8	9.5
2	10.5	11.9
3	12.1	14.2
4	14.3	16.9
5	17.2	20.9
6	20.6	19.7
7	24.4	27.1
8	28.6	26.9
9	32.9	30.2
10	37.3	42.3
11	41.8	36.1
12	46.1	37.2
13	50.3	47.3

14	54.2	54.2
15	57.7	50.1
16	60.6	73.6
17	63.0	73.5
18	64.8	71.1
19	65.7	58.1
20	65.7	61.0

The UK general population records average weight by age band (e.g., 13–15 years, 16–24 years). The percent difference between the average weight for the UK general population and the average weight for patients with LAL-D (non-rapidly progressing) is estimated for the age band with the last complete trial data available: age 13–15 years. The average weight for the UK general population aged 13–15 is 59.7 kg while the trial average for patients in the same age band is 50.5 kg, resulting in a percent difference of 18.20%. This percent difference is applied to the subsequent age bands provided by the UK general population weights to estimate a projection of patient weight, as shown in Table 36. The regression-predicted weights for ages 0–20 years and the projected patient weight based on the percent difference between the UK general population and LAL-D trial patients is used to determine dosing for each age band.

Table 36: Projection of patient weight based on percent difference from 13–15 age group

Age band	Predicted weight for people with rapidly progressive LAL-D (kg)
25–34 years	65.0
35–44 years	66.2
45–54 years	67.6
55–64 years	66.5
65–74 years	65.4
75+ years	60.5
Key: kg, kilogram.	

A method-of-moments approach is included as an alternative approach to calculate an average number of sebelipase alfa vials (20 mg) received for each age under 20 years and for each age band above 20, considering the weight-specific, and

therefore age-specific, dosing described above. This approach assumes a log-normal distribution for weight and calculates the proportion of patients distributed across increasing doses and number of vials. Standard deviation (SD), used to determine the spread of patients across this distribution, is assumed equal to the SD of the general UK population's weight. A proportional SD was calculated using the pooled survey data (for all children and adults) and is applied to the average patient weight by age.[50] The total acquisition cost per sebelipase alfa dose for each age and age band is derived by multiplying the vial price by the number of vials needed for each dose.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related-quality-of-life data from clinical trials

The included clinical trials of babies with Wolman disease (CL-03 and CL-08) did not collect or report HRQL data; no measures of HRQL are available for patients aged under 2 years. However, LAL-D in older patients is known to have a detrimental impact on their life, their family members' lives, and those involved in their care. Patients that participated in a European LAL-D patient/carer survey (EU LAL-D Survey) frequently reported having abdominal pain, fatigue, diarrhoea, nausea, loss of appetite, itchy skin and a swollen abdomen, and reported that these symptoms could be very burdensome and have a considerable negative effect on their lives. A low quality of life was consistently reported, and the mean utility score among children with LAL-D was 0.76 (n = 8); the mean score for adults was 0.34 (n = 2), suggesting a severely reduced quality of life. Affected infants with rapidly progressing disease require long-term hospitalization and often die before the age of 6 months after experiencing diarrhoea, vomiting, anaemia, thrombocytopenia (which may require transfusion support), and failure to thrive.[51, 52] The impact on the quality of life of the patients and parents and caregivers of these infants would be expected to be significant.

B.3.4.2. Mapping

Not applicable, no mapping was used.

B.3.4.3. Health-related quality-of-life studies

The SLR of HRQL studies conducted in 2015 for the NICE HST ID 737 revealed that infant patient health utilities did not exist in the public domain; however in the recently updated systematic search of Embase®, MEDLINE In-Process®, Cochrane Library, EconLit and CRD York, conducted on 26 June 2022, we identified one study for inclusion. Demaret et al. 2021 is a retrospective cohort study in patients with Wolman disease.[31] A total of 140 records were identified from the database search. Of these, 138 records were excluded at the primary screening stage as they were not relevant to the search question due to the following reasons: review/editorial publication type (n = 22), disease (n = 26), and study design (n = 90). The remaining two reports were assessed for eligibility, with one identified for review and subsequently included. Additionally, no reports were identified from health technology assessment (HTA) searches/conference searches/bibliographies. The search strategies conducted across the databases are presented in Appendix H.

Demaret et al. 2021 reported a French nationwide retrospective study of sebelipase alfa in five patients with Wolman disease, with a median follow-up of 7 years.[31] HRQL was evaluated by the Pediatric Quality of Life Inventory questionnaire (PedsQL 4.0).[53] It is composed of generic core scales and disease-specific modules designed to measure the core dimensions of health, as delineated by the WHO, as well as role (school) functioning in healthy children and those with acute or chronic health conditions. The PedsQL Generic Core Scales includes four multidimensional scales of physical functioning (eight items), emotional functioning (five items), social functioning (five items) and school functioning (five items). On the questionnaire, the item scores range from 0 (better) to 4 (poorer). For analysis purposes, the scores are converted to a scale from 0 (poorer = 4) to 100 (better = 0). The questionnaire assessed HRQL of the patients at last follow-up. Both parents and patients (when applicable) reported acceptable or high HRQL globally and in all 4-dimensional scales (Table 37). Cognitive development was normal, and no patient had special education needs. The authors conclude that ‘sebelipase alfa allowed 100% survival of five patients with Wolman disease with near-normal bio-clinical and growth parameters follow-up, up to 10 years.’

Table 37: PedsQL scores

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at last follow-up (months)	10y, 0m	5y, 11m	3y, 1m	6y, 0m	1y,4m
Patient evaluation	71	61	n/a	80	n/a
Physical functioning (8 items)	75	56	n/a	88	n/a
Emotional functioning (5 items)	60	60	n/a	960	n/a
Social functioning (5 items)	70	70	n/a	70	n/a
School functioning (3 or 5 items)	75	60	n/a	70	n/a
Parental evaluation	82	51	85	85	100
Physical functioning (8 items)	75	47	84	91	100
Emotional functioning (5 items)	80	75	70	80	100
Social functioning (5 items)	85	45	100	100	100
School functioning (3 or 5 items)	90	40	n/a	65	n/a
Key: y, years; m, months.					

B.3.4.4. Adverse reactions

AEs are understood to have a temporary impact on HRQL and are typically resolved by infusion adjustments and treatment. The safety and tolerability profile of sebelipase alfa is favourable. The most commonly reported types of AEs were gastrointestinal disturbances, headache, pyrexia/body temperature increases, and upper respiratory signs and symptoms. The majority of TEAEs were non-serious, mild or moderate in severity, and reported as unrelated to treatment with sebelipase alfa. To date, there does not appear to be any apparent cumulative toxicity based on review of TEAE incidence over time on treatment. Further details of the AEs experienced by patients receiving sebelipase alfa are found in section B.2.10. The impact of adverse reactions on HRQL was not therefore explicitly included; however, the emergence of ADAs in response to sebelipase alfa is implicitly considered with the inclusion of HSCT in the model, and provision is made within resourcing for inpatient admissions due to complications of disease.

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.5.1. Utilities used in the model

Based on the limited evidence from Demaret et al. in which there is evidence for near-normal development and HRQL, and in the absence of stronger evidence, it

was assumed the utility of both treated and untreated patients could be derived using UK general population norms.[31] To reflect the age-related varying quality of life for the general population, the model considers the age-adjusted utility norms outlined by Hernandez et al. in the recent NICE DSU report. Hernandez et al. provides both age-specific and sex-specific utilities, using EQ-5D-3L.[54] These utilities begin at age 16 so the model therefore assumes that general utility for those aged 16 applies for all patients under age 16. An alternative scenario is explored in which a hazard ratio of 0.8 is applied to the utility through the time horizon.

Table 38: Utilities used in the model by 5-year increment

Age (years)	Gender weighted utility
0	0.929
5	0.929
10	0.929
15	0.929
20	0.927
25	0.922
30	0.915
35	0.906
40	0.896
45	0.884
50	0.870
55	0.855
60	0.838
65	0.820
70	0.800
75	0.779
80	0.755
85	0.730
90	0.704
95	0.675
100	0.646

B.3.4.5.1.1. Utility decrements

Parenteral nutrition

The model considers utility values related to the number of cumulative days of parenteral nutrition received, based on the Ballinger et al. study that estimated

parenteral nutrition utility for patients with short bowel syndrome.[55] According to expert clinical opinion, patients receive parenteral nutrition for the duration of their initial hospitalization, post-diagnosis, which in the base case is 3.22 months or 98 days.[25] The model thus applies the most severe utility value assigned to patients with short bowel syndrome (0.26), for those who received 7 cumulative days per week of parenteral nutrition.

HSCT

No utility decrement is applied for HSCT in the base case. In a scenario analysis, a 0.57 utility decrement for HSCT follow-up is applied for a period of 3 months around the HSCT procedure, and a 0.13 decrement is applied for a further 9 months. The decrements and their duration are based on the preferred approach of the Evidence Review Group of NICE TA554 for tisagenlecleucel for HSCT when treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years.[56]

Bereavement

The base case does not include consideration for the spill-over effect of infant death on caregivers/family members, as no precedent for bereavement was identified amongst NICE technology appraisals. In a scenario analysis, the model includes a 0.04 decrement for family bereavement for a period of 65 years. This value and duration is based on the Song et al. publication which examined the long-term effects of child death on bereaved parents' HRQL.[20] This publication was also cited in the NICE HST committee paper (HST7), on Strimvelis® for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID), where caregiver QALY loss was also considered in a scenario analysis.[57]

Table 39: Utility decrements

Health state applied	Utility description	Utility value	Decrement duration	Source
HS1 Base case	Parenteral nutrition utility (7 days per week)	0.26 (absolute)	3.22 months (duration of initial hospitalization period)	Ballinger et al. 2018[55] Duration is informed by expert clinical opinion[25]
HS5 Scenario	HSCT decrement	Procedure 0.57 Recovery 0.13 (decrement)	3 months and 9 months, respectively	ERG report in TA554 committee papers. [56]
Decrement per patient death (Scenario)	Monthly family grieving decrement per parent/carer	0.04 per caregiver (decrement)	65 years; 2 caregivers	Song et al. 2010[20]]
Key: HS1-5, Health state 1-5; HSCT haematopoietic stem cell transplant.				

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

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1.1. Intervention

Sebelipase alfa is provided by Alexion Pharma UK Ltd. A single pack/unit contains one 20 mg vial (Table 40). Dosing is presented in section B.3.3. The SmPC discusses dose adjustments that have been evaluated in clinical studies, ranging from 0.35 mg to 5 mg/kg weekly infusions.

Table 40: Pack price of sebelipase alfa

Treatment	Pack size	Pack cost	RDI
Sebelipase alfa ERT	20 mg (1 unit)	£6,286.00 [redacted]	100%
Key: ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; kg, kilogram; mg, milligram; RDI, relative dose intensity.			

B.3.5.1.1.2. Administration

Sebelipase alfa is administered via IV infusion. The total volume of the infusion should be administered by a trained healthcare professional who can manage medical emergencies over approximately 2 hours. A 1-hour infusion may be considered after patient tolerability has been established.[1]

It is assumed that the cost of sebelipase alfa administration in the outpatient setting is equal to the cost of a visit to the paediatric metabolic disease specialist. The unit cost was sourced from the National Schedule of NHS Costs 2020–2022[58] (average £565.60) then inflated to the 2022 cost year, £577.29, using the Consumer Price Index with Housing (CPIH) 06: Health 2015 = 100 (Multiplier 1.02).[59]

Weekly vial requirement was calculated strictly according to the mg requirement of the QW dosing schedule. Irrespective of the proportion of a vial wasted the cost of a whole vial was included. Vials are for single use only. However, real-world practice is to modulate dose within a two-week cycle in order to reduce waste and the vial requirement. A scenario analysis explores the impact of this off-label but real-world approach. In either case, drug acquisition costs were implemented as a 1-month cycle cost.

At four months, after discharge from the initial hospital admission, a homecare service is funded by Alexion for the administration of sebelipase alfa, removing the cost to the payer/NHS. Before outpatient care begins, a cost of administration is applied with each in-hospital administration.

B.3.5.1.1.3. Comparator

BSC is defined as established clinical practice without sebelipase alfa. No drug costs were included except standard interventions included within the intensive care HRGs, applied during initial hospitalization and hospitalisation prior to LAL-D death (applicable to both strategies)

B.3.5.2. Health state unit costs and resource use

Health state 1: Investigation

The monthly cycle cost of initial care and investigation was based on the average duration spent in sequential hospital settings from birth. Unit costs were sourced

from the most recent publication of national NHS costs inflated to the analysis cost year (Table 41).[58, 59] The expected average time in each setting was elicited from expert opinion (Table 42).[25] The resultant weighted cost of investigative care per cycle was £37,396.04. Added to this is an additional monthly cycle cost for specialist hospital parenteral nutrition of £6,333.33, based on an annual estimates of £68,000 for specialist nutritional products and £8,000 in dietetic and feed preparation costs.[ref]

Table 41: Unit cost of neonatal critical care

Resource	HRG currency code	Unit cost, 2020/21	Unit cost, 2022
Neonatal Critical Care, Intensive Care [ICU day]	XA01Z	£1,816.33	£1,853.86
Neonatal Critical Care, High Dependency [HDU day]	XA02Z	£1,243.00	£1,268.68
Neonatal Critical Care, Normal Care [General ward day]	XA05Z	£769.19	£785.08
Key: ICU, intensive care unit; NHS, National Health Service. **Notes:** Sourced from the National Schedule of NHS Costs 2020/21. The 2022 unit cost is an inflation from the source cost using the CPIH Index 06: Health 2015 = 100 (Multiplier 1.02).[59]			

Table 42: Duration of neonatal critical care

Resource	Duration (weeks)	Source
Neonatal Critical Care, Intensive Care [ICU day]	4	Clinical expert opinion
Neonatal Critical Care, High Dependency [HDU day]	4	
Neonatal Critical Care, Normal Care [General ward day]	6	
Key: ICU, intensive care unit; NHS, National Health Service.		

Health state 2: Rescue care

Neonatal intensive care was consumed for a single monthly cycle prior to Wolman-related death, effectively representing the cost of end-of-life care. £1,853.86 was multiplied by 30.44 days for a cycle cost of £56,426.74.

Health state 3: Trial follow-up

Resource consumption in this health state was age-dependent. Ages 0–1, 1–2, 2–3 and 3–5 consumed different levels of physician and dietetic monitoring, blood tests,

magnetic resonance imaging (MRI), ultrasound, and neonatal critical care (Table 43). The type of resources and their rate of consumption was based on expert clinical opinion.[25]

Table 43: Rate of resource consumption in the first 5 years

Resource per cycle	Proportion	Age 0–1	Age 1–2	Age 2–3	Age 3–5
Paediatric metabolic physician monitoring	1	0[a]	0[a]	0.29	0.29
Dietician visits	1	2	1	1	1
Lab tests	1	0.33	0.33	0.33	0.33
Abdominal MRI	0.5	0.08	0.08	0.08	0.08
Abdominal ultrasound	0.5	0.08	0.08	0.08	0.08
Admission (5 days)	1	0.17	0.17	0.17	0

Key: MRI, magnetic resonance imaging.
Note: [a], Metabolic monitoring is part of SA administration in the first 2 years, so is not applied again here.
Source: Clinical expert opinion.[25]

Metabolic monitoring is part of sebelipase alfa administration in the first 2 years, so it was not applied again to avoid double counting. Laboratory tests were a weighted average of haematology and clinical biochemistry, £3.15. MRI was a weighted average cost including MRI with contrast under 5 years, MRI of two or three areas without contrast, and MRI requiring extensive patient repositioning, £229.85. Ultrasound was the weighted average cost of ultrasound under 20 minutes with and without contrast, £72.89. Inpatient admissions, resulting from AEs, were included for the first 3 years, total cost of stay, £3,925.42.

Table 44: Unit cost of monitoring resource in the first 5 years

Resource type	Procedure	Currency code[a]	Currency description	Unit reference cost in 2022 GBP[b]
Laboratory tests	Blood test	DAPS05	Haematology	£3.71
	Biochemistry	DAPS04	Clinical biochemistry	£1.89
Radiological tests	Abdominal MRI	RD01A	Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	£251.53
		RD01B	Magnetic Resonance Imaging Scan of One Area, without Contrast, between 6 and 18 years	£273.20
		RD01C	Magnetic Resonance Imaging Scan of One Area, without Contrast, 5 years and under	£281.30
		RD04Z	Magnetic Resonance Imaging Scan of Two or Three Areas, without Contrast	£225.65
		RD07Z	Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning	£319.75
	Abdominal ultrasound	RD40Z	Ultrasound Scan with duration of less than 20 minutes, without Contrast	£70.94
		RD50Z	Ultrasound Scan with duration of less than 20 minutes, with Contrast	£133.89
Admission	General ward	XA05Z	Neonatal critical care, Normal care	£785.08

Key: MRI, magnetic resonance imaging; GBP, British pound sterling.
Note: [a], Where there are multiple currency codes per procedure, overall cost input is calculated as an average of the unit reference costs. [b], All costs were sourced from NHS 2020-2021 reference costs[58] and inflated to 2022 GPB using the CPIH index.[59]

Health state 4: Stable

Resource consumption did not differ in rate after age 5 (Table 45).

Table 45: Rate of resource consumption after the first 5 years

Resource per cycle	Proportion	Age 5+
Paediatric metabolic physician monitoring	1	0.29
Dietician visits	1	1
Lab tests	1	0.17
Abdominal MRI	0.5	0.08
Abdominal ultrasound	0.5	0.08
Key: MRI, magnetic resonance imaging. **Source:** Clinical expert opinion.[25]		

Resource costs only differed by age in respect to the weighted blend of MRI before and after age 19, £241.53 versus £248.9, because MRI with contrast decreases slightly (though becomes much greater in weight). Other resource costs were unchanged from HS3, but the rate of consumption decreased.

Health state 5: HSCT

The consumption of healthcare professional time, laboratory and radiological tests continued uniformly regardless of transplant, but a period of intense resourcing was transiently included. This comprised two periods of 2-month courses of immunomodulator therapy for all planned recipients, followed by the allogeneic HSCT.

The first course of immunomodulation (£11,658.75) comprised 2 weeks in 21 days of bortezomib (1.3 mg/m^2 twice weekly [BIW]) for half of recipients (total £107.12) and 4 weeks of rituximab (375 mg/m^2 QW) for the remaining half of patients (total £11,551.63). The second course (£214.24) comprised only bortezomib, as two cycles of 2 weeks in 21 days (1.3 mg/m^2 BIW) for half of recipients.

The costing of HSCT is based on TA554 for tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years.[56] TA554 splits cost inputs into stem cell harvesting, procedure, and follow-up costs for both autologous and allogeneic transplants (Table 46 and Table 47). As Potter et al. 2021 describes stem cell transplants for patients with LAL-D as allogeneic, only those relevant currency codes are considered.[2] Follow-up costs are applied for 24 months and are gathered from UK Stem Cell Strategy Oversight Committee report[60] from November 2014 and inflated to 2022 GBP using the CPIH.[59] The report divides

costs into 6-month intervals and the same approach was applied in the model as shown in Table 47.

The weighted average cost of stem cell harvesting was £7,240.29; the weighted average cost of the HSCT procedure was £84,004,64; and the total follow-up costs were £47,877.96. Together, the total per person cost of allogeneic HSCT was £139,123.20. This unitary cost was applied for both early and late transplants.

Table 46: HSCT procedure costs

Currency code	Currency description	Unit reference cost in 2022 GPB
SA18Z	Bone Marrow Harvest	£4,873.06
SA20B	Bone Marrow Transplant, Allogeneic Graft (Sibling), 18 years and under	£91,480.21
SA21B	Bone Marrow Transplant, Allogeneic Graft (Volunteer Unrelated Donor), 18 years and under	£114,257.61
SA22B	Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 18 years and under	£145,000.82
SA23B	Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under	£60,069.75
SA34Z	Peripheral Blood Stem Cell Harvest	£7,700.72
SA38B	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 18 years and under	£78,804.18
SA39B	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 18 years and under	£103,570.10
SA40Z	Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified)	£64,231.45

Key: GBP, British pound sterling; HSCT, haematopoietic stem cell transplant.
Notes: All costs were sourced from NHS 2020–2021 reference costs[58] and inflated to 2022 GPB using the CPIH.[59]

Table 47: HSCT follow-up costs

Duration	Unit reference cost in 2022 GPB[a]
0–6 months	£31,147.80
6–12 months	£11,411.47
12–24 months	£5,318.69
Total follow-up cost	£47,877.96

Key: GBP, British pound sterling; HSCT, haematopoietic stem cell transplant.
Notes: [a], The UK Stem Cell Strategy Oversight Committee report estimates costs in 2012/2013 GPB so these costs have been calculated in 2022 GBP using the CPIH index.[59]

Specialist nutrition

People with rapidly progressive LAL-D require dietary restriction, even with ERT. A specially modulated formula is prepared by the dietetic service according to the protein, carbohydrate, fat, electrolyte, vitamin, and mineral needs of the patient. This may be consumed orally, parentally, by nasogastric tube (NGT) or gastrostomy (PEG). The model conservatively applies the product cost of specialist modular nutrition for life, irrespective of HSCT and any consequent discontinuation of ERT.

The cost of modular nutrition when parentally administered was advised by Birmingham Women's and Children's NHS Foundation Trust dietetic service as £43.45 per day. The cost of modular nutrition when delivered by NGT or PEG was based on an audit the same service which estimate the annual cost of modular nutrition products to be £10,000 in the first year; £13,000 in years two and three; and £16,000 in years four and five. Dietetic and feed preparation costs were also provided, estimated as £5,500 in the first year, £1,000 in the second year, and £500 in years three to five. Per day costs were applied as presented in Table 48.

Table 48 Cost of specialist nutrition

Route and period	Unit cost per day	Proportion requiring	Duration
Parenteral IV infusion	£43.45	100%	3.22 months
NGT/PEG			
First year	£42.44	100%	60 months
Second year	£38.33	100%	
Subsequent years	£45.17	100%	
Oral	£43.81		Life

Key: GBP, British pound sterling; HSCT, haematopoietic stem cell transplant.
Notes: [a], The UK Stem Cell Strategy Oversight Committee report estimates costs in 2012/2013 GPB so these costs have been calculated in 2022 GBP using the CPIH index.[59]

Summary of health state costs

The per-cycle health state occupancy cost for the respective health states are summarized in Table 49.

Table 49: Summary of health state costs

Health state	Per cycle cost
Investigation	£43,719
Rescue care	£56,427
Trial follow-up	Age 0–1, £828 Age 1–2, £748 Age 2–3, £913 Age 3–5, £259
Stable	Age 6–18, £259 Age 19+, £259
HSCT	Age 6–18, £259 Age 19+, £259 HSCT, one-off, £139,123.20
Key: HSCT, haematopoietic stem cell transplant.	

B.3.5.3. Home administration

Sebelipase alfa is the established option in the NHS for the treatment of rapidly progressive LAL-D in England, by means of the Alexion GATM programme. Homecare administration arrangements included as part of this programme will continue. Reimbursement of sebelipase alfa is not expected to have any impact on the way current services are organized or delivered.

B.3.5.4. Economic productivity

The impact of sebelipase alfa treatment on the economic productivity of caregivers and patients are assessed using the human capital approach. I.e., approximated by the value of an average individual's future earnings. For each strategy, the patient lifetime earnings consequent to survival was measured against caregiver loss of earnings to patient age 18. Net patient-caregiver earning in the BSC strategy was deducted from the net patient-caregiver earning in the sebelipase alfa strategy. It was assumed that UK parental leave regulations allow paid parental leave for all of the first year. This means that the BSC strategy is effectively unencumbered by productivity loss. The overall productivity output is represented as a productivity gain, which is deducted from the total costs in the sebelipase alfa strategy. Productivity is modelled as a function of patient and caregiver age. Patients are not economically productive until age 18, and both patient and caregiver retire age 65. It is assumed that one caregiving parent is impacted by the on-treatment patient, prior the patient

reaching 18 years old. The mean age of the impacted caregiving parent is considered so that only remaining years of parent economic productivity are included. Parent and child future annual earnings are equal except for annual wage inflation. Input values are presented in Table 50.

Table 50 Economic productivity scenario

Parameter	Value	Source
Average weekly earnings (UK 2020)	£600	ONS[61]
Unemployment rate	4.5%	ONS[62]
Year on year rate of salary growth	4.1%	ONS[62]
Working opportunity taken		
Parent, child aged 0 -1	0%	Assumption
Parent, child aged 2 - 5	50%	
Parent, child aged 6 – 12	50%	
Parent, child aged 13 -17	90%	
Parent, child aged 18 – 65	100%	
Patient from age 18	90%	
Key: ONS, Office for National Statistics.		

B.3.6. Uncertainty

There are significant sources of uncertainty in the modelling of the cost-effectiveness of sebelipase alfa for people with rapidly progressive LAL-D disease. Firstly, rapidly progressive LAL-D is an ultra-rare condition (incidence 1:350,000)[13], so inevitably small sample sizes reduce the certainty in statistical projections to whole population size. Secondly, sebelipase alfa is assumed to extend life significantly beyond currently observed on-treatment ages in the rapidly progressive form of the disease. Thirdly, contemporary survival data for untreated patients is not available given the long-standing provision of ethical access to ERT by Alexion. Finally, time-on-treatment is truncated by assumptions around HSCT that are based on a fast evolving clinical environment (in particular the intent to transplant in early in life), as well as projections about venous access and administration that are not well based in evidence. By necessity, some important parameters rely on the best judgement of clinical experts experienced in LAL-D and similar metabolic disorders.

B.3.7. Managed access proposal

No proposal is planned.

B.3.8. Summary of base case analysis inputs and assumptions

B.3.8.1. Summary of base case analysis inputs

The parameters used in the economic model are presented in Table 51.

Table 51: Summary of variables applied in the economic model

Variables used in the base case	Value	Confidence interval (distribution if included in PSA)	Reference to section in submission
Age at baseline	0	-	B.3.2.2.1
Proportion male	0.526	-	B.3.2.3
Gen pop utility norm for age range 0–17	0.965	0.950 to 0.977	B.3.4.5
Gen pop utility norm for age range 18–24	0.929	0.899 to 0.95	
Gen pop utility norm for age range 25–34	0.919	0.888 to 0.945	
Gen pop utility norm for age range 35–44	0.893	0.851 to 0.929	
Gen pop utility norm for age range 45–54	0.855	0.798 to 0.904	
Gen pop utility norm for age range 55–64	0.810	0.739 to 0.872	
Gen pop utility norm for age range 65–74	0.773	0.706 to 0.834	
Gen pop utility norm for age range 75+	0.703	0.634 to 0.767	
Utility decrement for 7 days per week on parenteral nutrition	0.260	0.017 to 0.677 (beta)	
Duration of parenteral nutrition (days)	98.000	136.42 to 59.58 (normal)	B.3.5.2
Patient weight in kg at age 0 years	9.92	6.03 to 13.81	B.3.3
Patient weight in kg at age 1 years	9.76	5.93 to 13.59	
Patient weight in kg at age 2 years	10.51	6.39 to 14.63	
Patient weight in kg at age 3 years	12.07	7.34 to 16.81	
Patient weight in kg at age 4 years	14.35	8.72 to 19.97	
Patient weight in kg at age 5 years	17.23	10.48 to 23.99	
Patient weight in kg at age 6 years	20.63	12.54 to 28.72	
Patient weight in kg at age 7 years	24.44	14.86 to 34.02	
Patient weight in kg at age 8 years	28.56	17.36 to 39.75	
Patient weight in kg at age 9 years	32.88	19.99 to 45.77	
Patient weight in kg at age 10 years	37.32	22.69 to 51.95	
Patient weight in kg at age 11 years	41.77	25.40 to 58.14	

Variables used in the base case	Value	Confidence interval (distribution if included in PSA)	Reference to section in submission
Patient weight in kg at age 12 years	46.13	28.05 to 64.21	
Patient weight in kg at age 13 years	50.29	30.58 to 70.01	
Patient weight in kg at age 14 years	54.17	32.93 to 75.40	
Patient weight in kg at age 15 years	57.65	35.05 to 80.25	
Patient weight in kg at age 16 years	60.65	36.87 to 84.42)	
Patient weight in kg at age 17 years	63.05	38.33 to 87.76	
Patient weight in kg at age 18 years	64.76	39.37 to 90.14	
Patient weight in kg at age 19 years	65.67	39.93 to 91.41	
Patient weight in kg at age 20 years	65.70	39.94 to 91.45	
Patient weight in kg at age 21+ years	65.02	39.53 to 90.51	
Cost per day of initial hospitalization: ICU	1816	1175 to 2594 (gamma)	B.3.5.2
Cost per day of initial hospitalization: HDU	1243	804 to 1775 (gamma)	
Cost per day of initial hospitalization: General ward	769	498 to 1099 (gamma)	
Cost per day of intensive care	1816	1175 to 2594 (gamma)	
Cost per visit of paediatric metabolic disease physician	566	366 to 808 (gamma)	
Cost per visit of dietician	79	51 to 112 (gamma)	
Cost per day of parenteral nutrition	43.45	4099 to 9047 (gamma)	
Cost per day of nasogastric feeding, year 1	42.44	27.46 to 60.62 (gamma)	
Cost per day of nasogastric feeding, year 2	38.33	24.81 to 54.75 (gamma)	
Cost per day of nasogastric feeding, year 3 onwards	45.17	29.23 to 64.52 (gamma)	
Cost per day of oral nutrition	43.81	28.35 to 62.58 (gamma)	
Cost of HSCT	139123	90033 to 198724 (gamma)	
Cost of Bone Marrow Transplant, Allogeneic Graft (Sibling), 18 years and under	89628	58003 to 128025 (gamma)	
Cost of Bone Marrow Transplant, Allogeneic Graft (Volunteer Unrelated Donor), 18 years and under	111945	72445 to 159902 (gamma)	
Cost of Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 18 years and under	142066	91937 to 202927 (gamma)	
Cost of Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under	58854	38087 to 84067 (gamma)	
Cost of Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 18 years and under	77209	49966 to 110286 (gamma)	

Variables used in the base case	Value	Confidence interval (distribution if included in PSA)	Reference to section in submission
Cost of Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 18 years and under	101474	65668 to 144945 (gamma)	
Cost of Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified)	62931	40726 to 89891 (gamma)	
Cost of Bone Marrow Harvest	4774	3090 to 6820 (gamma)	
Cost of Peripheral Blood Stem Cell Harvest	7545	4883 to 10777 (gamma)	
Cost of 0 to 6 months follow-up post HSCT	25551	16535 to 36497 (gamma)	
Cost of 6–12 months follow-up post HSCT	9361	6058 to 13371 (gamma)	
Cost of 12–24 months follow-up post HSCT	4363	2824 to 6232 (gamma)	
Cost of Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	246	159 to 352 (gamma)	
Cost of Magnetic Resonance Imaging Scan of One Area, without Contrast, between 6 and 18 years	268	173 to 382 (gamma)	
Cost of Magnetic Resonance Imaging Scan of One Area, without Contrast, 5 years and under	276	178 to 394 (gamma)	
Cost of Magnetic Resonance Imaging Scan of Two or Three Areas, without Contrast	221	143 to 316 (gamma)	
Cost of Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning	313	203 to 447 (gamma)	
Cost of Ultrasound Scan with duration of less than 20 minutes, without Contrast	70	45 to 99 (gamma)	
Cost of Ultrasound Scan with duration of less than 20 minutes, with Contrast	131	85 to 187 (gamma)	
Cost of blood test, haematology	4	2 to 5 (gamma)	
Cost of blood test, clinical biochemistry	2	1 to 3 (gamma)	
Proportion of patients that receive bortezomib during Course 1	0.500	0.31 to 0.69 (beta)	
Proportion of patients that receive rituximab during Course 1	0.500	0.31 to 0.69 (beta)	
Proportion of patients that receive bortezomib during Course 2	1.000	0.00 to 0.00 (beta)	
Proportion of patients that receive rituximab during Course 2	0.000	0.00 to 0.00 (beta)	
Duration of ICU stay prior to death	1.000	1.39 to 0.61 (normal)	
Duration of initial hospital stay: ICU, weeks	4.000	5.57 to 2.43 (normal)	

Variables used in the base case	Value	Confidence interval (distribution if included in PSA)	Reference to section in submission
Duration of initial hospital stay: HDU, weeks	4.000	5.57 to 2.43 (normal)	
Duration of initial hospital stay: General ward, weeks	6.000	8.35 to 3.65 (normal)	
Duration of parenteral nutrition, months	3.22	4.48 to 1.96 (normal)	
Duration of NST/PEG nutrition, months	60	83.52 to 36.48 (normal)	
Duration of inpatient visit following initial hospitalization, days	5.000	6.96 to 3.04 (normal)	
Proportion of patients that are admitted to the ICU during stay	1.000	1.00 to 1.00 (beta)	
Proportion of patients that are admitted to the HDU during stay	1.000	1.00 to 1.00 (beta)	
Proportion of patients that are admitted to the general ward during stay	1.000	1.00 to 1.00 (beta)	
Proportion of patients that visit the paediatric metabolic disease physician	1.000	1.00 to 1.00 (beta)	
Proportion of patients that visit the dietician	1.000	1.00 to 1.00 (beta)	
Proportion of patients that receive parenteral nutrition	1.000	1.00 to 1.00 (beta)	
Proportion of patients that receive an ultrasound	0.500	0.31 to 0.69 (beta)	
Proportion of patients that receive an MRI	0.500	0.31 to 0.69 (beta)	
Proportion of patients that receive a blood test	1.000	1.00 to 1.00 (beta)	
Proportion of patients with inpatient visits following initial hospitalization	1.000	1.00 to 1.00 (beta)	
Frequency of abdominal ultrasounds	0.083	0.054 to 0.119 (beta)	
Frequency of abdominal MRIs	0.083	0.054 to 0.119 (beta)	
Frequency of blood test during the first 5 years	0.333	0.210 to 0.470 (beta)	
Frequency of blood test after 5 years	0.167	0.107 to 0.237 (beta)	
Frequency of ped. metabolic visit during the first year, per cycle	4.000	0.000 to 0.000 (beta)	
Frequency of dietician visit during the first year, per cycle	2.000	0.000 to 0.000 (beta)	
Frequency of ped. Metabolic visit during the second year, per cycle	1.000	0.000 to 0.000 (beta)	
Frequency of dietician visit during the second year, per cycle	1.000	0.000 to 0.000 (beta)	
Frequency of ped. Metabolic visit after the second year, per cycle	0.286	0.181 to 0.404 (beta)	
Frequency of dietician visit after the second year, per cycle	1.000	0.000 to 0.000 (beta)	
Frequency of hospital visits following initial hospitalization	0.167	0.107 to 0.237 (beta)	

Variables used in the base case	Value	Confidence interval (distribution if included in PSA)	Reference to section in submission
Average age of patients when switched to home administration, months	3.22	4.48 to 1.96 (normal)	
Proportion of patients with first SA dose increase	1.000	Not varied in PSA	B.3.3
Proportion of patients with second SA dose increase (→early HSCT)	[redacted]	Not varied in PSA	
Proportion of patients reducing SA dose post early HSCT	1.000	Not varied in PSA	
Proportion of patients discontinuing SA dose post early HSCT	1.000	Not varied in PSA	
Proportion of patients reducing SA dose at adulthood (no prior HSCT)	0.00	Not varied in PSA	
Proportion of patients reducing SA dose at adulthood (prior HSCT) following no paediatric adjustment	0.500	Not varied in PSA	
Time to 1st SA dose increase	3.000	1.94 to 4.29	B.3.3
Time to 2nd SA dose increase	6.000	3.88 to 8.57	
Time to early HSCT	15.000	5.82 to 12.86	
Time to SA dose decrease, post-early HSCT	6.000	3.88 to 8.57	
Time to SA discontinuation, post-early HSCT	12.000	7.77 to 17.14	
Compliance sebelipase alfa	0.960	0.96 to 1.00 (beta)	

Key: HDU, high dependency unit; HSCT, haematopoietic stem cell transplant; ICU, intensive care unit; MRI, magnetic resonance imaging; SA, sebelipase alfa.

Note: When unknown, standard error was assumed to be 20% of the mean.

B.3.8.2. Assumptions

Assumptions in the modelling which are most likely to impact the cost-effectiveness of sebelipase alfa are listed in Table 52.

Table 52: Key assumptions in the economic analysis

Assumption	Justification
HRQoL is assumed equal to general-population quality of life; and for ages 0-15 this is approximated to age 16.	There is a lack evidence to inform population specific values. However, some support for general population HRQoL comes from the single study identified in a systematic search.[31] This ten-year follow-up of 5 cases in France evaluated pediatric QoL using the PedQL inventory questionnaire. Scores were acceptable or high globally and across all four-dimensional scales. Further, authors concluded that SA allowed near normal bio-clinical and growth parameters.
No long-term LAL-D related mortality. After the 5-year follow-up period of CL03 and CL08, there	LAL-D related survival in the model is informed by the LAL-CL03 and LAL-CL08 trials of SA, within which the last recorded LAL-D attributed death was before age 18 months.

Assumption	Justification
could be no LAL-D related mortality.	The larger ALX-LAL-D-5001 global registry (n=29; 7 UK patients) recorded a total of two deaths over up to 11 years follow-up. The second event occurred at 3.5 years from SA treatment initiation. Expert clinical opinion supported the assumption of no LAL-D related mortality after 5 years.
Sebelipase alfa dosing is based on expert clinical opinion.	Survival in the model was based on the LAL-CL03 and LAL-CL08 trials, however, their design had a dose finding element, follow-up was limited to 5 years, and they completed in 2018. The expert opinion of clinicians with experience of these trials and with cases since is the favoured source for informing dose requirement, both for the age range included in trials as well as older ages.
HSCT is not a rescue therapy in BSC (untreated patients).	Based on the Potter et al. HSCT is unlikely to be successful in the highly morbid states associated with untreated rapidly progressive LAL-D.[2]
HSCT cannot be received twice.	Expert clinical opinion.
Loss of venous access in early life recipients of HSCT results in LAL-D-related death.	Demaret et al. report challenging venous access in a participant of LAL-CL-03, who required 6 central venous access devices because of device infection or failure. Expert clinical opinion from the UK supports the use of HSCT for cases of venous access difficulty, reporting an example of rescue HSCT for this reason.
HSCT is the rescue option for loss of venous access in later life. Sebelipase alfa is discontinued thereafter, and mortality is unaffected.	This is a predicted challenge for patients with rapidly progressive LAL-D who have been administered ERT every week since birth. Over 1,500 infusions are anticipated by the 30th birthday. The assumption of serious difficulty with venous access which would interfere with ERT administration is supported by expert clinical opinion. Presently the only clinical option when faced with potential disruption of treatment is HSCT. No patient with rapidly progressive LAL-D has yet reached teenage years so no direct evidence exists to support his assumption, nor is there existing equivalent QW IV administered ERT treatment from which long-term experience can be taken.
HSCT in later life is modelled as occurring at a fixed time for all eligible patients; age 30 years.	In the absence of evidence from which an age at IV loss (treatment duration until IV loss) can be estimated, expert clinical opinion is the preferred source.
Key: BSC, best supportive care; HSCT, haematopoietic stem cell transplant.	

B.3.9. Base case results

B.3.9.1. Base case incremental cost-effectiveness analysis results

Base case results with PAS discount are presented in Table 53 and Table 54. Future costs and benefits are discounted at 1.5%.

Table 53: Base case results (deterministic), discounted at 1.5%

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,608

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

Table 54: Net health benefit (deterministic), discounted at 1.5%

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £100,000	NHB at £300,000
BSC	[redacted]	[redacted]	-	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	-45.68	6.59

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

Results with PAS discount at 3.5% are presented in Table 55 and Table 56.

Table 55: Results (deterministic), discounted at 3.5%

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,078

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

Table 56: Net health benefit (deterministic), discounted at 3.5%

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £100,000	NHB at £300,000
BSC	[redacted]	[redacted]	-	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	-40.07	-0.52

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

Results with PAS and without discount of future costs and benefits are presented in Table 57 and Table 58.

Table 57 Results (deterministic), undiscounted

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180,397

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

Table 58 Net health benefit (deterministic), undiscounted

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £100,000	NHB at £300,000
BSC	[redacted]	[redacted]	-	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22.23

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

Calculation of quantitative decision modifier

Based on an undiscounted QALY gain of [redacted] the QALY weighting for sebelipase alfa is 3.0; therefore establishing an HST willingness to pay threshold of £300,000 per QALY gained.

B.3.10. Exploring uncertainty

The character and impact of parameter and structural uncertainty was explored using both probabilistic and deterministic analyses.

B.3.10.1. Probabilistic sensitivity analysis

Base case point estimates were produced with accompanying 95% credible intervals in a probabilistic analysis. The PSA included a broad range of parameters which were varied simultaneously by sampling 1,000 times from individual probability density functions, (Table 59Table 59:). Standard error was assumed to equal 20% of the mean when it could not be established from source.

Table 59:Base case probabilistic result (with PAS)

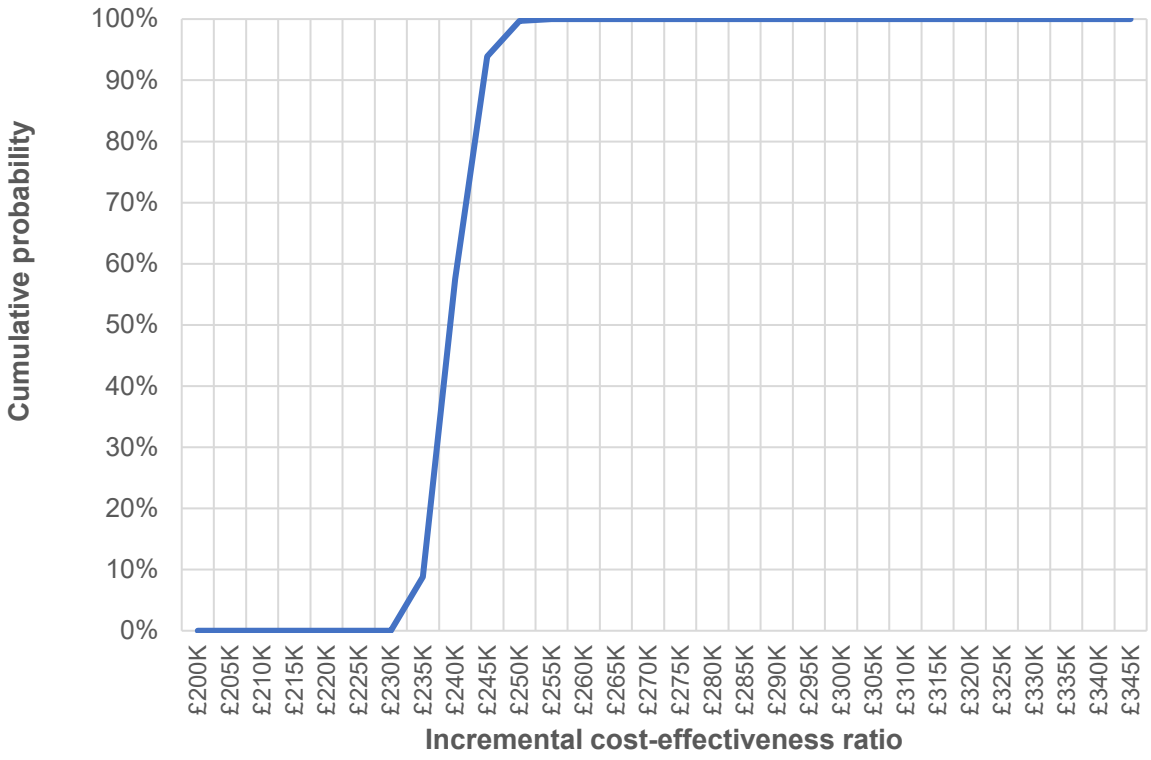
Technologies	Total costs (£) [95% CI]	Total QALYs [95% CI]	Incremental costs (£) [95% CI]	Incremental QALYs [95% CI]	ICER versus baseline (£/QALY) [95% CI]
BSC	[redacted]	[redacted]	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	£239,518 [£233,289 to £246,466]

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

Individual simulation outputs were plotted on the cost-effectiveness plane, presented in [redacted]. The distributions used for each parameter are given in Table 51. The probability that sebelipase alfa is cost-effective over a range of willingness to pay thresholds is presented as a cost-effectiveness acceptability curve, Figure 29.

Figure 28 Cost-effectiveness plane

Figure 29 Cost-effectiveness acceptability curve



B.3.10.2. Deterministic sensitivity analysis

A univariate deterministic sensitivity analysis has not been explored given that the ICER most sensitive to known parameters and assumptions, which are explored in scenario analyses.

B.3.10.3. Scenario analysis

A broad range of key parameters and assumptions were selected to test the impact on the ICER of using alternative positions. Outcomes are presented as a Tornado diagram . (Figure 30) and tabulated in Table 60.

[redacted]

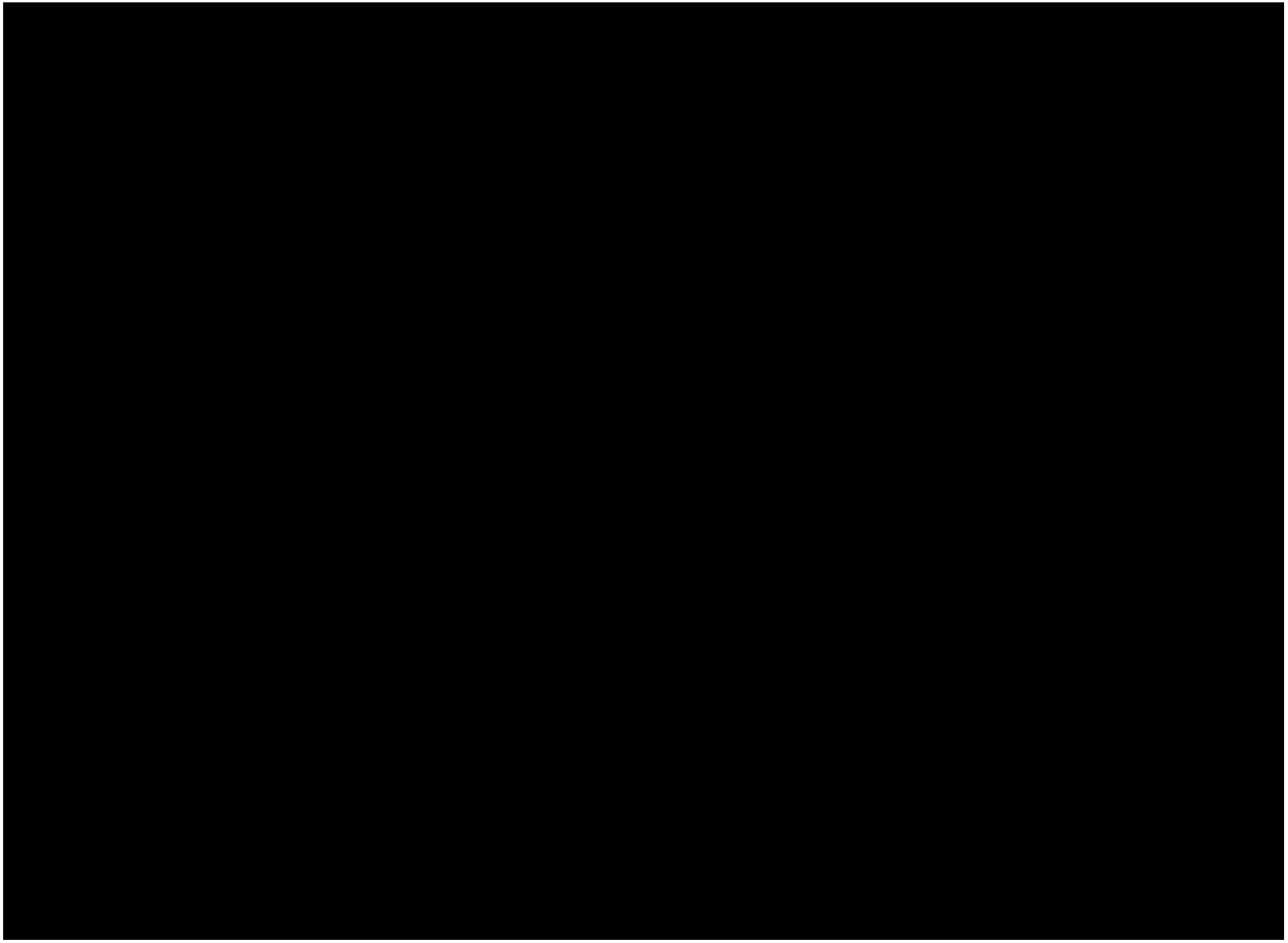


Table 60 Outcomes of deterministic scenario analysis (with PAS)

#	Sensitivity analysis	Original value	Costs			QALYs			ICER
			SA	BSC	Incremental	SA	BSC	Incremental	
1	Base case	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
2	Predicted survival - exponential	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£266,462
3	Predicted survival - Weibull	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£268,215
4	Predicted survival - Gompertz	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£269,300
5	Predicted survival - log-normal	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£335,369
6	HRQoL = EQ-5D VAS	EQ-5D TTO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£238,595
7	100% SA compliance	0.96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£248,469
8	No death after loss of venous access without HSCT	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£237,287
9	Only 50% of patients have early HSCT	0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£394,538
10	All patients have early HSCT	0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£63,794
11	No patients have early HSCT	0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£656,664
12	Only 50% discontinue SA after HSCT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£563,225
13	Venous access never fails	Age 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£408,641
14	Cost HSCT 20% higher	139123.1992	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£240,531
15	2-week round-up vial consumption	1 week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£224,458
16	No homecare service	Included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242,560
17	Cost & QALY discount rate = 0.0%	0.015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180,397
18	Cost & QALY discount rate = 3.5%	0.015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,078
19	Cost & QALY discount rate = 5.0%	0.015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£346,459
20	Horizon = 6 years	Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£415,975
21	SA patient cost cap at [redacted]	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£208,134
22	Patients who don't receive HSCT (No ADAs) increase to 5mg/kg	0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£296,679

23	Venous access loss at 30 years of age	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£284,115
24	Venous access loss at 20 years of age	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£187,641
25	20% have dose reduction at age 18	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£271,516
26	Only 50% have dose reduction after early HSCT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£686,352
27	20% hazard ratio applied to other cause mortality	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£241,826
28	10% reduction in HRQoL all ages	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£251,323
29	10% decrease HRQoL & 20% HR on other cause mortality	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£253,651
30	Lifecycle price - one-third lower SA price after 10 years	Static price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£145,355
31	Family bereavement disutility included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£230,490
32	HSCT procedure and recovery disutility	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£255,359
33	Specialist nutrition excluded	Included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£221,273
34	Economic productivity included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£149,072

Key: EQ5D, euroqol 5 dimensions; HRQoL. Health-related quality of life; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; QALYs, quality-adjusted life years; SA, sebelipase alfa; VAS, visual analogue score.

Sensitivity to HSCT

Regarding ICER sensitivity, the top five alternative scenarios all pertain to the use of HSCT in the lives of people with rapidly progressive LAL-D. They have in common a change from the base case in the use of sebelipase alfa because of transplant. That is whether the ERT is reduced in dose or discontinued altogether at an early age. The base case assumption is that [redacted] of patients will receive HSCT aged 24 months, reduce dose after six months, then discontinue after a further 12 months, at the age of three [redacted]. Whilst the remaining [redacted] discontinue treatment aged [redacted] after HSCT preceding concern for loss of venous access. The size of the impact of alternative proportions dose reducing or discontinuing is dependent on the proportion who receive early transplant, which sets up the possibility of dose modification. A test of the reality of venous access failure in later life identifies further sensitivity in the ICER. Similarly, the consequence of this event is the curtailment of ERT, again consequent to HSCT. The difficulty with the base case assumption is reflecting an accurate forecast of when venous access becomes a clinical concern. Scenario tests in which the base case assumption of age [redacted] is altered 10-years either side show relatively limited sensitivity compared to a scenario which removes any lifetime risk of venous access problems (mean life years in treated patients are 64.3).

Sensitivity of scenarios of sebelipase alfa acquisition cost

The other scenarios appearing in the top ten in respect to ICER sensitivity are: use of a patient-level cost cap; anticipation of future price competition with loss of intellectual property exclusivity; and an increased rate of cost and benefit annual discounting. These can be grouped together as impacting the total cost of acquiring sebelipase alfa through the time horizon. A lower future price clearly improves value, so too does placing a per-patient upper limit of sebelipase alfa cost (cost cap). However, heavier discounting of future costs and QALYS increases the ICER since in the base case HSCT creates a dynamic of greatest value in the early years when the combination of ERT and HSCT is effectively curative (QALYs are gained off-treatment).

Insensitive parameters and assumptions

The ICER is insensitive to alternative approaches to modelling survival, treatment compliance, the cost of drug administration, the cost of specialist nutrition, modifications to health-related quality of life, and increases in any-cause mortality.

B.3.11. Subgroup analysis

Subgroups were not a consideration of the decision problem.

B.3.12. Benefits not captured in the QALY calculation

Sebelipase alfa ERT is a life-saving treatment for people with rapidly progressive LAL-D, a rare condition qualifying sebelipase alfa for the highly specialised technology evaluation programme. Untreated patients are not expected to live beyond the first year of life, but treatment with sebelipase alfa is estimated to benefit a patient with an average gain of 64.3 life-years (37.1 when annually discounted at 1.5%). NICE process and methods guidelines describe the decision modifier applicable for a highly specialised technology providing this level of benefit as a weighting of 3 to the cost-effectiveness payer threshold of £100,000. i.e., the cost-effectiveness of sebelipase alfa should be judged against a threshold of £300,000 per QALY gained. However, the demonstration of the value even with this weighting remains profoundly challenging within the reference case framework. Consider that the life-years gained are double the qualifying threshold, amplified pricing constraints in the context of an ultra-rare condition (prevalent population in England is 6), and that treatment with sebelipase alfa for some patients remains long-term or life-long. Decision modifiers for consideration therefore presented below. They are based on broadening the reference case perspective and include family health spill-over and gain in societal economic productivity (Table 61). Fuller scenario descriptions, method and assumption are given for bereavement in B.3.4.5 and productivity in B.3.5.4.

Table 61 Decision modifiers

Scenario	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Base case	[redacted]	[redacted]	£239,608
Inclusion of family health spill-over (bereavement) (A)	[redacted]	[redacted]	£230,490
Inclusion of productivity gains (B)	[redacted]	[redacted]	£149,072
(A) and (B)	[redacted]	[redacted]	£143,400

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: Costs and QALYs are discounted at 1.5% per annum.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

The cost-effectiveness model was reviewed and validated against peer-reviewed checklists, in particular the CHEERS 2022 checklist.[63] The cost-effectiveness model was internally quality checked by a health economist and any errors or issues identified were addressed following the quality check. The key assumptions of the model have been validated by UK clinical experts, to ensure that the inputs and assumptions were plausible and relevant to UK clinical practice.

B.3.14. Interpretation and conclusions of economic evidence

The treatment of people with rapidly progressive LAL-D with sebelipase alpha ERT increases life-years from [redacted], and QALYs from [redacted]. These are gains of [redacted] life years, or [redacted] QALYs; or discounted at 1.5% per year they are gains of [redacted] life-years or [redacted] QALYs. Treatment is expected to increase discounted costs from [redacted] (including PAS), with the acquisition of ERT representing [redacted] of the increase. The incremental cost-effectiveness ratio (ICER) of the deterministic base case analysis is £239,608, discounting at 1.5%. This reduces to £180,397 without discounting and increases to £308,078 when discounting at 3.5% per year. The probabilistic ICER at 1.5% annual discount is

£239,518, with a 95% credible interval of £233,289 to £246,466. The costs and ICERs presented here include a PAS [redacted]

Limitations within the modelling of this condition create uncertainty which is demonstrated by the sensitivity of the ICER to particular assumptions relating to future life, as shown in the scenario analysis. Although all people with rapidly progressive LAL-D in the UK are currently treated with sebelipase alfa through the GATM programme.[12], the oldest participant is currently only 11 years old. Therefore, projections of survival, venous access, long-term drug safety, and HRQL unavoidably rely on the judgement of experienced clinical experts. The base case analysis assumes that people with the condition, treated with ERT, live near normal lives, in respect to health-related quality of life and length of life, however it is the role of HSCT in the discontinuation of ERT that is most important to the value calculation. Scenarios show that reduction from [redacted] early HSCT to [redacted] increases the ICER to [redacted], yet the ICER decreases to [redacted] if all patients receive early HSCT. Similarly, the ICER is sensitive to variation in the proportion discontinuing SA consequent to HSCT.

There are no alternative economic evaluations of cost-effectiveness by which to compare the outcomes here, except those produced by Alexion for regulatory submissions in England (NICE 2015) and Ireland (NCPE 2018). Compared to the findings of these evaluations we find ICERs are now lower. The main explanation beyond model structure is likely the increase in early use of HSCT in clinical practice in intervening years, and the accounting for future loss of venous access in this evaluation. This leading to rescue HSCT and consequent discontinuation of ERT in mid-life. On these aspects the advice of leading experts in the clinical field was sought.

Finally, there is an extremely high unmet need for the treatment of patients with rapidly progressive LAL-D, demonstrated by the high rate of early mortality. In the absence of sebelipase alfa, there are no alternative treatments for patients with rapidly progressive LAL-D that are able to address the pathophysiology of disease and ultimately achieve an effective clinical response; these patients therefore die at an early age. Presently, Alexion provides access to sebelipase alfa through the

GATM; this provision of access is an interim arrangement pending a reimbursement decision on this appraisal.

B.3.15. Cost to the NHS and Personal Social Services

As of October 2022 there are [redacted] patients in the UK with infantile rapidly progressive LAL-D who are receiving sebelipase alfa under GATM programme.[12] GATM also includes [redacted] of age. Therefore in England, there are [redacted] patients who form the prevalent population for budget impact assessment.

When assessing infantile rapidly progressive LAL-D epidemiology in the literature, the estimated incidence rate for Wolman disease is approximately 1 in 350,000 births according to Aguisanda and colleagues.[9, 13] Using the Office of National Statistics record of live births in England in 2021 (595,948 cases), the expected number on incident cases per year is 1.70.[64] However, the record of new diagnoses in England supports an incidence of [redacted].

Sebelipase alfa is the only licenced intervention indicated for the treatment of the modelled population. It currently assumes 100% market share, which is expected to be maintained in prevalent cases over a five-year projection. Similarly, the rate of uptake in incident cases is expected to be 100% and maintained there. The population expected to receive sebelipase alfa, taking account of expected disease mortality, is presented in Table 62.

Table 62 Population to receive sebelipase alfa

Incident and prevalent cases	**Current year**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Unadjusted for mortality	n/a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted for mortality	n/a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sebelipase alfa has reduced the occasions of intense resourcing associated with the period immediately before a death from LAL-D. This is estimated to be one-month of neonatal intensive care, costing £1,816 per day and totalling £56,427 over a month.

Expected 5-year budget impact for the NHS and PSS in England is calculated based on a positive recommendation of sebelipase alfa. In this event, the current world of acces to sebelipase alfa accessed under the Alexion GATM programme would move to a world of sebelipase alfaaccessed via the NHS in England. The resource costs impacted by this change include only the acquisition cost of the ERT (Table 63). In no year is the annual budget impact expected to reach £20 million.

Table 63 Annual budget impact over 5 years, with PAS

Net budget impact	Current year	Year 1	Year 2	Year 3	Year 4	Year 5
Sebelipase alpha acquisition cost	n/a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology appraisal

Sebelipase alfa for treating Wolman disease [ID3995]

Summary of Information for Patients (SIP)

November 2022

File name	Version	Contains confidential information	Date
		Yes/no	

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Sebelipase alfa (Kanuma®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Patients with rapidly progressive lysosomal acid lipase deficiency (LAL-D; historically known as Wolman's Disease).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The European Commission granted market authorisation of sebelipase alfa on 28 August 2015.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Interaction between The MPS Society and Alexion UK 2019: Sponsorship: UK National Conference on MPS and related disorders (£3,780) 2020: Grant; Reaching Families in Need: MPS Society UK Telephone Helpline and Bereavement Outreach Support (£5,000) 2022: Grant: Capturing the patient and carer experience of living with infantile LAL-D and capturing the clinical understanding and medical practices (£35,800.00)

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Disease that sebelipase alfa plans to treat – Patients with rapidly progressive LAL-D are born with a missing or dysfunctional enzyme that is important for the body.[1] This enzyme, called lysosomal acid lipase (LAL), plays a vital role in a key part of the body's cells (lysosomes) by breaking down fatty material. Build-up of fatty material in cells can cause continuous damage that may affect the function of many organs throughout the body.[1]

Main symptoms of disease – When infant patients present with rapidly progressive LAL-D, it is treated as a medical emergency. If not treated, these patients usually die within the first 6 months of life.[2] Patients with rapidly progressive LAL-D can show symptoms from as early as the first day of life, and usually start to show symptoms usually within the first 6 months of life.[2, 3] Symptoms may include vomiting, diarrhoea and a swollen abdomen beyond its normal size.[4-6] Patients may also present with 'failure to thrive', which means that the patient's weight or rate of weight gain is significantly below that of infants who do not have rapidly progressive LAL-D.[2] Furthermore, patients who experience vomiting and diarrhoea due to the build-up of fatty material can find it difficult to digest or absorb nutrients from food, resulting in the patient becoming underweight. Over time, this build-up of fatty material may also cause liver failure and cirrhosis.[5]

How many people have the condition – Rapidly progressive LAL-D affects fewer than 1 in 50,000 individuals and is therefore classed as an ultra-rare disease.[7] There are currently fewer than ten patients in the UK with rapidly progressive LAL-D.

Burden of disease – A study was conducted in patients with rapidly progressive LAL-D before treatment with sebelipase alfa was available.[2] This study showed that in 21 untreated patients diagnosed with rapidly progressive LAL-D with early signs of growth failure, the median age of death was just 3.0 months[2]. Patients usually die due to a combination of undernourishment, insufficient growth, difficulty in digesting and absorbing nutrients, and liver failure.

Impact on carers – Rapidly progressive LAL-D has a significant impact on the quality of life of caregivers. A recent survey explored the lived experiences of eight parents of children who had a confirmed diagnosis of LAL-D in the UK. [8] Parents expressed a sense of helplessness and powerlessness as they are unable to care for their child. Parents described their experience as a battle with loss, from the imagined loss of their child to the loss of visions of a healthy baby. Parents also experienced living in a hospital environment for a substantial period of time, which resulted in the loss of their support network and their temporary or permanent loss of employment. Furthermore, the death of a child has a long-term effect on bereaved parents; when assessing their quality of life, bereaved parents present with a significantly worse quality of life following child death compared with parents who did not experience the death of a child.[9]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How rapidly progressive LAL-D is diagnosed – Once suspected, LAL-D can be diagnosed using two different tests, a blood test that measures the activity of LAL enzyme or by genetic sequencing of the *LIPA* gene.[10, 11] Other supportive tests that a healthcare provider may order include magnetic resonance imaging (MRI) and a liver biopsy.[11] Patients may be offered treatment options to manage symptoms during the diagnostic process. Once the patient is diagnosed with rapidly progressive LAL-D, no additional diagnostic tests are required to be able to start treatment with sebelipase alfa.

Why speed of diagnosis matters – Due to the rapidly progressive nature of LAL-D and the high chance of death at an early age in patients who are not treated, a quick diagnosis is of high importance. Unfortunately, rapidly progressive LAL-D is an under-recognised condition; this is most likely because of the ultra-rare nature of the disease and limited disease awareness.[11] Rapidly progressive LAL-D can also be misdiagnosed as other conditions with similar symptoms, including haemophagocytic lymphohistiocytosis (HLH), heterozygous familial hypercholesterolaemia, or, more rarely, leukaemia.[12] The delay in diagnosis means that patients have a delay in access to sebelipase alfa, a potentially life-saving treatment.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - If there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatments are currently used, how they work and their side effects – The treatment goals for patients with rapidly progressive LAL-D are to prevent death at an early age by improving survival rates, improving growth and nutritional status and preventing the progression of liver disease whilst also improving quality of life.

There are no relevant published clinical guidelines for the management of rapidly progressive LAL-D, and besides sebelipase alfa, there are no other treatments available that treat the underlying cause of rapidly progressive LAL-D or are able to stop the patient's health from deteriorating. Figure 1 presents the pathway of care for patients with rapidly progressive LAL-D, and the proposed placement of sebelipase alfa within this treatment pathway.

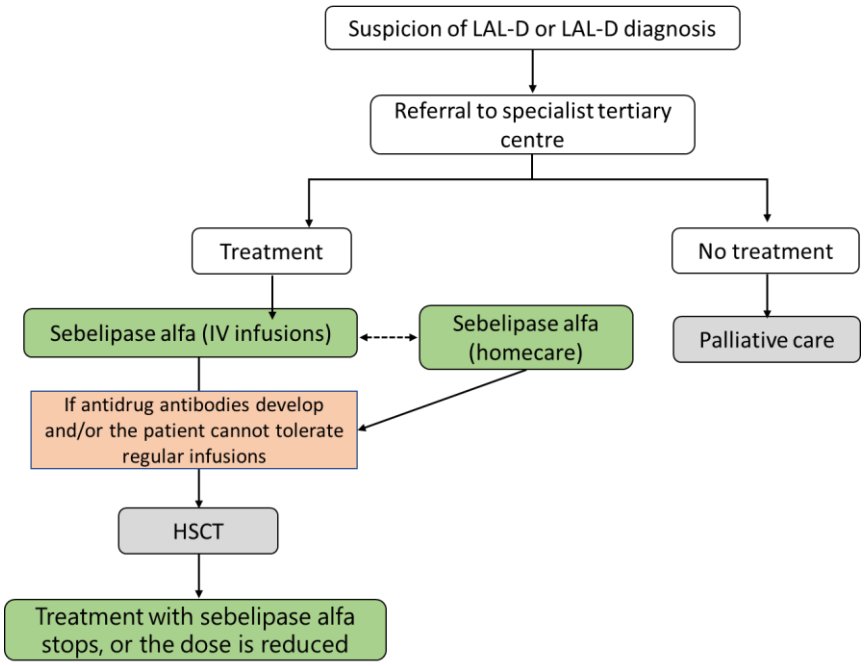
Because of the severity of the disease and the fact that no other disease-specific treatments are available, sebelipase alfa has been provided and funded by Alexion in the UK for the past 10 years under its Global Access to Medicines programme.[13] The aims of this programme are to:

- Support patients who have previously taken part in clinical trials
- Help patients who cannot take part in clinical trials gain access to sebelipase alfa

- Provide access to sebelipase alfa in countries where regulatory approval and/or reimbursement is not yet established, but where Alexion plans to enter for approval/reimbursement following marketing authorisation

Sebelipase alfa is the first and only targeted enzyme replacement therapy to be approved for LAL-D. Without access to sebelipase alfa, the focus is on supportive therapies that aim to manage the symptoms of rapidly progressive LAL-D. Before sebelipase alfa was available, liver transplant or haematopoietic stem cell transplant (HSCT) were both occasionally used as last resort options for patients who had rapidly progressive LAL-D; these procedures are intensive and often come with severe side effects.[2] Unfortunately, these options alone, without sebelipase alfa, have a low success rate and were unable to stop patients from deteriorating and ultimately dying due to the disease.[2]

Figure 1: Pathway of care for patients with rapidly progressive LAL-D in England, and the proposed positioning of sebelipase alfa



Key: HSCT, haematopoietic stem cell transplant; IV, intravenous.
Notes: Patients who develop antidrug antibodies normally receive treatment with either bortezomib or rituximab.[14]

One of the complications of being treated with sebelipase alfa is its potential to trigger an immune response that leads to the formation of anti-drug antibodies.[15] These antidrug antibodies can affect how well the treatment works, reducing its effectiveness. When the effectiveness of sebelipase alfa drops, patients are tested for levels of antidrug antibodies. If they are found to be present, a medication such as bortezomib or rituximab is given to try and prevent the immune response.[14] In some cases, clinicians may refer the patient for treatment with HSCT.

Hematopoietic stem cell transplantation (HSCT) – In recent years, clinicians have introduced the use of multimodal therapy, which includes the use of sebelipase alfa plus nutritional support, and HSCT.[16] This multimodal therapy was initially used in patients whose response to treatment diminished over time due to the development of anti-drug antibodies, but also has a potential for use when patients can no longer tolerate weekly infusions or in patients whose venous access has become an issue.[17, 18]

HSCT following treatment with sebelipase alfa may improve the median survival outcomes of patients with rapidly progressive LAL-D. A recently published case series explored the efficacy of sebelipase alfa and HSCT as a multimodal therapy in five patients with rapidly progressive LAL-D based in the Royal Manchester Children's Hospital, a specialised centre for the diagnosis and treatment of inherited metabolic disorders.[16] Four of the five patients were alive at least 10 months after HSCT. All four patients remain on treatment with sebelipase alfa, with three patients able to decrease their dosage and frequency.[16] As a follow on to the data presented here from 2021, clinicians provided an update in April 2022 for the four surviving patients. Please refer to Section B.1.3.4.1 of Document B for the April 2022 progress update. Evidence on file suggests that a few years after HSCT, patients might be able to reduce their dosage and/or frequency of sebelipase alfa, with the potential to possibly even stop treatment.

Multidisciplinary teams - As patients with rapidly progressive LAL-D are severely ill, extensive support is required from several different clinical teams from diagnosis and throughout their treatment. Alexion is currently funding homecare support for patients receiving sebelipase alfa through the Global Access to Medicines programme, with plans to continue this support if sebelipase alfa is to be reimbursed. This in-home patient support includes drug delivery and administration of the infusion at home (or in other locations such as school) by a trained nurse.

As the majority of patients with rapidly progressive LAL-D present with malnutrition and are underweight, the early involvement of an expert in nutrition is essential. Patients are usually put on a specialised diet, which may include total parenteral nutrition (TPN).[16, 19] TPN is a method of feeding a special formula through a catheter placed in a vein in patients who are not able to swallow food, move the food through the digestive system, or absorb nutrients from the food.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

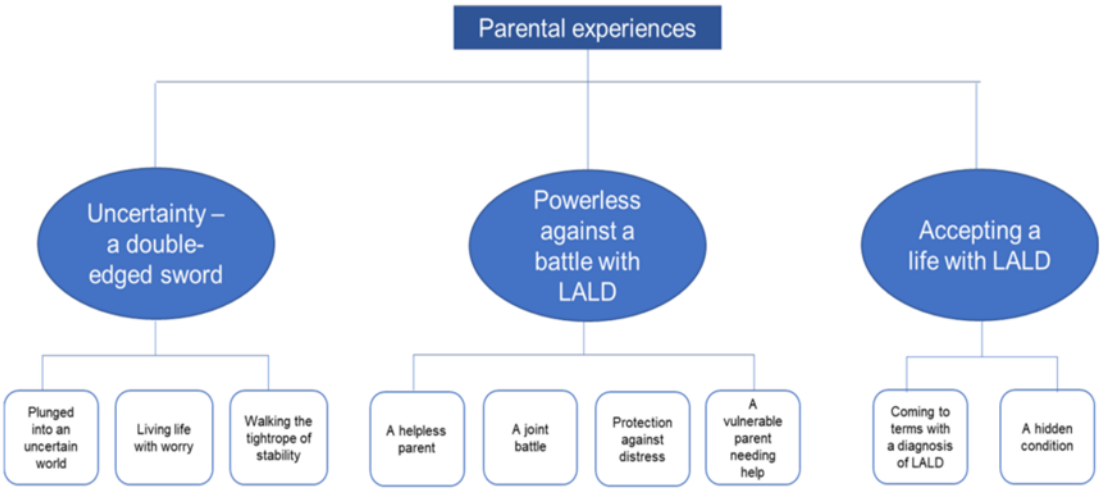
In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

As rapidly progressive LAL-D presents in infants, no patient-based evidence is available for their lived experience of the condition. Patients without access to sebelipase alfa die within the first 6 months of life.[2]

Qualitative caregiver experience study – A recently published study by Hassall et al. (2022) explored the lived experiences of eight parents of children with LAL-D.[8] Figure 2 presents the common themes identified in the eight parents interviewed. During the study, parents reflected on how the diagnosis of an incurable and rare condition was unexpected and extremely challenging.[8] The parents struggled with uncertainty, and how it felt not having many other children with LAL-D to compare their child with, which negatively impacted how they were able to make sense of the diagnosis. Parents also expressed a sense of helplessness and powerlessness as they were unable to care for their child in the way they once did or imagined they would.[8] Parents

found themselves living in a hospital environment for a substantial period of time, resulting in the loss of their support network and their temporary or permanent loss of employment. [8]

Figure 2: Common themes identified in parents of children with LAL-D



Key: LALD, lysosomal acid lipase deficiency.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Sebelipase alfa is the first and only approved treatment for patients with rapidly progressive LAL-D. Rapidly progressive LAL-D is a genetic disease, which means that the body's makeup does not allow it to produce a properly functioning LAL enzyme.[1] Sebelipase alfa helps to replace the LAL enzyme that is missing or not working correctly, helping to break down fats and stopping them building up in the body's cells.[1]

A link to the Patient Information Leaflet (PIL) for sebelipase alfa is provided below:[20]
https://www.medicines.org.uk/emc/product/7093/pil

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

The medicine is not intended to be used in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Method of administration – Sebelipase alfa is administered by intravenous (IV) infusion.[1] An IV infusion is a way of delivering medicine directly into the bloodstream. Sebelipase alfa is given to patients with rapidly progressive LAL-D once a week.[20] Sebelipase alfa should be started as early as possible after diagnosis and is intended for long-term use.

Dosage – For patients with rapidly progressive LAL-D, the recommended starting dosage of sebelipase alfa is 1 mg/kg or 3 mg/kg of body weight given by IV infusion once weekly.[1, 20] For infants under 6 months who do not respond to this dose, the doctor may increase the dosage from 1mg/kg to 3 mg/kg or from 3mg/kg to 5mg/kg of body weight once weekly.[1, 21]

An infusion of sebelipase alfa will last at least 2 hours, though the doctor in charge of the patient's care may decide to increase or decrease the infusion time.[1] For example, a 1-hour infusion may be considered after patient tolerability is established.[21]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Sebelipase alfa has been studied in two main trials in patients with rapidly progressive LAL-D: **LAL-CL08** and **LAL-CL03**.[22] These trials have been conducted as part of Alexion's clinical development programme for sebelipase alfa. Both trials lacked a comparator therapy, meaning all of the patients enrolled received sebelipase alfa. This is because comparative trials were not considered appropriate due to the unethical nature of withholding a potentially effective treatment from patients with such a progressive and life-threatening disease.

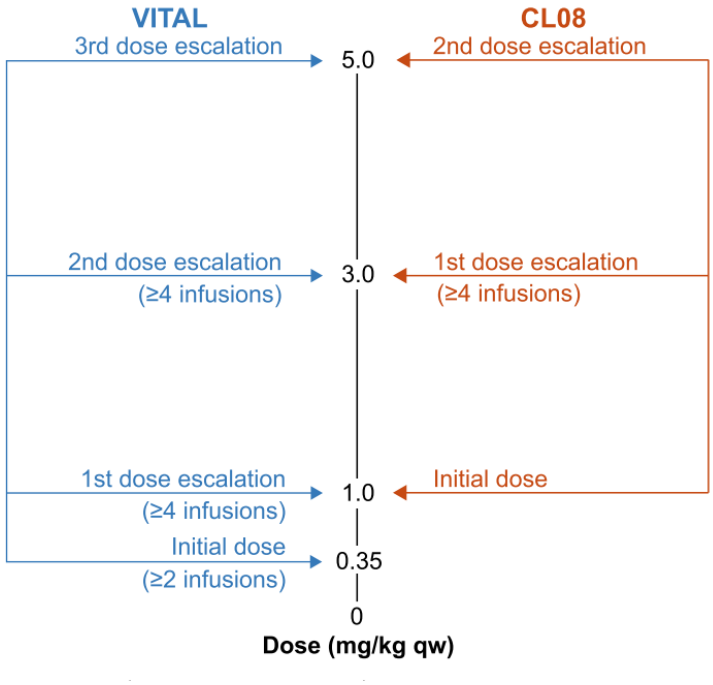
LAL-CL08 is a Phase II, open-label, multicentre trial conducted to evaluate the safety and effectiveness of sebelipase alfa in infants with a confirmed diagnosis of LAL-D who were < 8 months of age at the first dose of sebelipase alfa.[22] LAL-CL08 was conducted in Finland, Italy, the US, and the UK, with the majority of patients enrolled in the UK.[22]

LAL-CL08 provides information on 10 patients with rapidly progressive LAL-D.[22] Each patient's treatment was expected to last for at least 18 months, and patients could continue to receive sebelipase alfa in the trial for up to 3 years.[22, 23] In order to be enrolled in the trial, patients had to show signs or symptoms of rapid disease progression requiring urgent medical care, including, but not limited to:

- A swollen abdomen and enlarged liver
- Failure to thrive (i.e. the patient's weight or rate of weight gain is significantly below that of infants who do not have rapidly progressive LAL-D)
- Disturbance of coagulation (i.e. problems with blood clotting)
- Severe anaemia
- A sibling with a rapidly progressive course of LAL-D

Patients were started on once-a-week IV infusions of sebelipase alfa at a dose of 1.0 mg/kg.[22] Figure 3 (right-hand side) presents the dose escalation of sebelipase alfa in eligible patients. In order to move to the next dosage level, patients had to meet pre-defined dose-escalation criteria.

Figure 3: Dose escalation in LAL-CL03 (VITAL) and LAL-CL08



Key: qw, once weekly.
Notes: 'VITAL' refers to LAL-CL03.

Further information/publications for LAL-CL08:
Clinicaltrials.gov (NCT02193867)[24] - https://clinicaltrials.gov/ct2/show/NCT02193867
Vijay et al. (2022)[22] - https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01577-4

LAL-CL03 is a Phase II/III, open-label, multicentre trial conducted to evaluate the safety and efficacy of sebelipase alfa in patients with rapidly progressive LAL-D with early-onset growth failure (i.e. growth failure within the first 6 months of life).[22, 25, 26] LAL-CL03 was conducted in the UK, the US, France, Italy, Egypt and Turkey.

LAL-CL03 provides information on nine patients, consisting of a screening period of up to 3 weeks, a treatment period of up to 5 years, and a follow-up visit of at least 30 days after the last dose of sebelipase alfa.[22] In order to be enrolled in LAL-CL03, patients had to show growth failure or evidence of a rapidly progressive disease course where symptoms appeared before 6 months of age.

Patients were started on once-a-week IV infusions of sebelipase alfa at a dose of 0.35 mg/kg.[22] Figure 3 (left-hand side) presents the dose escalation of sebelipase alfa in eligible patients. In

order to be escalated to the next dosage level, patients had to meet pre-defined dose-escalation criteria.

Further information/publications for LAL-CL03:
Clinicaltrials.gov (NCT01371825)[27] - https://www.clinicaltrials.gov/ct2/show/NCT01371825
Vijay et al. (2022)[22] - https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01577-4
Jones et al. (2017)[25] - https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0587-3

Natural history study (LAL-1-NH01)
As both LAL-CL08 and LAL-CL03 lacked comparator treatments, the trials were compared with a historical group of patients who were diagnosed with rapidly progressive LAL-D in their first 2 years of life, before sebelipase alfa was available.[2] This study, LAL-1-NH01, is referred to as a historical control study.[2]

Publications for LAL-NH01:
Jones et al. (2016)[2] - https://www.gimjournal.org/article/S1098-3600(21)04358-6/fulltext

Global LAL-D registry
Although it is not classed as a clinical trial, evidence on the effectiveness of sebelipase alfa is collected through the global LAL-D registry. This registry provides us with real-world evidence of all patients with LAL-D both treated with sebelipase alfa and untreated.

Further information on the registry is provided in Document B, Section B.2.6.3.2 of the submission.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

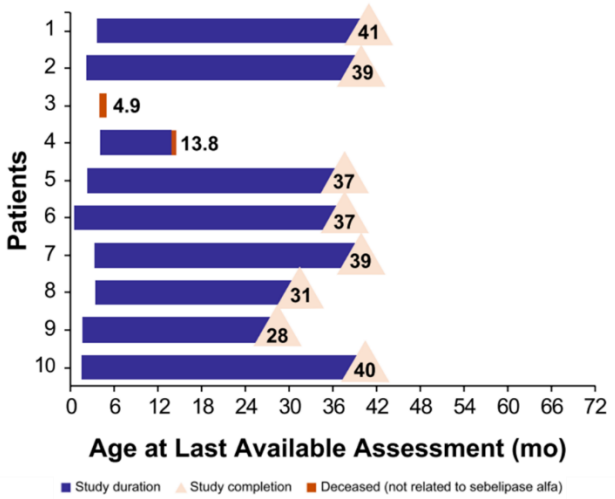
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The LAL-CL08 and LAL-CL03 trials provide evidence for the effect of sebelipase alfa on survival, growth and functional development, the liver, and the patient's nutritional status.[22]

Survival
LAL-CL08
Figure 4 presents the age of patients in the LAL-CL08 trial at the last available assessment, including the age of the two patients who died during the trial.

In LAL-CL08, the proportion of patients treated with sebelipase alfa and surviving to 12, 18, 24 and 36 months of age was 90%, 80%, 80% and 75%, respectively.[22] Please note that two patients were < 36 months of age at the time of study completion and were excluded from the analysis for survival to 36 months. At the last follow-up, the surviving eight patients were 27.8, 30.7, 36.8, 37.3, 39.1, 39.4, 40.1 and 40.6 months old.[22]

Figure 4: Patient survival in LAL-CL08



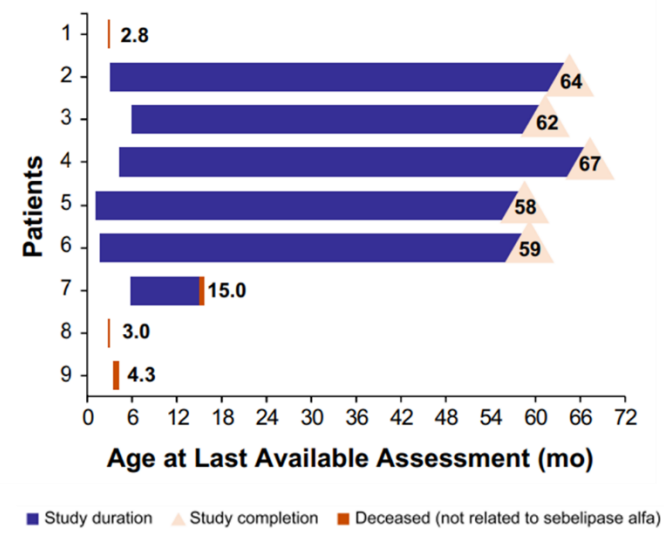
Key: mo, months.
Source: Vijay et al. (2021).[22]

LAL-CL03

Figure 5 presents the age of patients in the LAL-CL08 trial at the last available assessment, including the age of the four patients who died during the trial.

Six of the nine (67%) patients treated with sebelipase alfa survived beyond 12 months of age, and five (56%) patients survived beyond 18 months of age.[22] All five of these patients survived to the last available assessment at the 60-month follow-up. The five patients alive at the end of the trial were 67.0, 63.7, 62.4, 58.5 and 58.1 months of age at their last assessment. The remaining four patients died at 15.0, 4.3, 3.0 and 2.8 months of age. [22]

Figure 5: Patient survival in LAL-CL03



Key: mo, months.
Source: Vijay et al. 2021.[22]

Body weight and nutrition

Patients treated with sebelipase alfa experienced improvements in median weight-for-age percentiles, a key measure of growth, in both LAL-CL08 and LAL-CL03.[22]

In LAL-CL08, sebelipase alfa treatment led to clinically meaningful improvements in growth from baseline through last assessment in all patients who had a low baseline weight-for-age percentile and survived beyond Week 4.[23] In LAL-CL03, the weight-for-age percentile improved significantly for all patients from baseline through to the last assessment. [22]

Data for other growth parameters such as length-for-age supported the trends observed for weight-for-age.

Liver

Treatment with sebelipase alfa led to improvements in liver function, as demonstrated by normalisation in the levels of two enzymes found in the blood, aspartate transaminase (AST) and alanine transaminase (ALT).[22]

In LAL-CL08, normalisation of ALT was achieved for the three patients with abnormal baseline ALT levels, and normalisation of AST was achieved for 50% of patients with abnormal baseline AST levels.[22]

In LAL-CL03, among the six patients who survived beyond Week 4, four patients had abnormal ALT levels at baseline.[22] Normalisation was achieved for four of the six patients with elevated baseline AST and all four patients with elevated baseline ALT, with normal levels achieved between Week 1 and Week 5.[25]

Neurological development

In both LAL-CL08 and LAL-CL03, patients remained generally stable in all 4 skill areas of the Denver II Developmental Screening Test (language, fine motor–adaptive, gross motor, personal-social) through end of study.[22]

Real-world evidence of effectiveness of sebelipase alfa

Long-term survival was also demonstrated in the global LAL-D registry. As the data collected in this registry are confidential, please refer to Document B, Section B.2.10.2 of the submission for further information.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

As rapidly progressive LAL-D presents in infants, no patient-based evidence is available for their lived experience of the condition. Quality of life of patients and their families/caregivers was not assessed in the LAL-CL08 and LAL-CL03 trials.

Semi-structured interview with a patient's mother – Cossette et al. (2022) presents a case report of a female Canadian patient diagnosed with rapidly progressive LAL-D at 3 months of age who received treatment with sebelipase alfa and was followed up for approximately 5 years.[28] A semi-structured interview was conducted with the patient's mother, who expressed the importance of transfer of knowledge from clinicians, dieticians and specialised nurses in order to provide appropriate care, and to enable care sharing with family members and day-care facilities.[28]

For more information regarding the burden of rapidly progressive LAL-D on the quality of life of caregivers, please refer to Question 2d.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Considering the life-threating nature of rapidly progressive LAL-D, treatment with sebelipase alfa was well tolerated in the two clinical trials.[22] There were no unexpected side effects, and those that did occur were managed and resolved.

A total of 1,249 infusions of sebelipase alfa were administered in LAL-CL03, and 1,193 infusions of sebelipase alfa were administered in LAL-CL08.[22]

Table 1 presents a summary of the number of side effects patients experience during LAL-CL08 and LAL-CL03.
Treatment-emergent side effects (i.e. unexpected medical events that arises during treatment with a sebelipase alfa) occurred in all patients in LAL-CL08 and LAL-CL03.[22] Of all the adverse events that were observed, 98% of events in LAL-CL08 and 95% of events in LAL-CL03 were mild or moderate in severity. Seven (70%) patients in LAL-CL08 and four (44%) patients in LAL-CL03 experienced more than one severe adverse event. The most frequently reported adverse events that were related, or possibly related, to treatment with sebelipase alfa were vomiting, fever, hives, irritability and tachycardia.[22]

Across both trials, none of the patients stopped treatment due to treatment-emergent side effects.[22]

Table 1: Summary of side effects

Event	Number (and percentage) of patients experiencing an event	
	LAL-CL08 (N = 10)	**LAL-CL03 (N = 9)**
Any treatment-emergent side effects	10 (100)	9 (100)
Mild or moderate treatment-emergent side effects	3 (10)	0 (0)
Side effects associated with the intravenous infusion	8 (80)	5 (56)

Side effects that lead to a patient stopping treatment	0 (0)	0 (0)
Death	2 (20)	4 (44)
Key: N, number of patients in the trial. **Source of information:** Vijay et al. 2021.[22]		

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of sebelipase alfa to patients include:

- Long-term survival in patients with rapidly progressive LAL-D who, without sebelipase alfa, would die within the first 6 months of life[22, 29]
- Improvements in weight gain that are sustained over time, helping the infant to develop into a child[22]
- Improvement of liver function demonstrated through normalisation in the levels of two enzymes found in the blood, aspartate transaminase (AST) and alanine transaminase (ALT)[22]
- Stable neurological development, as assessed through the Denver-II developmental screening test[22]

Sebelipase alfa is also expected to have wider benefits:

- Reduction in the need for other invasive therapies like parenteral nutrition (a form of nutrition that is delivered into a vein) and liver transplant
- It is more likely that infants will live to be able to attend school and may go on to lead normal and productive lives
- For a parent caring for an infant that is thriving, gaining weight and has the possibility to enjoy childhood and have a normal life, the burden of care is expected to be substantially reduced and the gain in quality of life immeasurable

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The key disadvantages to patients, carers and society include:

- Patients require long-term repeat infusions of sebelipase alfa
    - Despite requiring a large number of infusions, patients in the LAL-CL08 and LAL-CL03 trials had a relatively low number of severe infusion-associated reactions[22]
    - Infusion-associated reactions were reported in 13 of 19 patients, of which 94% were mild or moderate in LAL-CL03 and 88% were mild or moderate in LAL-CL08. All infusion-associated reactions were successfully managed and resolved[22]
- Patients surviving due to sebelipase alfa require support with their nutrition, which tends to be a restrictive diet or through parenteral nutrition, where artificial nutrition is fed directly into a vein

- Frequent adjustments are needed to meet the nutritional needs of each patient during treatment, which may include a decrease in the level of support needed as the health of the patient improves[22]

- Side effects of sebelipase alfa: common side effects include vomiting, fever, hives, irritability and tachycardia[22]
  - The side effects associated with sebelipase alfa are far less severe than in patients who do not have access to sebelipase alfa and ultimately die within 6 months[2]

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

The company has developed an economic model to understand the cost effectiveness of sebelipase alfa versus best supportive care (BSC), which in this case is treatment if sebelipase alfa was not available and predominantly includes palliative care. The model accounts for resources and costs, as well as the impact on quality of life and survival of patients on both potential treatment options (sebelipase alfa or BSC).

The model aims to simulate patients with rapidly progressive LAL-D throughout their lifetime. It is a Markov type model, which tracks the health state of patients as it changes over time. At any given time, a patients can be in one of any of five pre-determined health states. Each one represents a different health risk and/or health setting. Also, whether or not a patient has received a stem-cell transplant, which can have a significant impact on whether the ERT can be reduced or stopped. The amount and cost of ERT itself, which is based on patient weight and dose requirement, is tracked using a decision tree.

Modelling how much treatment extends life

The model reflects that sebelipase alfa is expected to extend a patient's life. Compared to BSC, where patients on average will pass away before their first year, patients on sebelipase alfa are expected to gain up to 64 years of life.

Modelling how much a treatment improves quality of life

Given the severity of the disease and that it impacts infants, it is challenging to capture quality of life measures as per the usual processes. In some trials, patients or caregivers will provide

responses to a questionnaire to better understand quality of life of the patient and also the caregiver, collection of this information was not part of the sebelipase alfa clinical trials and has not been captured elsewhere. Instead, the model assumes that ERT restores health-related quality of life in additional years to the normal level expected in the UK but takes account of difficulties associated with stem cell transplant.

Modelling how the costs of treatment differ with the new treatment

Sebelipase alfa is considered a lifesaving but also a long-term treatment. It must be administered weekly throughout the patient's lifetime - or until successful stem cell transplantation - to ensure that morbidity and mortality associated with rapidly progressive LAL-D is reduced. Therefore, there are significantly higher health care costs compared to the world before sebelipase alfa, when costs did not include ERT and were accrued over a short period of intense care.

Uncertainty

Given the rarity of the disease and its rapid onset in this population, there is limited data available to populate the cost-effectiveness model. Taken together, the clinical trials of sebelipase alfa LAL-CL03 and LAL-CL08 included only 19 participants in total and the last published outcomes followed these patients for a maximum of five years. Contemporary data from patient registries now provide information about patients on-treatment for 10 years but the oldest patient is yet to reach adolescence. Therefore, assumptions have been necessary to forecast health and resource use through a whole lifetime, in particular the evolving role of stell cell transplantation. Altogether, some uncertainty in the cost effectiveness analysis is inevitable. The company has tested uncertainty around key aspects of the modelling by exploring alternative scenarios designed to help decision makers understand its importance. These are described in Document B, section B.3.10.3.

Cost-effectiveness

The most representative incremental cost-effectiveness ratio (ICER) presented by the company, for the NICE committee to determine cost-effectiveness, is below the modified ICER threshold for life-saving treatments for rare diseases (and therefore cost-effective).

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Sebelipase alfa is the first and only approved treatment for rapidly progressive LAL-D. Sebelipase alfa is a highly innovative therapy that acts as a replacement for the missing or dysfunctional LAL enzyme, meaning that it is able to treat the underlying causes of LAL-D. Supportive therapies used in the absence of sebelipase alfa are unable to alter the prognosis of death.[2]

Since the EU approval of sebelipase alfa in 2015, over 13 years of experience has been collated from a combination of clinical trials and subsequent real-world use; infants treated with sebelipase alfa are the first to have shown prolonged survival compared with historic controls,

proving that sebelipase alfa enables patients to break down the fatty material (e.g. triglycerides and cholesterol esters) in their body that previously resulted in their health problems.[22]

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Following the previous appraisal by NICE for sebelipase alfa (ID737), the decision was made to focus this appraisal solely on the treatment of patients with rapidly progressive LAL-D, the most severe form of LAL-D that starts in infants. This decision was made as patients with rapidly progressive LAL-D have the highest level of unmet need and are therefore more likely to experience a greater relative improvement in their health compared to the overall LAL-D population.

As age is a protected characteristic in UK law, it is possible that not including patients with LAL-D in this appraisal due to their age could result in equality issues. Older children, adolescents and adults with LAL-D may be negatively impacted by not having access to treatment with sebelipase alfa, despite evidence of proven clinical efficacy in these groups.

No further equality issues were identified based on disability, gender reassignment, relationship status, pregnancy and maternity, race, religion or belief, sex and/or sexual orientation.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement
- NICE's guides and templates for patient involvement in HTAs: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/support-for-vcs-organisations/help-us-develop-guidance/guides-to-developing-our-guidance
- EUPATI guidance on patient involvement in NICE: https://toolbox.eupati.eu/resources/guidance-for-patient-involvement-in-hta/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf

- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: https://apps.who.int/iris/bitstream/handle/10665/332207/WHO-EURO-2005-611-40346-54035-eng.pdf?sequence=1&isAllowed=y

Patient groups and charities:

- The MPS society: https://www.mpssociety.org.uk/lald
- Children's Liver Disease Foundation: https://childliverdisease.org/
- Genetic Alliance UK: https://geneticalliance.org.uk/

Further information about rapidly progressive LAL-D:

- Alexion website: LAL-D
- Video LAL-D: Hope Begins with Understanding

4b) Glossary of terms

Antibody: A protein component of the immune system that circulates in the blood, recognizes foreign substances like bacteria and viruses, and neutralizes them.[30]

Antidrug antibodies: Drugs such as sebelipase alfa can trigger an unintended immune response in which the body forms anti-drug antibodies that actually "fight" the drug.[15]

Clinical trial: a type of research that studies new tests and treatments and evaluates their effects on human health outcomes.[31]

Cirrhosis: A type of chronic, progressive liver disease in which liver cells are replaced by scar tissue.[32]

Failure to thrive: When the weight or rate of weight gain is significantly below that of other children of similar age and sex.[33]

Health Technology assessment (HTA): the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology.[34]

Hematopoietic stem cell transplant (HSCT): The process of providing a patient with healthy stem cells that can replace diseased cells intentionally destroyed by therapy.[32]

HTA bodies: Private or public organizations that perform HTAs.[34]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion.[32]

Intravenous (IV): Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein.[32]

Lysosomes: A sac-like compartment inside a cell that has enzymes that can break down cellular components that need to be destroyed.[32]

Parenteral nutrition: A form of nutrition that is delivered into a vein. Parenteral nutrition does not use the digestive system. It may be given to people who are unable to absorb nutrients through the intestinal tract because of vomiting that won't stop, severe diarrhoea, or intestinal disease. It may also be given to those undergoing high-dose chemotherapy or radiation and bone marrow transplantation. It is possible to give all of the protein, calories, vitamins and minerals a person needs using parenteral nutrition. Also called hyperalimentation, total parenteral nutrition, and TPN.[32]

Quality of life: An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[35]

Side effect: An unexpected medical event that arises during treatment with a drug or other therapy. Side effects can be classified as mild, moderate or severe.[32]

Undernourished: A person who has less than the minimum amount of the nutrients and food essential for good health and growth[36]

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Alexion pharmaceuticals. Patient Infusion Brochure 2022. Available at: Accessed: 18 October 2022.
2. Jones SA, Valayannopoulos V, Schneider E, et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. *Genet Med*. 2016; 18(5):452-8.
3. Bernstein DL, Hülkova H, Bialer MG and Desnick RJ. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. *Journal of Hepatology*. 2013; 58(6):1230-43.
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5. Reiner Ž, Guardamagna O, Nair D, et al. Lysosomal acid lipase deficiency – An under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis*. 2014; 235(1):21-30.
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7. Sardella M and Belcher G. Pharmacovigilance of medicines for rare and ultrarare diseases. *Ther Adv Drug Saf*. 2018; 9(11):631-8.
8. Hassall S, Smith DM, Rust S, et al. “Why them, why me, why us?” The experiences of parents of children with lysosomal acid lipase deficiency: an interpretative phenomenological analysis study. *Orphanet J Rare Dis*. 2022; 17(1):193.
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12. Santos Silva E, Klaudel-Dreszler M, Bakuła A, et al. Early onset lysosomal acid lipase deficiency presenting as secondary hemophagocytic lymphohistiocytosis: Two infants treated with sebelipase alfa. *Clin Res Hepatol Gastroenterol*. 2018; 42(5):e77-e82.
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15. van Brummelen EM, Ros W, Wolbink G, et al. Antidrug Antibody Formation in Oncology: Clinical Relevance and Challenges. *Oncologist*. 2016; 21(10):1260-8.
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18. Middleton SJ and Jamieson NV. The current status of small bowel transplantation in the UK and internationally. *Gut*. 2005; 54(11):1650-7.
19. Slae M, Ghosh A, Arvonen M, et al. Experience of the nutritional management of infantile onset lysosomal acid lipase deficiency (LAL-D). *JPGN*. 2018; 66:928.
20. Alexion pharmaceuticals. Patient Information Leaflet. 2022. (Updated: 15 April 2022) Available at: Accessed: 31 October 2022.
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22. Vijay S, Brassier A, Ghosh A, et al. Long-term survival with sebelipase alfa enzyme replacement therapy in infants with rapidly progressive lysosomal acid lipase deficiency: final results from 2 open-label studies. *Orphanet J Rare Dis*. 2021; 16(1):13.
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28. Cossette A, Castilloux J, Bouffard C, et al. Early diagnosis and successful long-term management of a rare, severe lysosomal acid lipase deficiency/Wolman disease patient: Infancy to age five. *Can Liver J*. 2022; 5(3):428-34.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Appraisal

Sebelipase alfa for treating Wolman disease (rapidly progressive LAL-D) [ID3995]

Clarification questions

November 2022

File name	Version	Contains confidential information	Date
ID3995 sebelipase alfa clarification letter [ACIC]_121222	2	Yes	20/12/2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision Problem

A1. With reference to the decision problem presented in the company submission (Document B Table 1 page 9-13), the population defined by NICE in the final scope (people with Wolman disease) appears to be different to the company submission and accompanying rationale, which appears to be patients with rapidly progressive LAL-D up to the age of 24 months.

To understand the population of interest can the company address the following points:

a) **Provide a precise definition of rapidly progressive LAL-D, including the maximum age of onset and clinical diagnostic features; please highlight any deviations from the NICE scope and provide justification for these deviations.**

b) **On page 19 of Document B, the company states, *"The clinical experience in the UK has shown that, rarely, patients can present with rapidly progressed and advance LAL-D between 6 and 24 months of age. These patients present with severe impairment of liver function (advance fibrosis) and require treatment intervention with ERT. There have been***

[redacted] ***cases of such presentation in the UK over the last 7 years."*** **Could the company confirm if the two UK cases experienced clinical onset between 6-24 months or presented earlier but experienced delayed diagnosis?**

a) There are no differences between the definitions for rapidly progressive LAL-D and Wolman disease. As mentioned in the company submission, the term "rapidly progressive LAL-D" is used instead of the historical term "Wolman disease" as it describes better the nature of the condition and is also more frequently used in recently published literature. Despite the usage of the more recent term "rapidly progressive LAL-D", the definition and description of the population has not changed. The description/definition of the population remains the same as it is described in the NICE final scope document as well as Alexion's submission documents. For example, in the NICE final scope document (Page 1), the description is as follows:[1]

"Wolman disease is a type of LAL deficiency that presents in babies and children under 2 years as rapidly progressing multisystem disease. Wolman disease is characterised by intestinal failure and severe malabsorption, growth failure, hepatosplenomegaly and progressive liver fibrosis and cirrhosis. The condition normally results in death in the first 6 months of life, usually due to multiple organ failure. For the smaller group of children diagnosed slightly later (under 2 years), there is still usually evidence of growth failure in the first 6 months of life"

In Document B (pages 18-19) of the company submission, the description of the population is as follows:

"The rapidly progressive infantile-onset form (historically called Wolman disease) where symptom onset is usually within the first 6 months of life represents a medical emergency and is typically fatal in a matter of months. Without treatment, death usually occurs in the first 6 months of life. The clinical experience in the UK has shown that, rarely, patients can present with rapidly progressed and advance LAL-D between 6 and 24 months of age. These patients present with severe impairment of liver function (advance fibrosis) and require treatment intervention with ERT"

Therefore, there is no difference in the clinical symptomatology or time from birth that the rapidly progressive LAL-D (or Wolman Disease) is described/defined in the scope document and the company submission.

b) [redacted]. If the EAG requires further information on [redacted], the treating clinicians should be contacted as Alexion does not hold patient specific information due to relevant laws/regulations.

A2. In a similar format to Table 3 in Document B of the company submission (page 34-35), complete the following table to clarify which data sources have been used to derive data for the outcomes listed in the first column of the table. Please detail in the relevant box the corresponding sections of the company submission where the outcome data are presented. Please justify if data for any of these outcomes have been omitted from the company submission.

Table 1 presents a cross-reference from each of the data sources presented in the company submission to each of the outcomes outlined in the decision problem.

Table 1: Summary of outcomes presented in the company submission

Outcomes	Data source					
	LAL-CL03	LAL-CL08	LAL-1-NH01	ALX-LALD-501	GATM[c]	SLR† 2015 and 2022 update
Mortality	✓ - Document B, Section B.2.6.2.1	✓ - Document B, Section B.2.6.1.1	✓- Document B, Section B.2.9.1	✓- Document B, Section B.2.6.3.2.2	✓- Document B, Section B.2.6.3.2.2	No additional relevant studies were identified in either the 2015 or 2022 SLRs. All relevant information is therefore provided in the previous columns of this table.
Body weight and nutritional parameters	✓- Document B, Section B.2.6.2.2	✓- Document B, Section B.2.6.1.2	✓- Document B, Section B.2.9.2	✓- Document B, Section B.2.6.3.2.2	✗ - The GATM does not provide data for this outcome	
Haematological parameters	✓- Document B, Section B.2.6.2.4	✓- Document B, Section B.2.6.1.4	✗ - Although LAL-1-NH01 did assess haematological and lipid parameters, these results were not presented in the submission. As the survival of patients enrolled in LAL-1-NH01 was so poor (i.e. median survival of ~3.0 months), this data was not considered a key focus. For further detail, please refer to the LAL-1-NH01 CSR in the reference pack provided alongside the company submission	✗ - The ALX-LALD-501 registry does not provide data for this outcome	✗ - The GATM does not provide data for this outcome	
Lipid parameters	✓- Document B, Section B.2.6.2.6/ Appendix L.3.4	✓- Document B, Section B.2.6.1.6/ Appendix L.2.4		✗ - The ALX-LALD-501 registry does not provide data for this outcome	✗ - The GATM does not provide data for this outcome	
Liver function	✓- Document B, Section B.2.6.2.3.1	✓- Document B, Section B.2.6.1.3.1	✓- Document B, Section B.2.9.3	✗ - Although the ALX-LALD-501 registry did collate data on liver	✗ - The GATM does not provide data for this outcome	

Liver disease progression	✓- Document B, Section B.2.6.2.3.2	✓- Document B, Section B.2.6.1.3.2	✗ - Although LAL-1-NH01 did assess liver and spleen volume through autopsy reports, these results were not presented in the submission. As the survival of patients enrolled in LAL-1-NH01 was so poor (i.e. median survival of ~3.0 months), this data was not considered a key focus. For further detail, please refer to the LAL-1-NH01 CSR in the reference pack provided alongside the company submission	function/ liver disease progression, these results were not presented in the submission. Please refer to the text below this table for the liver function and liver disease progression data from the ALX-LALD-501 registry.[2] As more robust evidence is provided through data from LAL-CL08 and LAL-CL03, and as data from the ALX- LALD-501 registry largely overlaps with data from LAL-CL03/LAL-CL08, this data was considered to be superfluous. This data was not used in the economic model.	✗ - The GATM does not provide data for this outcome	
Adrenal gland function	✗ - No adrenal gland function evidence was captured in LAL-CL08 or LAL-CL03, so we will not be able to include this outcome as requested in the pre-invitation scope. Clinicians have noted adrenal failure has not been a reported finding, even in long-term follow-up of affected infants receiving treatment.		✗ - The LAL-1-NH01 study does not provide data for this outcome	✗ - The ALX-LALD-501 registry does not provide data for this outcome	✗ - The GATM does not provide data for this outcome	

Neurological development parameters	✓- Document B, Section B.2.6.2.5	✓- Document B, Section B.2.6.1.5	✗ - The LAL-1-NH01 study does not provide data for this outcome	✗ - The ALX-LALD-501 registry does not provide data for this outcome	✗ - The GATM does not provide data for this outcome	
Cardiovascular events	✓- Document B, Section B.2.10.2.3	✓- Document B, Section B.2..10.1.3	✗ - The LAL-1-NH01 study does not provide data for this outcome	✓- Document B, Section B.2.10.3.3 [b] Please refer to the table notes for further information	✗ - The GATM does not provide data for this outcome	
Anti-drug antibodies	✓- Document B, Section B.2.10.2.4	✓- Document B, Section B.2.10.1.4	Not applicable – patients did not received treatment with sebelipase alfa	✓- Document B, Section B.2.10.3.2	✗ - The GATM does not provide data for this outcome	
Adverse effects of treatment	✓- Document B, Section B.2.10.2.2-B.2.10.2.3	✓- Document B, Section B.2.10.1.2-B.2.10.1.3	Not applicable – patients received treatment with sebelipase alfa	✓- Document B, Section B.2.10.2-B.2.10.3	✗ - Although adverse event data is monitored, and clinicians are required to report any adverse events through the defined channels, the GATM does not formally collect patient level clinical data. No safety data from the GATM is therefore available for this submission. Please note the patient population captured in the GATM programme largely overlaps with the UK patients enrolled in the ALX-LALD-501 registry and the LAL-CL08 and LAL-CL03 trials.	

Health-related quality of life	✗ - No HRQL evidence was captured in LAL-CL08 or LAL-CL03[a]	✗ - No HRQL evidence was captured	✗ - No HRQL evidence was captured	✗ - The GATM does not provide data for this outcome	

Footnotes:
† Please report relevant evidence for the SLR in 2015 [ID 737] (which matches the Decision Problem in ID3995) and the 2022 update reported in this submission.

Key: AE, adverse event; CV, cardiovascular; GATM, Global Access to Medicines programme; HRQL, health-related quality of life; SLR, systematic literature review.
Notes: [a] HQRL evidence was not written into the protocol for the LAL-CL08 and LAL-CL03 trials. This is due to the very young age of the patients enrolled and therefore the inability to provide any accurate readings using self-report HRQL instruments.
[b] Table 22 (Document B) of the company submission presents a summary of AEs reported by ≥ 4 patients in ALX-LALD-501. Less than four patients in the ALX-LALD-501 registry experienced a CV event, meaning these patients were omitted from this table.
[c] As the GATM programme has no formal data collection requirements, the data collected is limited to commentary provided by clinicians.

Liver function data from the ALX-LALD-501 registry is presented below in Table 2. The liver function data presented from the ALX-LALD-501 registry was generally consistent with that presented in the LAL-CL08 and LAL-CL03 trials.

Liver disease progression data was provided for each individual patient, and can be found as a Listing in the reference pack provided alongside this document (i.e. ALX-LALD-501, Listing 5).[2]

Table 2: Liver function laboratory results at baseline and last follow-up (study population)

	UK patients (n = 7)	Non-UK patients (n = 20)	All patients (N = 27)
ALT, U/L			
Baseline			
n	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Last reported value			
n	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Change from baseline			
n	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
AST, U/L			
Baseline			
n	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Last reported value			
n	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Change from baseline			
n	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Source: Additional ALX-LALD-501 registry data.[2]

Clinical care pathway

A3. On page 24 of Document B of the company submission, it states [redacted] Could the company please confirm:

a) What dose reduction/dose interval criteria was used for each of the patients who changed dose?

b) What criteria were used to assess whether a patient was able to stop treatment with sebelipase alfa?

c) Will these same criteria be used in practice if sebelipase alfa received NICE approval? If not, please confirm what the proposed criteria will be.

a) / b) The information outlined in the question is clinician feedback provided in April 2022 of the four surviving patients presented in the Potter et al. 2021 study.[3] All patients received treatment with sebelipase alfa and HSCT, also referred to as multi-modal therapy. The evolution of the use of multimodal therapy is being led out of the UK by Dr Simon Jones (Manchester). It was stated in Potter et al. 2021 that the dose of sebelipase alfa received by the patients was based upon clinical need. Current UK clinical practice aligns with the publication.

In July 2022, an interview was conducted with Dr Jones, alongside another UK clinical expert, Dr Suresh Vijay (Birmingham).[4] These clinicians are responsible for treating [redacted] infants in the UK with rapidly-progressing LAL-D who are currently receiving treatment with sebelipase alfa under the GATM programme. During the interview, it was stated that the dosage of sebelipase alfa received would not change until at least 1-year post-HSCT, as in the year following HSCT there remains an abnormally high concentration of lipids and macrophages in tissues, such as the duodenum. The clinicians also stated that it takes a while to see the benefits of the HSCT, and therefore the clinician does not reduce the dose of sebelipase alfa until the patient has stabilised and no longer requires additional supportive treatment with immunosuppressants.

All patients who receive early HSCT are expected to discontinue treatment with sebelipase alfa, and is generally based on clinical opinion and the holistic approach to assessing key clinical parameters. Clinicians estimated that the process of weaning off sebelipase alfa completely can take up to two years, during which patients may be able to reduce from weekly dosing to alternate weekly dosing of sebelipase alfa.

c) As rapidly progressive LAL-D patients based in the UK have had access to sebelipase alfa through the Alexion GATM programme for the past 10 years and are treated by UK clinicians[5], it is anticipated that a recommendation from NICE would not change the way in which sebelipase alfa will be used in UK practice. Clinical

practice for the treatment of rapidly progressive LAL-D is rapidly evolving, and expert clinicians in the UK are at the forefront of new pioneering approaches to treatment, including the use of the multimodal therapy of sebelipase alfa followed by HSCT. If further clarification is required, the company would recommend reaching out for additional consultation with key opinion leaders in the UK.

Systematic Review

A4. The NICE health technology evaluations manual (2022) recommends the systematic review relating to effectiveness evidence should be completed using a pre-defined protocol. Could the company please provide the protocol (if available).

The systematic reviews were conducted as per the methodology laid out in a pre-defined protocol. The protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for designing, performing, and reporting the systematic literature review. This pre-defined protocols for the clinical and utility SLRs have been embedded here for reference.


Clinical SLR Protocol


Utility SLR Protocol

A5. In Section D.1.3 (page 9) of the Appendices of the company submission it is stated that *"the PRISMA and list of included studies of the original SLR conducted on 01 June 2015, as presented in ID737, can be found in the SLR report"*.

a) **Please could a PRISMA checklist and list of included and excluded studies from ID737 relevant to the ID3995 NICE scope be provided?**

b) If any of the 2015 SLR studies are relevant to the ID3995 NICE scope, could these please be detailed in full and cross-referenced to outcomes listed in the Decision Problem as per the table described in A2 above?

Two relevant to the ID3995 NICE scope: LAL-CL03 and LAL-1-NH01 were identified. The SLR update conducted in June 2022 identified both of these studies as their primary publications which were published after the searches had been conducted for ID737 (Jones et al. 2017[6] and Jones et al. 2016[7], respectively). Please therefore refer to question A2 for the cross-reference of LAL-CL03 and LAL-1-NH01 to the outcomes listed in the decision problem.

a) The list included studies from ID737 relevant to the ID3995 NICE scope is provided below in the embedded document

List of studies inlcuded for ID737

PRISMA checklist for the clinical and utility SLRs informing ID3996 is presented below. Please note that a detailed SLR report was not prepared and information from the SLR was incorporated into the ID3995 NICE submission dossier. Hence, the items have been mapped to their location within the ID3995 NICE submission dossier, wherever applicable:

ID3995 PRISMA Checklist

b) Two studies from the 2015 SLR that are relevant to the ID3995 NICE scope have been detailed below. The details on these studies are also available in Document B:

1. LAL-1-NH01

The natural history study, LAL-1-NH01, evaluated data on 35 infants with confirmed LAL D (mean age at onset of disease, 1.5 months). The study provided the first systematic evaluation of the natural history of LAL D presenting in infants and confirmed the rapidly progressive nature of the

disease in this population. The study also provides a comprehensive understanding of important aspects of disease progression and factors which appear to influence the disease course. Data from this study are used as an historical control for the Phase 2/3 sebelipase alfa study in infants, LAL-CL03. The control group from Study LAL-1-NH01 selected for comparison includes 21 patients with growth failure who did not receive transplant (HSCT or liver).

Median age at death was 3.7 months and the estimated probability of survival past age 12 months was 0.114 (95% CI: 0.009-0.220). Among 26 patients with early GF, median age at death was 3.5 months; estimated probability of survival past age 12 months was 0.038 (95% CI: 0.000-0.112). Treated patients (HSCT, n=9; HSCT + liver transplant, n=1) in the overall population and the early GF subset survived longer than untreated patients, but survival was still poor (median age at death, 8.6 months).

The final results of the LAL-1-NH01 study are published in the Genetics in Medicine journal (Jones SA, Valayannopoulos V, Schneider E, et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. *Genetics in Medicine*. 2016; 18: 452-8). This publication was not available in 2015 during ID737 submission.

2. LAL-CL03

The pivotal Phase 2/3 study in infants, LAL-CL03, was designed to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of sebelipase alfa in subjects with LAL-D who developed growth failure before 6 months of age. The study has completed enrolment with 9 infants treated, having median age of 3.0 months (range 1.1–5.8 months) at baseline.

67% of infants treated with sebelipase alfa survived to 12 months of age compared with 0% (exact 95% CI 0%–16%) for a historical control group of 21 infants. Infants who survived to age 12 months exhibited improvements in weight-for-age, reductions in markers of liver dysfunction

and hepatosplenomegaly, and improvements in anaemia and gastrointestinal symptoms. Three deaths occurred early (first few months of life), two patients died because of advanced disease, and a third patient died following complications of abdominal paracentesis. A fourth death occurred at 15 months of age and was related to other clinical conditions. The five surviving patients have survived to age ≥24 months with continued sebelipase alfa treatment; all have displayed marked improvement in growth parameters and liver function. Serious adverse events considered related to sebelipase alfa were reported in one of the nine infants (infusion reaction: tachycardia, pallor, chills, and pyrexia). Most infusion-associated reactions were mild and non-serious.

The final findings of the LAL-CL03 study are published in the Orphanet Journal of Rare Diseases (Jones SA, Rojas-Caro S, Quinn AG, et al. Survival in infants treated with sebelipase Alfa for lysosomal acid lipase deficiency: an open-label, multicenter, dose-escalation study. *Orphanet Journal of Rare Diseases*. 2017; 12). This publication was not available in 2015 during ID737 submission.

A6. Appendix G (page 23) of the company submission mentioned "*a new targeted search identified a recent systematic review of economic evaluations of ERT in LSDs, including infantile-onset LAL-D (published 19 September 2022).*[8] *Only one relevant study was found, which was the National Centre of Pharmacoeconomics (NCPE) assessment of sebelipase alfa in 2018.*" The company have not defined what a targeted literature review is as it lacks a standardised definition. Could you please clarify what do you mean by 'targeted search' (description of the method) and which databases you have searched for the targeted literature review of economic evaluations? Please could you describe in more detail the methods that the targeted literature review has adopted and whether there was a prespecified protocol for this targeted literature review.

Given sebelipase alfa is the only active treatment available for rapidly progressive LAL-D; has previously been assessed by NICE and is already in use within UK

clinical practice the findings of any literature review of economic evaluations were considered likely to be of limited use. Given this only ad-hoc searches were conducted to supplement consideration of the learnings from the prior appraisal. This is in line with the NICE guidance produced in 2022 which takes a more pragmatic approach to identification of economic evidence: "Reviews may not be exhaustive if additional studies identified would merely provide further support that is consistent with the already-identified evidence (rather than necessarily identifying all relevant studies)." The SLR by Katsigianni et al. 2022 was identified following an ad hoc search of PubMed and ovid Medline, using terms such as, 'enzyme replacement therapy', 'LAL-D', 'Wolman disease' 'cost effectiveness model OR economic model' and 'economic evaluation'. This reference provides an up to date summary of the evidence, and so, the company concluded that the Katsigianni SLR would provide decision makers with the relevant information required over and above the previous appraisal. The only additional reference found was the NCPE submission for sebelipase alpha which was conducted with input from Alexion using a model adapted from the one used originally for the first NICE appraisal in 2015.

A7. Figure 1 (page 10) in the appendices document of the company submission (PRISMA flow chart) details 488 records were excluded initially, with a further 41 reports excluded subsequently. Could the company please clarify the studies excluded at full-text screening as the numbers in the PRISMA flow chart and the 540 records included in the embedded Excel spreadsheet do not appear to correspond?

The PRISMA flow chart depicts 11 records excluded as duplicates before initiating the screening process, 488 records excluded during abstract screening, and 41 records excluded during full-text screening. The list of excluded studies provided in the Excel spreadsheet comprise of records excluded at three stages depicted in the PRISMA flow chart (i.e., deduplicates (n=11), abstract screening exclusion (n=488), and full-text screening exclusion (n=41). Hence, the list includes a total of 540 excluded records (i.e., 11+488+41). For clarity, the 11 records excluded during the de-duplication stage have also been highlighted under Exclusion Reason with the Excel spreadsheet.

Trial evidence

A8. The eligibility criteria of LAL-CL08 required at least one of the symptoms listed in the table below to be included in the study. Please could you report what proportion of participants met each of the criteria listed in the first column of the table.

Table 3 presents the proportion of patients presenting with clinical concerns of rapidly progressing LAL-D, as outlined in the eligibility criteria; each patient must have at least one of these symptoms to be enrolled in the trial.

Table 3: Proportion of patients presenting with each clinical concern outlined in the eligibility criteria of LAL-CL03

Eligibility Criteria	LAL-CL08 (n = 10)
Failure to thrive/growth failure, n (%)	[redacted]
Marked abdominal distension and hepatomegaly, n (%)	[redacted]
Disturbance of coagulation (e.g. 2 values of prothrombin time > 15 seconds, or partial thromboplastin time > 40 seconds), n (%)*	Prolonged aPTT: [redacted] Shortened aPTT: [redacted] Shortened prothrombin time: [redacted]
Severe anaemia, n (%)	[redacted]
Sibling or cousin with rapidly progressive course of LAL-D, n (%)	[redacted]
Other (please specify)	

Key: aPTT, activated partial thromboplastin time; LAL-D, lysosomal acid lipase deficiency.
Notes: * Coagulation parameter data were available for six patients at baseline.
Source: LAL-CL08 Listing 16.2.2.1.1[9]

A9. Please also detail whether the nine patients in LAL-1-NH01 who were not classified as having early growth failure had other symptoms of rapidly progressive LAL-D (aside from being diagnosed before 2 years of age).

Table 4 presents the proportion of patients with no confirmed growth failure within the first 6 months in the LAL-1-NH01 study presenting with clinical concerns of rapidly progressing LAL-D.

Table 4: Proportion of patients with no confirmed growth failure within the first 6 months presenting with specific clinical features

Presenting Features	LAL-1-NH01 (Eligible Patients with no Confirmed Growth Failure Within 6 Months; n = 9)
Failure to thrive/growth failure	[redacted]
Marked abdominal distension and hepatomegaly	[redacted]
Disturbance of coagulation	[redacted]

Severe anaemia	[redacted]
Sibling or cousin with rapidly progressive course of LAL-D	[redacted]
Severe and persistent diarrhoea and vomiting	[redacted]
Key: LAL-D, lysosomal acid lipase deficiency. **Notes:** * Consanguinity data was available for six of the nine patients. **Source:** LAL-1-NH01 presenting clinical features[10]	

A10. Please provide details of how many patients were from England/UK/Europe in LAL-NH01 (untreated with early growth failure), LAL-CL08 and LAL-CL03?

Table 5 presents the proportion of patients in England, the UK and Europe in LAL-CL08, LAL-CL03 and in the overall population of the LAL-1-NH01 study. Please note that the location of study sites for patients enrolled in LAL-1-NH01 was only available for the overall population (n = 35).

A large proportion of the patients enrolled in LAL-CL08 and LAL-CL03 were based in the UK and received treatment in UK hospitals. It has been confirmed by UK clinicians that the LAL-CL08 and LAL-CL03 trial populations are representative of the patients seen within UK clinical practice.

Table 5: Proportion of patients in England, the UK and Europe in LAL-CL08, LAL-CL03, and LAL-1-NH01 (overall population)

	LAL-CL08 (N = 10)	LAL-CL03 (N = 9)	LAL-1-NH01 (overall population; n = 35)
England, n (%)	[redacted]	[redacted]	[redacted]
UK, n (%)	[redacted]	[redacted]	[redacted]
Europe, n (%)	[redacted]	[redacted]	[redacted]
Source: LAL-CL08 demographic data[11]; LAL-CL03 demographic data[12]; LAL-1-NH01 demographic data[13].			

A11. For patients in LAL-CL03 and LAL-CL08, please detail:

a) **How many patients in each trial had HSCT, liver transplantation or both?**
b) **Why was transplantation given (did this relate to patient preference or clinical need)?**

c) The outcome measures separately as per NICE Scope for those who have/have not received HSCT.

As discussed with the EAG and the NICE team on the call on 1 December 2022, it is important to highlight the difference between the way that HSCT has been used historically (i.e. before the availability of sebelipase alfa, and during the early years of its use, such as during the clinical trials) and how it is being used now and planned to be used in the future, as part of a rapidly evolving clinical practice. This evolution in treatment practice is being led out of the UK by Dr Jones, as experience with the use of sebelipase alfa grows.

Historically, prior to the availability of sebelipase alfa, HSCT was used as a last resort in some infants in an attempt to prevent rapid progression and deterioration; however, these were usually unsuccessful. In LAL-1-NH01, a natural history study of infants with rapidly progressive LAL-D, only four of 35 (11.4%) infants in the overall population survived beyond 12 months of age and all four infants died by 4 years of age despite some receiving HSCT and/or liver transplant.[14] During the LAL-CL03 and LAL-CL08 sebelipase alfa clinical trials, HSCT was sometimes used in this way in a small numbers patients with ADAs who demonstrated a lack of response, as a last resort in order to try and slow or prevent progression and keep the patients alive; these patients are discussed in more detail in response to question A.11 b) below.

As experience with the use of sebelipase alfa has grown, treatment practice in the UK has evolved in the time period since the clinical trials ended. This multimodal therapy was initially used, and continues to be used in patients whose response to treatment diminished over time due to the development of anti-drug antibodies (ADAs). Despite being stable on treatment, there are estimated to be a large proportion of patients who will no longer be able to tolerate weekly infusions, for whom venous access becomes an issue, or who may choose to receive an HSCT in order to be able to reduce the burden associated with regular infusions. Outcomes in these patients who receive HSCT after being stable on long-term sebelipase alfa are expected to be significantly different from the outcomes associated with historical use of HSCT, and this is what has been included in the company economic model to more accurately reflect the thinking around current and future UK clinical practice.

a) Three patients in the LAL-CL08 trial received HSCT, and no patients received a liver transplant. In LAL-CL03, no patients received HSCT or liver transplant during the trial.[15, 16]

b) As outlined in Section B.1.3.4.1, Document B of the company submission, treatment with sebelipase alfa followed by HSCT was initially used in patients whose response to treatment diminished over time due to the development of anti-drug antibodies (ADAs), as confirmed by UK clinicians.[17] In LAL-CL08, [redacted] underwent HSCT at [redacted] after experiencing a variable clinical course in the presence of persistent high-titer ADAs.[16] Following HSCT, [redacted] experienced a reduction in high ADA titers, which was associated with an improvement in the clinical efficacy of sebelipase alfa. [redacted] due to an inflammatory HLH-type condition that failed to improve to a rapid dose escalation of sebelipase alfa.[16] This patient died later, at 13.8 months of age due to sepsis.[3] These patients therefore underwent HSCT as a last resort due to lack of response to treatment due to persistently high ADAs, or as an attempt to keep the patient alive.

   HSCT also has the potential for use when patients have stabilised with treatment with sebelipase alfa, but can no longer tolerate weekly infusions or in whom venous access becomes an issue.[18, 19] [redacted]

c) As discussed with the EAG and the NICE team on the call on 1 December 2022, the conduct of HSCT in the three patients of the LAL-CL08 trial is not related to the multimodal approach with HSCT that Alexion is modelling in the submission and the Potter et al.2021 publication analyses clinically.

   The multimodal therapy of sebelipase alfa and subsequent HSCT in LAL-CL08 took place, as a last resort, only for patients (with entire deletion of the LIPA gene) that did not improve adequately on sebelipase alfa and had also very high anti-drug antibody titres. Therefore, no formal analyses were conducted on the three patients who received HSCT during the LAL-CL08 trial.

   The approach modelled in the submission and described in the Potter publication goes beyond those types of patients and, as modelled, includes HSCT as a tool for a broader patient population in conjunction with sebelipase

alfa treatment with the aim to reduce or eliminate the need for sebelipase alfa treatment in the transplanted patients.

Of note, narratives for the three patients in LAL-CL08 who received HSCT are reported in the Potter et al. 2021 publication, specifically patients 1, 2 and 3.[3] Patient 5 of the Potter et al. 2021 publication was also enrolled in LAL-CL08, but received HSCT post-completion of the trial under the GATM programme.

A12. In Document B Section B2.8 (page 79) of the company submission report mentioned "*results from LAL-CL08 and LAL-CL03 have been pooled to provide results for a larger sample of patients*" and data from the natural history study (LAL-1-NH01) have been used to provide historical control data

a) **Please provide justifications and rationale of pooling data regarding using different dosage and different populations across two studies (CL03 & CL08)?**

LAL-D is an ultra-rare disease, in which only a small fraction of patients present with rapidly progressive LAL-D in infancy. The number of patients recruited into LAL-CL03 and LAL-CL08 were nine and 10, respectively. There are no other systematic studies in this patient population. A pooled analysis of the total population of 19 patients was carried out to provide the best overview of baseline and treatment effects on a variety of endpoints, including survival. LAL-CL03 and LAL-CL08 assess the safety and efficacy of sebelipase alfa in patients with rapidly progressive LAL-D symptomatic in infancy. The patient populations, endpoints and visit schedules are very similar between both studies. There was no prior experience with sebelipase alfa in these patients. The starting dose of 0.35 mg/kg QOW in LAL-CL03 was a low (safety) dose with a scheduled dose increase to 1 mg/kg QOW. From 1 mg/kg QOW, there was no scheduled dose increase, but the provision for dose increase as clinically necessary in both studies.

b) **Please provide a description of the methods used to pool the data across these two studies**

Given the similarity across both studies, the patient populations from LAL-CL03 and LAL-CL08 were directly pooled into one database for statistical analysis and no other adjustments were made.

c) **Please clearly describe how the data from LAL-1-NH01 have been adjusted to provide a fair natural history control for the pooled data from LAL-CL08 and LAL-CL03.**

Analyses for the natural history study (LAL-1-NH01) were presented for the overall patient population and for two sub-populations: patients with early growth failure, and patients without early growth failure.[14] Given the inclusion and exclusion criteria in LAL-CL03 and LAL-CL08 as well as the baseline characteristics of the patients enrolled, the patient population with early growth failure was the most appropriate one to present alongside the patient population recruited into LAL-CL03 and LAL-CL08. The statistical analysis was descriptive and there was no formal statistical comparison between LAL-1-NH01 and LAL-CL03/LAL-CL08.[20]

Literature searching

A13. For the EAG to fulfil part of its remit, to critically appraise the searches performed, could the company please provide further details for the following searches for: 1) clinical effectiveness studies; 2) cost-effectiveness studies; and 3) health-related quality of life studies. Specifically, could the company please provide:

a) The complete search strategies for all the databases, exactly as run, including the number of records (hits) retrieved by each line of the search.


Clinical SLR Search Strategy


Utility SLR Search Strategy

b) Date ranges and dates of coverage of the databases searched.

For clinical as well as utility SLRs, searches were conducted from January 2015 till June 2022 across all databases (i.e., Embase, MEDLINE, Cochrane, EconLit, HTA and NHS EED)

c) Host sources for all the databases searched, e.g., *Ovid*.

i) Embase and MEDLINE: embase.com

ii) MEDLINE In-Process: pubmed.ncbi.nlm.nih.gov

iii) Cochrane: www.cochranelibrary.com

iv) EconLit: eds.p.ebscohost.com

v) HTA & NHS EED: www.crd.york.ac.uk

d) Please provide a full description of the database 'segments' searched e.g., *Ovid MEDLINE® and/or Ovid MEDLINE® In-Process & In-Data-Review Citations.*

i) Embase and MEDLINE: 'Embase' and 'MEDLINE' using embase.com

ii) MEDLINE In-Process: Search string for In-Process records using pubmed.ncbi.nlm.nih.gov [i.e., (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint) OR (inprocess[sb])]

iii) Cochrane: Cochrane Library publications using www.cochranelibrary.com

iv) EconLit: 'EBSCO Discovery Service' using eds.p.ebscohost.com

v) HTA & NHS EED: 'HTA' and 'NHS EED' using www.crd.york.ac.uk

e) The date(s) on which each search was performed.

Dates for searches conducted in each database are provided in the response documents embedded under Query A13a

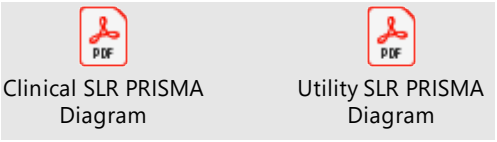
f) The strategies should include any limitations imposed on the search and for updated searches should also include any terms/syntax/limits applied and/or any date fields specifically searched.

Detailed syntax, search terms, and limits applied to the search strategies are provided in the response documents embedded under Query A13a

g) Where search filters, designed by a third party, have been used please provide the reference(s) for these.

No search filters were applied in addition to the detailed search strategies provided in the response documents embedded under Query A13a

h) Please include fully populated PRISMA diagrams for all the documented searches.



Section B: Clarification on cost-effectiveness data

B1. Document B of the company submission: Please explain the methods used for eliciting clinical expert opinion for the economic analysis sections mentioned below:

a) Dose requirement of sebelipase alfa (Section B.3.2.2. Figure 21 page 114)
b) Decision on early and late HSCT (Section B.3.3.3 page 125-126 & Table 32 page 127)
c) Dosing levels and dosing distributions (Section B.3.3.4 Table 33 page 127)
d) Duration of neonatal critical care (Section B.3.5.2 Table 42 page 138)
e) Rate of resource consumption in the first 5 years (Section B.3.5.2 Table 43 page139)
f) Assumptions as outlined in the economic analysis (Section B.3.8.2 Table 52 page 150-152)

The model structure is *de novo* and was built in a collaboration of health economists and the foremost clinical specialists in the management of rapidly progressive LAL-D. That rapidly progressive LAL-D is very rare, and there being so few clinicians who treat the people with the disease, has precluded systematic elicitation methods designed to minimise potential bias, such as structured panel methods. However, the inclusion of the two leading specialists in England including the only clinician currently undertaking stem cell transplant in this population provides a large sample

of the total population in England and inclusion of the most contemporary clinical practices.

a) The decision tree illustrated in CS Figure B21 details the framework for clinical decisions that impact the mean dose requirement per kg weight in the modelled cohort at any time in the model horizon. Decision nodes facilitate the opportunity for division based on any clinically advised alteration of dose requirement, including change consequent to HSCT. Each node allows 0-100% of the preceding fraction to pass down one or more options. E.g., Figure B21 Node 1: Level 2 dosing (after first increase for all patients) to level 3 dosing (preceding early HSCT) or L2 dosing (no change). Derivation of the framework was incremental in development. Two validation stage-posts were used to ensure that the tree was representative of the SA dosing paradigm for the modelled population. The flexibility provided by dosing levels options should facilitate observed dosing patterns in the prevalent treated population (aged up to 11 years old) as well as the expected dosing patterns of older age (unobserved). Validation of the decision tree including dose levels was by means of interviews with Dr Simon Jones (Manchester) and Dr Suresh Vijay (Birmingham).

b) Dr Simon Jones is the leading exponent in England for HSCT in people with rapidly progressive LAL-D (Dr Jones is an author of the paper 'Enzyme replacement therapy and hematopoietic stem cell transplant: a new paradigm of treatment in Wolman disease'[3]. The principle of early and late in life HSCT was developed by the company with Dr Jones and the validation process included Dr Vijay. The proportion of patients estimated to be recipients of HSCT at these respective stages (CS Table B32) was based on the experience and opinion of Dr Jones, taking account of most recent methods, risk, and rates of success.

c) Table B33 in the CS details six possible dosing levels. Each level describes a distribution of doses (E.g., 50% at 3mg/kg, 50% at 5mg/kg) to be applied to the cohort fraction as clinical decisions are made and as set out by the decision tree nodes. Sebelipase alpha dose in the model, using these levels, was based on the clinical experience of Dr Jones and Dr Vijay according to

their own practices, including the projection of future dosing based on experience to date in rapidly progressive LAL-D and experience with ERT in older populations of people with other lysosomal storage disorders. Elicitation of dose distribution at each of the levels was by independent interview with Dr Jones then Dr Vijay. Note that the starting dose in the model (3mg per kg); the starting dose in the summary of product characteristics is 1mg per kg or 3mg per kg; and the starting dose in trial CL-03 was 0.35 mg per kg, and 1mg per kg in CL-08. The higher starting dose was used in the model based on the clinical experience and advice of Dr Jones and Dr Vijay.

d) The duration of neonatal intensive care (CS Table B42) was elicited by independent interview with Dr Jones then Dr Vijay.

e) The rates of resource consumption (CS Table B43) were elicited by independent interview with Dr Jones then Dr Vijay.

f) Table B52 in the CS describes eight key assumptions made in the model. They are not numbered but are to be read descending from numbers 1 to 8. Assumptions 2-8 are based on Alexion health economist interpretation of information elicited in interview with Dr Simon Jones in the context of the modelling exercise. Assumption 1 is supported by disease-specific evidence from the literature.

Health-related quality of life

B2. Please answer the following questions in relation to utility values for Adverse Events (AEs).

a) **The company submission (Section B.3.3.2.1 page 110) states that they modelled "*utility as a function of age*". Could the company clarify how they inform the model for adverse events for utility? Please also see question B5 below.**

Change in utility from treatment emergent adverse events (TEAEs) with sebelipase alpha was not included in the model due to insensitivity of the ICER. Note that imaging and investigational resource consumption was included through the time

horizon, accounting for some resources relating to disease and treatment complications.

In LAL-CL08 severe TEAEs were reported in only one patient (Infusion-associated reaction) after 12 months of treatment and in no patients after 24 months of treatment [CS section B.2.10.1.2]. The most commonly reported TEAEs with lower severity included pyrexia (n = [redacted], [redacted] %), diarrhoea (n = [redacted], [redacted] %), vomiting (n = [redacted] %), tachycardia (n = [redacted] %), gastroenteritis (n = [redacted] %) and respiratory distress (n = [redacted] %) [CS section B.2.10.1.3].

In LAL-CL03 only one patient had an SAE that was deemed related to sebelipase alfa, which was further categorised as an IAR. Overall, IARs were reported in five (56%) patients [CS section B.2.10.2.2]. The most commonly reported TEAEs included diarrhoea (n = [redacted] %), vomiting (n [redacted] %), cough (n = [redacted] %), nasopharyngitis (n = [redacted] %), pyrexia (n = [redacted] %) and rhinitis (n = [redacted] %) [CS section B.2.10.2.3].

Most IARs are understood to have only a very temporary impact on HRQL and are successfully managed by infusion interruption/discontinuation, infusion-rate reduction and/or conventional treatment with antihistamines, corticosteroids, analgesics or antipyretics. To date, there does not appear to be any apparent cumulative toxicity based on review of TEAE incidence over time on treatment.

In interview, Dr Vijay noted the key adverse events as being line infections and routine infections with most patients. Line infections are considered manageable and transient (relative to the time horizon), and routine infections are not directly attributable to sebelipase alpha (only by consequence of the patient remaining alive). We do not believe that the inclusion of utility decrements for sebelipase alpha related adverse events would therefore have a meaningful impact on the ICER. Scenario 28 (CS Table B60) demonstrates low to moderate sensitivity of the ICER towards a relatively large 10% reduction in utility scores (11% impact on the base case ICER*). The safety profile of sebelipase alpha supports the anticipation that adverse events would have a cumulative impact which is considerably less than 10% over lifetime.

See response to clarification B3 for detail on the modelling of disutility associated with HSCT.

*Following correction. See answer to B3.

b) Please clarify if the duration of adverse events is determined and modelled?

The duration of adverse events is not applicable given their exclusion in the model.

B3. In Section B.3.4.5.1, on page 134 of Document B of the company submission it is stated that: "*An alternative scenario is explored in which a hazard ratio of 0.8 is applied to the utility through the time horizon.*"; and on page 135 "*No utility decrement is applied for HSCT in the base case. In a scenario analysis, a 0.57 utility decrement for HSCT follow-up is applied for a period of 3 months around the HSCT procedure, and a 0.13 decrement is applied for a further 9 months*". Could you please clarify the method used to arrive at these utility values for these timeframes?

In regard to the hazard ratio (more accurately termed 'adjusting multiplier') applied to utility (page 134, and scenario 28), the correct figure should be 0.9 not 0.8. A hazard ratio of 0.9 was applied to the general population utility scores applied through the time horizon of the model. The gender weighted average utility for an individual aged 16 or below was 0.929 in the base case. This was adjusted to 0.9*0.929=0.836 in scenario 28. However, in answering this clarification question we identified an error and note that the coding in P6:P91 in the 'HU norms' worksheet of the submitted excel file should be corrected using autofill according to this code for cell P6:

=(O6*P_Prop_Male)+(N6*(1-P_Prop_Male))*DSA_HU_norms, to

=((O6*P_Prop_Male)+(N6*(1-P_Prop_Male)))*DSA_HU_norms

This correction changes the outcomes of scenarios 28 and 29 to the following:

			Costs			QALYs			ICER
#	Sensitivity analysis	Original value	SA	BSC	Incremental	SA	BSC	Incremental	
28	10% reduction in HRQoL all ages	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£266,223
29	10% decrease HRQoL &	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£268,687

	20% HR on other cause mortality								

The selection of the 0.9 utility multiplier was arbitrary, intended only as an indicative method to illustrate the level of ICER sensitivity to an alternative lower set of utility values.

In regard to HSCT disutility, a systematic literature search for utility evidence did not identify any studies of the impact of HSCT on utility of people with rapidly progressive LAL-D (see CS Appendix). However, we conducted a targeted ad hoc search of NICE technology appraisals for utility evidence using increasingly broad search criteria. In the absence of hits in populations receiving ERT, with lysosomal storage disorders, and both, we broadened the search to include any health disorder in which HSCT was an intervention. We identified one relevant source in a search of previous NICE technology appraisals.

In the CS scenario 32 we cite to the source; the ERG (EAG) report for NICE technology appraisal TA554, Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (ERG report published 16 November 2018: https://www.nice.org.uk/guidance/ta554/documents/committee-papers) [Reference 56, CS Document B]. Specifically, we refer to Section 6.3.5 page 134 paragraph one where estimates are used by the ERG based on a study by Felder-Puig and colleagues. This was study of 68 paediatric patients with an assortment of mainly leukemias.[21]The described EAG preferred method has been applied directly in the absence of disease-specific evidence that might be used to optimise the approach for the modelled population. The stated preference is that used in our scenario: a decrement of 0.57 for 3 months following HSCT, which reduces to 0.13 for 9 months.

Estimation of costs

B4. In Document B (Section B.3.5.1.1.2 page 137) of the company submission the company states that "*a homecare service is funded by Alexion for the administration of sebelipase alfa, removing the cost to the payer/NHS*". Could the company advise whether they have considered the cost implications to the

NHS should this homecare service stop being provided by Alexion? Please conduct a scenario analysis to consider the costs of NHS long term homecare provision.

Alexion have provided a homecare service for people with LAL-D receiving sebelipase alpha since regulatory approval in 2015. Alexion provide homecare for all patients receiving their specialist products (E.g., NICE HST1, eculizumab for treating atypical haemolytic uraemic syndrome). There is no plan to withdraw this service. In anticipation of this question, please refer to CS Table B60 scenario 16.

B5. In Document B (Section B.3.5.2 page 139) of the company submission the company has provided Table 43 which outlines the healthcare resource use for this population group for the first 5 years. However, there is no information about the healthcare use and concomitant medication use associated with any adverse events or co-morbidities typical of this population group, which has been described in detail in the clinical trials. Could the company provide justification as to why this healthcare expenditure has been excluded?

Please refer to the answer given to clarification question B2 regarding adverse events. Resources described in CS section B.3.5 *do include* costs relating to specialised care for co-morbidities, as part of disease management (CS section B.3.5.2 Table 43 before age 5, Table 45 after age 5). Furthermore, the cost of specialist nutrition is included in the base case, an indirect cost consequent to the life-sustaining treatment of sebelipase alpha.

B6. The company states that the base case analysis, is in alignment with the NICE reference case, taking the payer perspective of the UK NHS setting (in Document B Section B.3.2.2 page 109 of the company submission). However, the resource use included does not seem to consider care services received in a primary care setting nor any personal social service care. Could the company provide justification for this exclusion? Could the company provide justification for this exclusion?

Costs relating to sebelipase alpha treatment in people with rapidly progressive LAL-D come from specialised NHS services. Treatment related costs are not expected to

spill into primary care or social care. The nature and rate of consumption of resources have been validated in interview with Dr Jones and Dr Vijay.

Economic model

B7. In Document B (Section B.3.3.2 page 122) of the company submission mentioned "*Parametric distributions were estimated…. Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used together with visual inspection to assess the model fit and plausibility*". Could you please clarify if you also considered the clinical plausibility (clinical expert elicitation) of fitted distribution for patients` lifetime in the model? If clinical plausibility was considered how was this done?

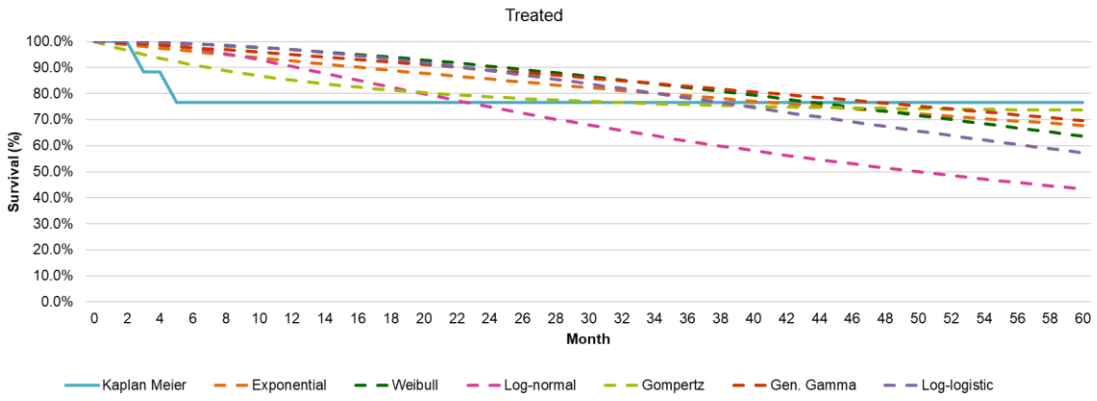
Note. The parametric curves fitted to the Kaplan Meier plots of overall survival are not used in the model base case.

Yes, the alternative long-term estimates of survival were assessed for their clinical plausibility. Since the untreated arm has complete data, we are referring here only to the treated arm (approximately 72% survival by the maximum 5-year follow-up).

The premise of plausibility assessment is the assumption of no LAL-D mortality beyond 5 years. (See trial outcomes in excel file 'KM survival analysis' worksheet, table B7:F17). The final on-treatment event was at 4.86 months (Note. With reference to the 2015 NICE HST ID 737, this survival analysis excluded patient 005 because cause of death was not attributed to LAL-D or SA). In the context of no long-term LAL-D mortality on treatment we compared the expected long-term estimates of the parametric alternatives (See excel file 'Survival summary' worksheet, plot labelled 'Treated') and found that the exponential, Weibull, log-normal, generalised gamma, and log-logistic interpolations would over-estimate mortality over a life-time horizon versus clinical expectation. Only the Gompertz curve flattened enough offer to plausible long-term prediction. Nonetheless, all offered poor short-term fits and remained less favourable compared to direct use of Kaplan-Meier extrapolated under an assumption of no further LAL-D mortality. Please refer to CS Table B60 scenario 4 to see the impact of the Gompertz approach when used as an alternative to the KM plot through years one to five.

Erratum. In answering this clarification question, the KM curve in CS Figure B25 was found to be incorrect. The correct illustration is here. The KM curve refers to 'Survival summary' cells J62:J122. Also provided is the accompanying AIC and BIC goodness of fit data, replacing Table B30 in the company submission (sebelipase alpha on-treatment).

Replacing CS Document B Figure 25



Replacing CS Document B Table 30

Distribution	AIC	AIC Rank	BIC	BIC Rank
Exponential	319.3	4	322.6	3
Gen. Gamma	310.2	1	316.8	1
Gompertz	318.7	3	323.6	4
Log-logistic	324.4	5	329.3	5
Log-normal	330.8	6	335.7	6
Weibull (AFT)	314.5	2	319.5	2

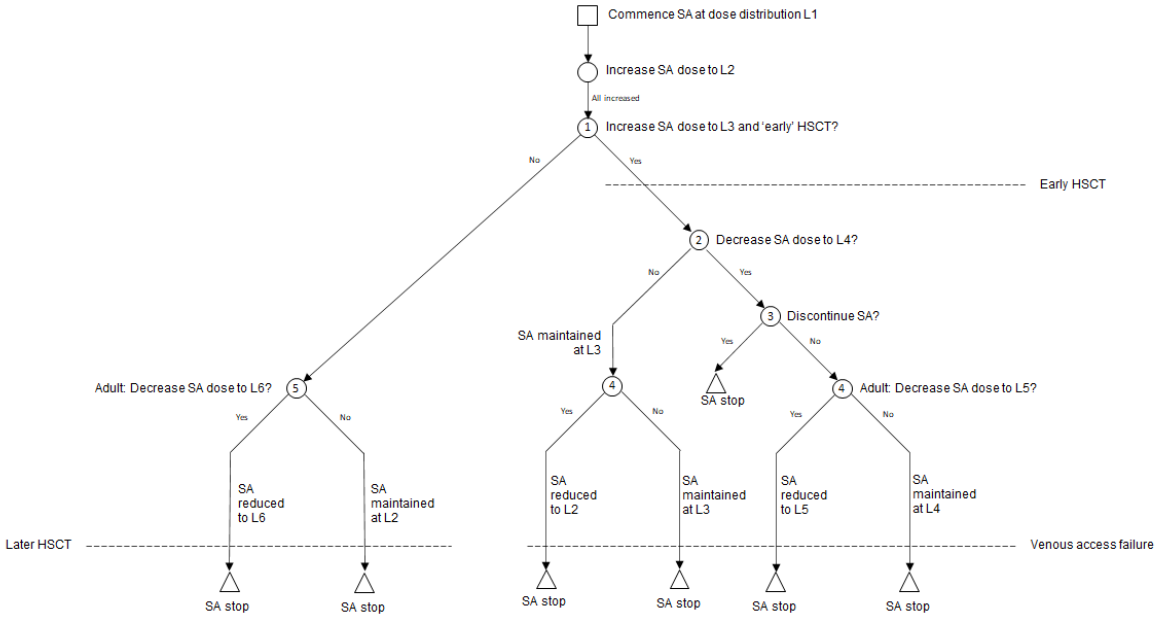
Key: AFT, accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: Cells are shaded according to their rank, where dark green is best fit, and red is worst fit.

B8. In Document B (Section B.3.2.2.2 Table 26 page 115) of the company submission, the dose distribution is provided for each of the decision nodes in the company economic model. The text of the company submission describing this (see page 113) is very brief. Please clarify in more detail how the decision tree was informed by "*Dose distribution according to clinical decision; Yes/No.*"

Please refer to the answer supplied to clarification question B1a for a some further description of the decision tree development.

The decision tree, CS Table B26 and CS Table B33 should be taken together understand the pattern of dosing in the base case. Each of the nodes 1-5 in the decision tree represents an opportunity for a change in the distribution of doses (per kg) administered to the sub-cohort from that point until the next clinical decision / node. As previously stated (CS table B33 and again in response to clarification question B1) the distribution of doses at each distribution level was clinically derived with the input of Dr Jones and Dr Vijay.

CS Figure B21.



CS Table B26

Node	Clinical question	Dose distribution according to clinical decision	
		Yes	No
-	Commence sebelipase alfa?	L1	
1	Increase sebelipase alfa dose a second time in the face of anti-drug antibodies and diminishing response and commence multi-modal treatment?	L3	L2
2	Decrease sebelipase alfa dose post early HSCT?	L4	L3
3	Discontinue sebelipase post early HSCT?	Nil	L4
4	Decrease sebelipase alfa dose post early HSCT now patient is no longer paediatric?	L5	L4
5	Decrease sebelipase alfa dose now patient is no longer paediatric?	L6	L3

Key: HSCT, haematopoietic stem cell transplant.

CS Table B33

Treatment milestone	Dosing levels	Dose	Proportion of patients	Source/note
Treatment initiation	L1	3 mg/kg QW	100%	Expert clinical opinion
1st dose increase, following initial exploratory dose	L2	3 mg/kg QW	50%	
		5 mg/kg QW	50%	
2nd dose increase and initiation of immunomodulators and HSCT (multi-modal treatment)	L3	5 mg/kg QW	100%	
Dose decrease post early HSCT	L4	3 mg/kg QW	100%	
Dose decrease with adulthood post early HSCT	L5	1 mg/kg QW	50%	
		3 mg/kg QW	50%	
Dose decrease with adulthood (without early HSCT)	L6	3 mg/kg QW	50%	
		5 mg/kg QW	50%	

Key: BIW, twice weekly; HSCT, haematopoietic stem cell transplant; kg, kilogram; mg, milligram; QW, once weekly; Q2W, once every 2 weeks.

B9. In Document B (Section B.3.3.2 page 122) of the company submission notes that a "*proportional hazard*" assumption was used when estimating relative survival. Could you please provide the rational for making this "proportional hazard" assumption in the economic analysis?

As noted above, given the maturity and the long follow-up period of the Kaplan-Meier data, the base case was not reliant on any parametric survival models, and therefore the proportional hazard assumption is not relevant for the base case. However, visual inspection of on- and off- treatment arms in Figures B24 and B25 shows no violation of proportional hazard (statistical testing was not performed).

B10. About the model structure provided in the Microsoft Excel file (overview sheet):

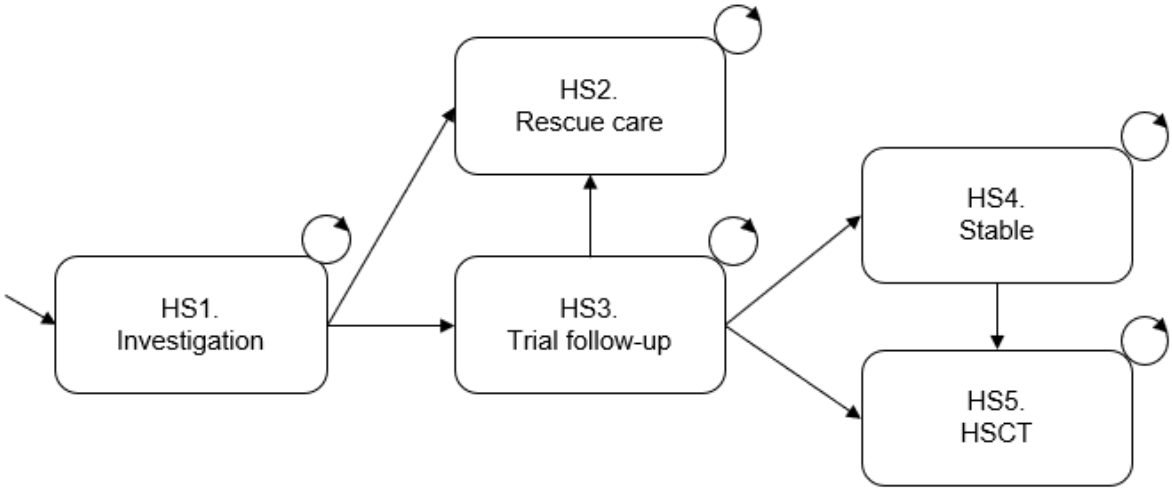
a) **Could the company provide the details of transition probabilities for health states (HS3 to HS6). Please clarify this apparent inconsistency between company submission document and the submitted model.**

Transition probabilities are included within the economic model. There is no single probability matrix although temporal risks (mortality) are given in the 'Markov Traces' worksheet. The Markov traces bring together into one place the probabilities and timing of events which trigger transition. These are: mortality due to rapidly progressive LAL-D (to HS2 then HS7), mortality due to HSCT (to HS2 then HS7), mortality due to other causes (to HS6), discharge from initial hospital admission (to HS3), end of trial follow-up (to HS4), preparation/indication for HSCT (to HS5). Please refer to the respective sections in the CS Document B, largely section B.3.3.

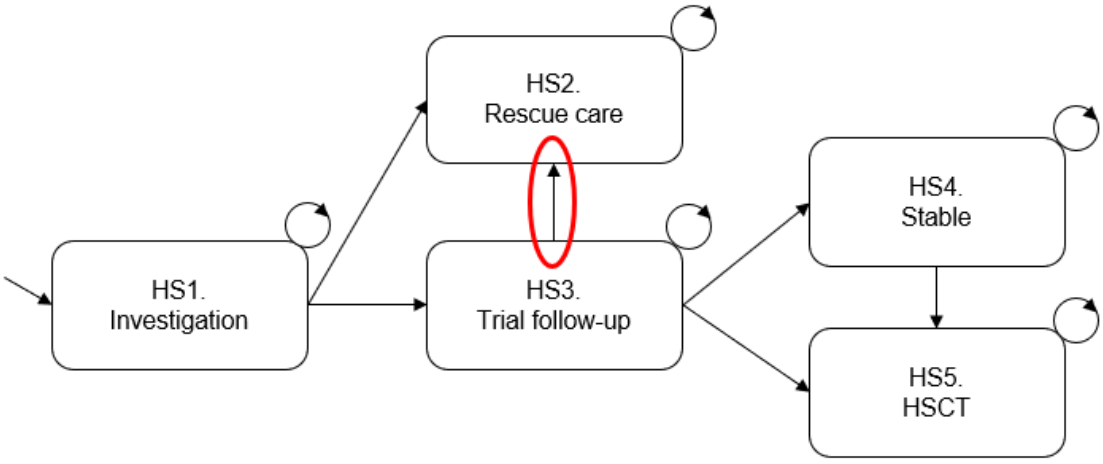
See answer to part b. We understand it is the same inconsistency being referred to.

b) **The model structure in Figure 20 (Health state diagram Document B page 112 of the company submission) allows the movement from HS2 to HS3. However, in the model in the Excel file the movement is from HS3 to HS2. Could the company confirm if this apparent inconsistency of movement in the model between HS2 and HS3 in the company submission document is a typographical error please.**

With reference to the model diagram, CS Figure B20, the arrow between health states 2 and 3 should be pointed in the opposite direction, allowing transition from HS3 to HS2. HS2 is effectively a tunnel state for residency prior to mortality from rapidly progressive LAL-D. Therefore, transition is only from HS3 to HS2. The figure below displays the correction to the typographical error. Note that in a scenario (non-base case) in which people receiving early HSCT do not discontinue sebelipase alpha, transition from HS5 to HS2 becomes possible (LAL-D death due to loss of venous access and no second HSCT).



Key: Rectangles represent living health states (mortality is a risk from every health state); Arrows represent allowable transition and direction between health states. Abbreviations: HRQoL, Health-related quality of life; LAL-D, Lysosomal acid lipase deficiency.



Key: Rectangles represent living health states (mortality is a risk from every health state); Arrows represent allowable transition and direction between health states. Abbreviations: HRQoL, Health-related quality of life; LAL-D, Lysosomal acid lipase deficiency.

c) Could the company clarify if the model includes the impact of "*loss of venous access*" on both costs and utility.

The base case model includes the impact of loss of venous access. Loss of venous access threatens viable ERT delivery. The expectation of serious problems gaining venous access indicates HSCT which provides the opportunity for safe discontinuation of sebelipase alpha. In the basecase model the impact of HSCT is multiple. There is a 20% risk of transplant-related mortality (CS section B.3.3.1 and Figure B23). If HSCT is not available under these circumstances, there is a 100% risk of LAL-D related-mortality. There is no direct impact on utility of loss of venous access, only consequent to HSCT. Disutility due to HSCT is explored outside the basecase in scenario analysis 32 – please refer to the answer given to clarification answer B3.

There is a significant one-off cost attributed to HSCT (CS section B.3.5.2 Tables B46 and B47).

B11. In the company economic model, for the probabilistic sensitivity analysis parameters spreadsheet (see also Table 51, starting page 146, section B.3.8.1 Document B, company submission) could you please clarify how you chose

the distributions (normal, beta, and gamma) parameters and provide references or other justification to support these choices.

Standard statistical methods were chosen, i.e., beta distributions for binomial data (e.g., utilities and utility decrements); and gamma for right skew parameters (e.g., costs); lognormal for relative risks or hazards, and logistic for odds ratios.[22] Durations of time and patient weights were sampled using the normal distribution. The normal distribution was chosen for patients weights because source data was judged sufficient for distributions to adhere to the central limit theorem.

B12. In Document B (Section B.3.3.2 page 123-125) of the company submission there is a description of how the Kaplan-Meier curve was used for the first five years when estimating survival. It is unclear how subsequent years were modelled either from the company submission and the Excel model (see Markov traces spreadsheet). What survival models were used/considered and how were they operationalised in order to estimate the impact on survival after the first 5-years?

Please refer to the answer given for clarification question B7.

Section C: Textual clarification and additional points

C1. Table 31 (page 123 of Document B of the company submission) mentioned "*multi-modal therapy*". Could the company explain if this is a typo for (sebelipase alfa + HSCT)?

Yes, the table refers to mortality attributable to the HSCT when on-treatment (sourced from Potter 2021), shorted to sebelipase alfa + HSCT. The table aligns the graphic representations in Figure B26 titled 'Parametric curves and Kaplan–Meier data: sebelipase alfa + HSCT'. The term 'Multi-modal therapy' is used interchangeably, referred to in CS Section B.2.6.3.3 (page 78) and Section B.3.2.3.1 (page 118).

C2. On page 138 (Document B of the company submission) for "*Added to this is an additional monthly cycle cost for specialist hospital parenteral nutrition of £6,333.33,*

based on an annual estimates of £68,000 for specialist nutritional products and £8,000 in dietetic and feed preparation costs. [ref]" could you please provide the reference used for this.

The estimated costs were provided by the specialist paediatric dietic service at *Birmingham Children's Hospital NHS Foundation Trust, a* centre treating rapidly progressive LAL-D patients.

However, in responding to this question we have identified an error in the description of the method used to calculate the cost of specialist nutrition for health state 1. I.e., during the initial hospital admission when the route of delivery is parenteral intravenous.

The text quoted in the question:

"*Added to this is an additional monthly cycle cost for specialist hospital parenteral nutrition of £6,333.33, based on an annual estimates of £68,000 for specialist nutritional products and £8,000 in dietetic and feed preparation costs.*"

Should be replaced with the following text:

"*Added to this is an additional monthly cycle cost for specialist hospital parenteral nutrition of £1,322.51 for specialist nutritional products (£43.45 per diem) based on audit data from Birmingham Children's Hospital. In two patient episodes totalling 34 days the consumption totalled four units Babiven maint500 and thirty units Quest bespoke. A combined cost of £1,477.14 over 34 days.(2022 cost year). This estimate was correctly specified in CS Table B48". [ref]*

Section D: Technical team queries

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation
Sebelipase alfa for treating Wolman disease [ID3995]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Children's Liver Disease Foundation
3. Job title or position	Head of Support
4a. Brief description of the organisation (including who funds it). How many members does it have?	Children's Liver Disease Foundation (CLDF) is the only UK charity dedicated to fighting all childhood liver diseases. We do this by providing information to families and to health professionals, emotional support to young people with liver disease and their families, funds for research and a voice for all affected. CLDF currently provides emotional support and practical assistance to approximately 4,000 children, young people and their families affected by a childhood liver disease. CLDF is reliant on voluntary donations to fund the work of the charity. This is provided largely by the fundraising efforts of the families and young people we support.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the evaluation stakeholder list.] **If so, please state the name of the company,**	No

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?	This condition is incredibly rare and so we are unable to gather information and the experiences of patients and carers as we have not supported a family affected by the condition.

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?	Wolman Disease is incredibly rare, so rare in fact that we have been unable to put forward an expert patient/ family for this appraisal. Even though we have over 5000 families/ young people in touch with the charity who are affected by childhood liver disease (we have families affected by over 85 different liver diagnoses), we don't have any families directly affected by this condition. Without treatment infants are unlikely to live past 6 months so access to a licensed, effective treatment for babies with Wolman Disease would be life changing for affected children and their families

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	We are not in touch with carers to ask them about current care as explained above.
8. Is there an unmet need for patients with this condition?	Yes, as this is the only treatment available.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We are not in touch with carers to ask them about advantages of the technology as explained above

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We are not in touch with carers to ask them about disadvantages of the technology as explained above but as this is lifesaving, we would suggest there are no disadvantages.

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.	We are unable to answer this question as we don't have the expertise/ knowledge to do so

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	
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 evaluation.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• As there are no alternatives treatments, it is vital that a clinically proven treatment that saves lives is made available. • This will be life changing for babies with the condition and their parents as if untreated they will lose their child within the first 6 months of life. • • •

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation
Sebelipase alfa for treating Wolman disease [ID3995]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	The MPS Society
3. Job title or position	Senior Head of Patient Services and Clinical Liaisons
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MPS Society is the only organisation in the UK that provides support to patients diagnosed with one of 27 MPS or related lysosomal disorder. The organisation supports over 1,500 children, adults and families. The MPS Society was established in 1982, with the aim of providing support, information, and advice to affected individuals and families. The MPS Society does not receive any statutory funding in England, therefore the MPS Society relies upon a rolling programme of grant applications to Trusts and Foundations, together with monies raised by members and the public through fundraising. The MPS Society receive grants from pharmaceutical companies to support the different activities it provides.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the evaluation stakeholder list.]	The MPS Society received a grant of £35,800 from Alexion. This was to carry out a patient and caregiver experience survey and clinical meeting to discuss patient carer reports / observations to see how these fit within the current clinical and treatment pathway.

If so, please state the name of the company, 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?	The MPS Society has been gathering patient / carer experiences and case studies since NICE started its evaluation of Sebelipase alfa in 2016. The case studies originally shared with NICE in 2018, have been updated and are reflected in this submission (1). In addition to this The MPS Society carried out a survey on the patient and caregiver experience of Lysosomal Acid Lipase Deficiency (Wolman's disease) treated with Enzyme Replacement Therapy (ERT). The survey was circulated across the UK and Republic of Ireland and incorporated both a short survey and in-depth semi-structured interviews. The study is currently ongoing with initial analysis of three parent/carer responses (representing over 33% of known patients). Areas covered included first signs and symptoms, impact of diagnosis, experience of treatment (including both ERT and HSCT), impact of health on activities of daily living and carer burden at different stages. The survey was conducted by Rare Disease Research Partners (RDRP) (2) A clinical round table, was convened to gather clinical experiences and opinions in the management and treatment of Infantile LAL D (3) A study lead by the clinical team at Manchester Children's Hospital further explored the experience of parents of children with LAL D (4) (1) MPS Society. Patient / carer experience and case studies (2) MPS Society & Rare Disease Research Partners. Patient and caregiver experience of Lysosomal Acid Lipase Deficiency (Wolman's disease) treated with Enzyme Replacement Therapy (ERT) Unpublished / in development /initial findings November 2022. (3) Infantile LAL D clinical meeting. Unpublished / in development November 2022 (4) Hassall S et al. "Why them, why me, why us?" The experiences of parents of children with lysosomal acid lipase deficiency: an interpretative phenomenological analysis study, 2022 PMID 35550173

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?	Infantile LAL D (Wolmans) is a ultra rare fatal condition. Babies are usually acutely unwell within weeks of being born. Symptoms include severe failure to thrive, including vomiting, malabsorption, diarrhoea, liver disease, hepatosplenomegaly and appear lethargic, irritable, distressed and unhappy. Untreated children typically die within the first few months to 12 months of life. It is estimated that there will be around 1 to 3 new babies born with this condition every year in the UK. The MPS Society is aware of 10 living patients across the UK and EIRE with infantile LAL D. Reports from three clinical centre included 13 patients (7 alive / 6 deceased). Of these patients, 69% had a double deletion and 31 % had a missense mutation. All living patients, were deemed to have a severe onset of disease whether they had a double deletion or missense mutation (3). All patients had received ERT either through Clinical trial or through compassionate use. **First symptoms**, generally appeared within the first few days / weeks of life. Reported difficulties include: difficulties with feeding, vomiting, diorrhea and violent / explosive nappies, suspected reflux, milk intolerance, failure to thrive or put on weight. One parent commented, *"Diarrhoea started after a few weeks, advised change formula, always appeared hungry but vomited after every feed. We made multiple trips to doctors and health visitors; formula was changed comments such as your child has a 'milky belly'. Due to distended belly, diagnosed as lactose intolerant at 6 weeks, no one checked for enlarged liver, despite swollen abdomen. At 7/8 weeks referred to doctor's with lethargy and failure to wake, appearing not hungry, vomiting after feeds, hernia in groin. At 13 weeks patient was admitted NG tube fitted pt appeared bloated, in pain, vomiting, diarrhoea, tested for cystic fibrosis"(1)* Another parent commented *"We experienced difficulties with feeding, violent nappies, projectile vomiting. Milk intolerance was suspected. We were referred to the clinical assessment unit. Despite feeding well continued to have severe vomiting, not putting on weight, gaviscon prescribed but not working and distended abdomen".(1)* One patient experienced; an extremely enlarged distended stomach pain and discomfort, enlarged liver and spleen, failure to put on weight, chronic constipation and explosive diarrhoea, walking difficulties, unsteady gait, poor muscle tone, laboured breathing.

	Diagnosis was significantly delayed for most patients. Parental reports state that despite swollen abdomens, initial investigations did not test or scan for enlarged liver. Other conditions were suspected in most cases, with reports of TB, cystic fibrosis, portal vein thrombosis and autoimmune disease. Whilst parents shared their concerns over missed symptoms and delayed diagnosis, they acknowledged that the rarity of LAL D meant it was challenging, for symptoms to be linked together. One patient took 18 months to be diagnosed despite repeated visits to hospital and GP from being a few weeks old. **Impact on patients** Nearly all patients at the time of diagnosis are acutely ill; requiring intensive multidisciplinary care and prolonged stays in hospital. They may need blood transfusions, parenteral nutrition and need immediate access to ERT. Some patients who were to unwell / severely unwell to rescue with treatment, sadly died (3) Natural History data clearly shows that without treatment of Sebelipase alfa 100% of all infant patients died, 89% of patients died before their 1st birthday with the mean age of death being 3.7 months (Jones et al 2015) One patient was diagnosed at 3 months. Parent commented that *'their child weighed just 6lbs and the majority of this was their liver, which measured 8cm's and extended from ribs to groan'*. The patient was started on ERT immediately on transfer to specialist hospital. After 5 weeks of ERT their liver size reduced from 8cm to 4cms and patient was beginning to put on weight. This patient spent 10 months in hospital, had multiple line infections, feeds were being managed and adapted to prevent vomiting. Once through the rescue stage they started putting on weight, were more alert and meeting developmental milestones. **Impact on parents** One parent shared their experience of loosing a child *'We know what it is like to lose a child at such a young age, where from birth it was evident that he had complex difficulties. Trying to get through the maze of healthcare professionals and tests to try and get a diagnosis and for a child to deteriorate to a life threatening stage in a matter or not just days but hours is unbearable and as parents we were helpless. He was our first child, we had prepared his room, brought new clothes and family and family and friends had brought gifts. Many of these remained un-opened. No one prepared you for*

	parenthood so the thought of losing your first child was unexplainable and no one could tell you how to manage yourself or your emotions. Waiting for the death is the worst thing'. (1) One parent spoke about how they were given the diagnosis written on a piece of paper and told to look it up on the internet (2) One parent on receiving the diagnosis said they were *'devastated and could not begin to think about the future as they had just been told that there was no cure for the disease'.(2)* One parent said *'we were shocked and upset upon hearing the diagnosis and was not aware that the disease was a lifelong condition and would need lengthy hospital admissions'. (2)* Children are usually very sick when first admitted to hospital and can deteriorate suddenly. Children very often have multiple IV lines, nasogastric tubes, making handling and caring very daunting. This can be a very difficult, stressful time for parents and families, at a time when they should be bonding, forming attachments with their new baby. Psychologist report of this period concluded *'The role that the parents had in relation to their child changed when their child was diagnosed with LALD, leaving parents feeling a sense of helplessness and powerlessness against the condition - unable to care for their child in that way that they once were and the way in which they thought a parent should' (4)* One parent stated '*it was unbearable for him to see his child so vulnerable and sick, maintaining hope by imagining a future'.(4)* One parent shared '*I've become more socially awkward, I found it difficult doing normal things, seeing normal people. You just kind of become a person that lives within the four walls of the hospital or the home. You're not you anymore'. (4)*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Significant delays, misdiagnosis, mean that babies are in critical condition when referred to specialist centre. Referrals to a specialist centre with experience of LAL D is crucial to prevent children being too ill to treat or the disease being too advanced to recover from. Although there may have been an opportunity for earlier diagnosis, one participant acknowledged that specialists rarely encounter LAL-D and so are not aware of the symptoms.(1) ICU care and understanding of the disease has been problematic for some centres. Some have wanted to withdraw treatment and supportive care early as they deemed patients were not recoverable. Situations include patients presenting with coagulopathy, pancytopenias, and possible HLH, which is typical for Infantile LAL D patients and is treatable with patients recovering well in most instances (3) Parents spoke very highly of the care provided by the multidisciplinary specialist teams, including; dieticians physiotherapists, speech and language therapists, play therapists, psychologists, especially in the first few months. Parents are understandably angry, upset and concerned that a decision to provide treatment through the NHS has not been decided to date but are enormously grateful that the company have provided compassionate drug, not just for existing clinical trial patients but for new patients diagnosed during this time.
8. Is there an unmet need for patients with this condition?	Currently, Sebelipase alfa is not available on the NHS. Clinical teams are required to make an urgent IFR which is invariable declined before approaching the company for compassionate use. Given the acuteness of the condition, delays in accessing treatment could be the difference between a child surviving or dying.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Sebelipase alfa is an innovative treatment. It is the first therapy that specifically targets the underlying cause of LAL D and is considered to be a step change, in managing the condition. All living patients have been treated with sebelipse alfa. Nutritional management goes alongside ERT and is integral part of the treatment alongside ERT. Children cannot thrive without a strict no fat diet (3) 100% of patients known to the MPS Society are over the age of 1 years with 90% of patients being aged 6 years or above. The oldest patient in England is now 10 years of age. Although the cohort of infant patients is small, the life survival and demonstrated long-term benefits of treatment is undeniable compared to the alternative, which is death. One parent reported that *'during the early treatment phase their child continued to thrive, put on weight and was meeting developmental milestones both physical and cognitive. Their liver and spleen returned to normal size, had no swollen abdomen, stomach issues were much improved. Whilst they are still gastrotomy fed at night, they do suffer food aversion from spending so long not eating orally, require a low fat diet, they are however, sampling foods. GI symptoms such as vomiting are managed at home and episodes are becoming more infrequent. All clinical assessments showed child was at expected levels and school reports corroborate this'(1).* One parent reported their child is now *'putting on weight, issues with diorrhea and constipation have improved and reported their child to be a lot happier, have alot more energy*'. They also commented that If an infusion was missed for any reason, there was a notable impact on energy and their child was more tired (2) One parent said their child *'rarely experiences explosive, smelly stools and was full of energy and runs around like a normal child*'. The patient was also able to wear age-appropriate clothes as the abdomen was now much smaller (2). Some parents reported their child's dose being increased early on in treatment as they were not responding as expected. Clinicians commented that '*Clinical practice, at present is patients are treated with either 3 mg or 5 mg per kilogramme, depending on severity and presentation Patients who present acutely unwell, may require a period in intensive care along with rescue therapy of twice-weekly ERT' (3)*

	Patient experience has proven to show that the life survival and long term benefits for patients on Sebelipase alfa is both compelling and positive compared to the untreated patient population where the disease is fatal within the first months of life. Height and weight has improved with a combination of ERT and nutritional support. One parent described how the changes in growth and weight were slow to start with after their child began ERT. After 6 weeks of ERT and TPN their child began to gain weight and continued to gain weight steadily reaching the 50th and 75th centile. Current weights reported for three patients showed they were all within the normal range for their sex and age. All patients known to the MPS Society are mobile with no current issues reported. Some patients have needed input from a speech and language therapist but have not required long-term intervention. All families spoken to confirmed that their child attends mainstream school. Some children had an Education Healthcare Plan (EHCP) to keep them safe when playing, moving around due to them having gastrostomies and port-a-caths, to support the childs low fat dietary needs and to ensure what was offered was safe. Only one child had some additional learning / behaviour needs that needed learning support input. One child was also incontinent but this is not expected to be long term. All children bar one, were working towards expected academic levels. One child although at a lower academic level to peers was progressing and the delays are attributed to the amount of school missed due to hospitalisation. All children are reported to enjoy school with one parent describing *'their child having lots of friends'* (1,2) Clinical reports from one centre stated that *'all children are doing cognitively well, with all school age children attending mainstream school. This is even taking into account the acuteness of their condition on diagnosis and the number of hospitalisations in the first few years of life'(3).* All children are able to take part in most everyday activities. One parent described their child *'as a completely different child now, talking, moving about, eating and growing'.* Outside of school, the patient goes to the park, plays board games and enjoys reading and writing. They take part in after school clubs such as football, cricket rounders, technology, crafts, and mindfulness. They are slightly restricted with some physical activities such as boxing and gymnastics due to the risk of displacement of the button gastrostomy and port-a-cath. (2) Another parent also explained that although the patient is able to do most activities that peers do, the patient is very aware and worried about the port becoming dislodged. They know that they must tell someone if they fall over or receive an impact. The child goes to Beavers, swimming and enjoys crafts. Some activities such as horse riding, trampolining or activities that require a harness are restricted due to their port-a-cath and gastrostomy (2).

	One child attends boxing (no contact), rides a motorbike and has a keen interest in animals and collecting different species of animals and insects. They would like to be a boxer when they grow up (1) All parents consulted felt that the current treatment for late infantile LAL-D had a great impact upon them, without the treatment their child would have died (2). One parent shared *'when given the diagnosis of LAL-D we did not think our child would reach school age. The treatment has given the patient a chance to live a relatively normal life, including being able to go to mainstream school. ERT has also improved the quality of life for the whole family and was far less invasive than the liver transplant, which was also discussed before the patient was approved for ERT' (2).* One parent said *'if the treatment was not made available to them, they would have lost their child and would not have had any time with their loved one'*. Another parent explained that *'ERT had been a lifeline for the family and is extremely concerned about what the future holds if the treatment is not approved'. (2)*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	No disadvantages were raised about the technology itself. Without access to treatment their children would have died.

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.	All patients with symptoms of faltering growth that present under the age of 12 months should be treated.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It is important that decisions made do not discriminate against patients, all of who are accessing ERT compassionately.

Other issues

13. Are there any other issues that you would like the committee to consider?	Enzyme Replacement Therapy is the first line therapy and is the only lifesaving treatment available for patients. ERT is required to be administered without delay on diagnosis. Patients who present acutely unwell, may require a period in intensive care along with rescue therapy of twice-weekly ERT. Whilst some patients in the UK have undergone HSCT, this is a unique single centre experience and is not extensively observed worldwide. HSCT has been necessary where treatment has failed and there are no other treatment options available. HSCT should not be viewed as a bridging therapy. Children are too acutely unwell to undergo a HSCT and there is not enough information and data to say that this is the treatment pathway for all patients.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Children do not survive without access to ERT • Enzyme Replacement Therapy is the first line therapy and is the only lifesaving treatment available for patients. ERT is required to be administered without delay on diagnosis • All patients with symptoms of faltering growth that present under the age of 12 months should be treated • Long term survivors show normal development and only have residual disease in the GI tract. Patients and carers have a good quality of life with IQ and cognitive function being unaffected • HSCT is not accepted practice currently

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Sebelipase alfa for treating Wolman disease (rapidly progressive LAL-D) [ID3995]

Produced by Newcastle University

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Declared competing interests of the authors

None.

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[redacted]

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Gurdeep Sagoo acted as project lead. Katie Thomson acted as lead effectiveness reviewer. Hosein Shabaninejad acted as lead health economist. Sheila Wallace acted as lead reviewer of the literature search methods. Nicole O'Connor and Madeleine Still acted as assistant effectiveness reviewer. Cristina Fernandez-Garcia, Najmeh Moradi, and Tumi Sotire acted as assistant health economics reviewers. Oleta Williams assisted in reviewing the literature search methods. Luke Vale acted as specialist health technology assessment reviewer.

Abbreviations

AASLD	American Association for the Study of Liver Disease
ADA	Anti-drug antibody
AE	Adverse event
AiC	Academic in confidence
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BMI	Body mass index
BMT	Bone marrow transplant
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost effectiveness acceptability curve
CEM	Company economic model
CENTRAL	Cochrane Central Register of Controlled Trials
CESD	Cholesteryl ester storage diseases
CI	Confidence Interval
CiC	Commercial in confidence
CPIH	Consumer Prices Index including owner occupiers' housing costs
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CS	Company's submission
DENVER II	Denver Developmental Screening Test II
dL	Decilitre
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EAS	European Atherosclerosis Society
EASL	European Association for the Study of the Liver
EBM	Evidence based medicine
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERT	Enzyme replacement therapy
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology & Nutrition
FAS	Full analysis set
g	Gramme
GATM	(Alexion) Global Access to Medicines programme
Gen Gamma	Generalised gamma
GGT	Gamma glutamyltransferase
HDL-C	High density lipoprotein cholesterol
HDU	High dependency unit
HLH	Haemophagocytic lymphohistiocytosis
HMG-CoA reductase	ß-hydroxy, ß-methylglutaryl co-enzyme A reductase
HR	Hazard ratio
HRG	Healthcare resource groups
HRQoL	Health-related quality of life
HS	Health State 1 - 5
HSCT	Haematopoietic stem cell transplant
HSUV	Health state utility value

HTA	Health technology assessment
IAR	Infusion-associated reaction
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
IQ	Intelligence quotient
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous
K	Thousand
kg	Kilogram
K-M	Kaplan-Meier
L	Litre
LAL	Lysosomal acid lipase
LAL-D	Lysosomal acid lipase deficiency
LDL-C	Low density lipoprotein cholesterol
LDN	Lysosomal Disease Network
LIPA	Lipase A lysosomal acid
LLM	Lipid lowering medication
LYG	Life years gained
MedDRA	Medical dictional for regulatory activities
MeSH	Medical subject headings
mg	Milligram
mL	Millilitre
mmol/L	Millimoles per litre
MN	Multiples of normal
MO	Months
MRI	Magnetic resonance imaging
N	Number of people
n	proportion or percentage of people
NA	Not applicable
NASH	Non-alcoholic steatohepatitis
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology & Nutrition
ng	Nanogram
NGT	Nasogastric tube
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NLA	National Lipid Association
NORD	National Organization for Rare Disorders
NR	Not reported
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PedsQL	Pediatric Quality of Life Inventory questionnaire
PEG	Percutaneous endoscopic gastrostomy
PES	Primary Efficacy Set
PfC	Points for clarification
PK	Pharmacokinetics
pmol	Picomole
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QW	Once weekly
QOW	Once every other week

Q2W	Once every 2-weeks
Q3W	Every three weeks
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SA	Sebelipase alfa
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SoC	Standard of care
SSIEM	Society for the Study of Inborn Errors of Metabolism
TG	Triglycerides
TEAE	Treatment emergent adverse events
TFHN	Transfusion-free haemoglobin normalisation
TTO	Time trade-off
UK	United Kingdom
U/L	Units per litre
USA	United States of America
VAS	Visual analogue scale
VLDL-C	Very low density lipoprotein cholesterol
WFA	Weight-for-age
WHO	World Health Organization
WTP	Willingness-to-pay
µg/L	Micrograms per litre
µkat/L	Microkatal per litre
µmol/L	Micromole per litre

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1 EXECUTIVE SUMMARY

1.1 Overview of the EAG's key issues

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model assumptions. Section 1.3 discusses the decision problem, Section 1.4 presents issues related to the clinical effectiveness, and Section 1.5 discusses issues related to cost-effectiveness. Other key issues are discussed in Section **Error! Reference source not found.**, while a summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) 5, 6 and 7 (cost effectiveness results).

All issues identified represent the EAG's views, not the opinions of The National Institute for Health and Care Excellence (NICE).

Table 1.1: Summary of key issues

ID3995	Summary of issue	Report sections
1	The age of symptom onset in Wolman disease/rapidly progressive LAL-D	3.1, 4.2.1, 4.7
2	The role of HSCT in the pathway for patients with rapidly progressive LAL-D	**Error! Reference source not found.**, 4.7
3	Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa	4.3.1.7.2, 4.3.1.8, **Error! Reference source not found.**, 4.7
4	Trial eligibility criteria and generalisability to rapidly progressive LAL-D population in England	4.2.1, 4.2.3, 4.7
5	Uncertainty around ability to change dose of sebelipase alfa	5.1.7, 5.1.9, 7.1.2
6	Choice of discount rate for costs and QALYs	5.1.10, 7.1.2
7	Uncertainty in extrapolation models used to estimate Wolman related survival	5.1.11, 7.1.2
8	Uncertainty in the utility estimates applied for those treated with sebelipase alfa	5.1.13, 7.1.2
9	Uncertainty over life cycle price of sebelipase alfa	5.1.14, 7.1.2
10	Uncertainty over feasibility of vial sharing	5.1.14, 7.1.2

Abbreviations: HSCT, haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency; QALYs, quality adjusted life years.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

1. Discount rate used for the base-case analysis
2. Methods for estimating Wolman disease related survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

1. Increasing survival
2. Increasing health related quality of life (HRQoL) both for initial treatment with sebelipase alfa and subsequent management with haematopoietic stem cell transplant (HSCT)

Overall, the technology is modelled to affect costs by:

1. Different levels of sebelipase alfa (SA) dosage for patients` lifetime
2. Allowing a bridge towards HSCT

The modelling assumptions that have the greatest effect on the ICER are:

1. Including a Kaplan-Meier (K-M) approach to extrapolate Wolman disease related survival instead of best fitted distribution for each treatment group
2. Assuming 1.5% discount rate instead of the rate generally proposed by NICE for base-case (3.5%)
3. Assuming general UK population life expectancies (survival) and utility value for patients with Wolman disease receiving sebelipase alfa and HSCT
4. Proportion and age at which patients receive early/late HSCT
5. Proportion of patients who have dose reduction or discontinuation after early HSCT
6. Vial sharing and life cycle price of sebelipase alfa

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

Table 1.2: Key issue [1] – The age of symptom onset in Wolman disease/rapidly progressive LAL-D

Report section	3.1, 4.2.1, 4.7
Description of issue and why the EAG has identified it as important	Key Issue [1] links to Key Issue [4] Wolman disease, used in the NICE scope,[1] is now more commonly referred to as rapidly progressive LAL-D. Typically, symptom onset is in the first weeks of life, and most often within 6-months. The clinical trial evidence for LAL-CL03 centres on patients who were eligible for enrolment if they had growth failure with onset before 6-months. The company states however that rarely patients can present with the rapidly progressive and advanced form of LAL-D between 6 and 24-months of age; there have been [redacted] where the patient presented with an advanced form of LAL-D between 6 and 24 months.[2] Consequently, some of the clinical trial evidence used in the CS (LAL-CL03) may not be indicative for the use of sebelipase

Report section	3.1, 4.2.1, 4.7
	alfa in this rapidly progressive population seen in English clinical practice. Therefore, there is uncertainty in the efficacy results in patients with symptom onset after 6-months for which little clinical trial evidence is presented.
What alternative approach has the EAG suggested?	No alternative approaches are suggested. The EAG suggests that the upper age limit of symptom onset is carefully considered by the committee.
What is the expected effect on the cost effectiveness estimates?	Unknown. Increasing the age will most likely reduce treatment costs and QALYs. However, the data for best supportive care (BSC) is not directly comparable as the majority of these patients will have died before these later onset patients are identified. Nevertheless, as all these events occur very early in the life course of those treated with sebelipase alfa the EAG considers that the cost-effectiveness estimates provided by the EAG provide a reasonable approximation.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends long-term data collection for the efficacy in patients with onset between 6 and 24-months. The EAG also recommends that these data are then used to provide revised estimates of cost effectiveness.
Abbreviations: BSC. best supportive care; CS, company submission; EAG, Evidence Assessment Group; LAL-D, lysosomal acid lipase deficiency; NICE, National Institute of Health and Care Excellence; QALY, quality adjusted life year	

Table 1.3: Key issue [2] - The role of HSCT in the pathway for patients with rapidly progressive LAL-D

Report section	4.4, 4.7, 5.1.11, 5.1.13, 7.1.2
Description of issue and why the EAG has identified it as important	Key issue [2] Links to Key Issue [7] and Key Issue [8] Increasingly, sebelipase alfa, nutritional support and HSCT are combined in a multimodal treatment for rapidly progressive LAL-D patients who have sub-optimal response to ERT alone, or have other disease-related complications. The CS reports that [redacted] patients had HSCT during LAL-CL03 (none had HSCT in LAL-CL08).[2] It is unknown how many patients had HSCT after the trial had completed. Efficacy estimates therefore include some patients with ERT and nutritional support, and others with ERT, nutritional support and HSCT. The SLR undertaken by the company highlight Potter *et al*., 2021,[3] which reported patient outcomes for rapidly progressive LAL-D post-HSCT. Due to the immaturity of the longer-term follow-up data, there is limited evidence to ascertain the ages of patients when they require HSCT (if at all), and how efficacy outcomes differ between those patients who have transplant in infancy, compared to patients who receive transplant in early adulthood (as proposed in the CEM) and whether or not assumptions that survival and quality of life 5-years after receiving HSCT are the same as the general population. These uncertainties all have a potential impact on cost effectiveness.

What alternative approach has the EAG suggested?	In the absence of better information the EAG has not altered the assumption made in the CS that all surviving patients ultimately receive HSCT. The EAG however has modelled changes to the assumptions around the proportion of patients who require early HSCT. The EAG has also modelled alternative assumptions than those adopted in the CS that survival (Key Issue [7]) and quality of life (Key Issue [8]) following HSCT are the same as the general population.
What is the expected effect on the cost effectiveness estimates?	Due to uncertainty surrounding the proportion and age at which patients receive early/late HSCT, the EAG investigated the effect of this issue on the ICER value through replicating three scenarios included in the CS on the proportion of patients undergoing early HSCT including 100%, 50%, and 0%. In the CS base-case it was assumed [redacted]% of patients undergo early HSCT. The EAG base-case analysis ICER which included this assumption was £308,960. Assuming 100% of patients had early HSCT reduced the ICER to £92,093. When the proportion of patients receiving early HSCT was reduced to 50% and 0% the ICER increased to £499,604 and £823,700, respectively.
What additional evidence or analyses might help to resolve this key issue?	Additional real-world evidence data could be routinely collected if sebelipase alfa was to be given a NICE recommendation. Specifically, further research should centre on when HSCT should be performed in this patient population. These data could be used to revisit conclusions about effectiveness and cost-effectiveness.
Abbreviations: CEM, company economic model; CS, company submission; EAG, Evidence Assessment Group; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost effectiveness ratio; LAL-D, lysosomal acid lipase deficiency; NICE, National Institute of Health and Care Excellence; SLR, systematic literature review	

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

Table 1.4: Key issue [3] – Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa

Report section	4.3.1.7.2, 4.3.1.8. 4.4, 4.7, 5.1.11, 5.1.13, 7.1.2
Description of issue and why the EAG has identified it as important	Key issue [3] links to Key Issue [7] and Key Issue [8] Whilst sebelipase alfa has been shown to improve clinical outcomes, including survival in the short-term, there are considerable uncertainties about the potential long-term use and associated benefits of treatment in patients as they transition to adolescence and beyond. Of particular concern is the role of neutralising ADAs which attenuate therapy efficacy, and mediate disease progression despite treatment with sebelipase alfa. Furthermore, patients require long-term venous access for the frequent administration of sebelipase alfa and blood transfusions. Poor venous access due to previous repetitive puncturing and other complications is extremely problematic and if severe (without subsequent treatment), would likely result in disease progression owing to the withdrawal of sebelipase alfa treatment. Whilst the use of multimodal therapy, using HSCT as a 'rescue therapy' is becoming common, there is limited efficacy data in the time period immediately following the transplant, and no evidence for its long-

	term use in this patient group. These uncertainties all have a potential impact on cost effectiveness.
What alternative approach has the EAG suggested?	We believe this to be a currently unresolvable issue that is a cause of great uncertainty. The CS makes the assumption that all surviving patients treated with sebelipase alfa ultimately progress to HSCT and that this occurs no later than the patient reaching 30-years of age. This same assumption is made in the EAG base-case analysis. Furthermore, the CS assumes that survival and HRQoL are the same as the general population 5-years after receiving HSCT (see Key Issue [7] and Key Issue [8]). The EAG explored scenarios for loss of venous access at 20- and 40-years of age in the EAG base-case model. The EAG also considered the CS scenario that venous access never fails. The CS did not consider the impact of disutility associated with loss of venous access or developing ADAs in terms of changes in HRQoL. Although these were indirectly explored in Key Issue [8].
What is the expected effect on the cost effectiveness estimates?	The EAG acknowledges the uncertainty in the assumptions based in the CEM which link to the loss of venous access, and the rise of ADAs which lead to HSCT, and its long-term effectiveness (particularly related to HRQoL and mortality). The uncertainty regarding age at which loss of venous access occurs was investigated in three scenarios. These were: (i) venous access never fails; (ii) loss at age 20-years; and (iii) loss at age 40-years. The EAG base-case analysis which assumed the loss of venous access at age 30-years had an ICER of £308,960. The ICER when it was assumed that venous access never failed was £414,649. The ICER fell when venous access failure occurred by age 20-years to £255,085. The ICER increased to £346,924 when venous access occurred by age 40-years. The EAG did not directly assess the impact of disutility associated with loss of venous access or developing ADAs in terms of changes in HRQoL. Given the assumptions made in the EAG base-case analysis incorporating these impacts would increase the ICER (see also Key Issue [8] where decrements to utility are considered).
What additional evidence or analyses might help to resolve this key issue?	Additional real world evidence data could be routinely collected if sebelipase alfa was to be given a NICE recommendation. These data could be used to revisit conclusions about effectiveness and cost-effectiveness.
Abbreviations: ADA, anti-drug antibodies; CEM, company economic model; CS, company submission; EAG, Evidence Assessment Group; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation	

Table 1.5: Key issue [4] – Trial eligibility criteria and generalisability to rapidly progressive LAL-D population in England

Report section	4.2.1, 4.2.3, 4.7
Description of issue and why the EAG has identified it as important	Key Issue [4] links to Key Issue [1]

Report section	4.2.1, 4.2.3, 4.7
	Primary efficacy evidence is derived from the LAL-CL08 cohort and the included population/eligibility, specified in Table 4.3 (of this report) as, substantial clinical concerns requiring urgent medical intervention (enlarged organs, growth failure, family history, anaemia and disturbance of coagulation) in children who are under 8-months of age at first dose, appears to be representative of the rapidly progressive LAL-D population seen in clinical practice. LAL-CL03 provides supportive efficacy data, and estimates for some outcomes, such as survival, are sometimes presented as pooled data with LAL-CL08. To facilitate comparability and limit confounding factors between LAL-CL03 and LAL-1-NH01 the trial population/eligibility was restricted to patients who had early growth failure in the first six-months of life (weight decreasing across at least 2 major centiles on a WHO standard chart). Whilst this approach improves internal validity, it limits the generalisability and does not reflect the entire rapidly progressive LAL-D population in practice who are likely to receive treatment.
What alternative approach has the EAG suggested?	The EAG recognises that onset of growth failure before six-months of age is a prominent clinical feature with plausible prognostic link to early mortality and appreciates the rationale for limiting the trial eligibility in the earlier dose escalation clinical trial, LAL-CL03. We also believe the generalisability is increased by the pooling of data from LAL-CL08 which has broader eligibility criteria. We believe this to be a currently unresolvable issue that is of limited cause of concern.
What is the expected effect on the cost effectiveness estimates?	The CEM essentially used pooled data across the different studies to estimate impacts on survival, this is primarily due to the very limited data available and represents a pragmatic choice in the CS to use the data available. The precise impact of having the narrower eligibility criteria was not estimated by the EAG who took the same view as the CS that making maximal use of the available data would be more useful for such a rare condition.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends long-term data collection for the efficacy in patients with onset between 6 and 24-months.
Abbreviations: CS, company submission; CEM. company economic model; EAG, Evidence Assessment Group; LAL-D, lysosomal acid lipase deficiency; WHO, World Health Organization	

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

Table 1.6: Key issue [5] Uncertainty around ability to change dose of sebelipase alfa

Report section	5.1.7, 5.1.9, 7.1.2
Description of issue and why the EAG has identified it as important	There is currently a lack of data on the long-term follow up of patients. This gives rise to uncertainties regarding dose of sebelipase alfa over time, the duration of treatment, and the proportion of patients who may be able to discontinue treatment

	with sebelipase alfa. Change in the amount of sebelipase alfa received (along with the reasons for those changes) will affect effectiveness and cost and accordingly, and will in turn change the ICER.
What alternative approach has the EAG suggested?	The EAG investigated uncertainty around changes to the dose of sebelipase alfa. This included situations where dose may increase, decrease or be discontinued.
What is the expected effect on the cost effectiveness estimates?	The CS assumed that all patients who underwent early HSCT will have dose reduction and considered that sebelipase alfa could be discontinued 18-months after HSCT. This assumption was used by the EAG in its base-case analysis. The EAG explored scenarios where: (i) only 50% have a dose reduction after early HSCT; and (ii) only 50% discontinue using sebelipase alfa after early HSCT. In the EAG base-case analysis where all patients discontinue sebelipase alfa 18-months after HSCT the ICER was £308,960. For (i) the ICER increased to £742,174. For (ii) the ICER increased to £606,398. Other scenarios considered by the EAG analysis were increasing sebelipase alfa dosage to 5mg/kg for patients who did not have early HSCT (and had no ADAs) and assuming 20% of patients have a dose reduction at age 18-years. The EAG ICERs were £379,112 and £343,072, respectively.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends long-term data collection on sebelipase alfa dosage in patients and the incorporation of these data into a revised economic evaluation.
Abbreviations: ADA, anti-drug antibodies; CS, company submission; EAG, Evidence Assessment Group; HSCT, haematopoietic stem cell transplant; ICER, incremental cost effectiveness ratio	

Table 1.7: Key issue [6] Discount rate used for CS base-case analysis

Report section	5.1.6, 5.1.10, 7.1.2
Description of issue and why the EAG has identified it as important	In their base-case analysis, the company assumed a 1.5% discount rate for future costs and effects. This was justified by the company on the basis that "*treatment with sebelipase alfa restores people who would otherwise die to full or near full health, and this is sustained over a very long period.*".[2] The NICE reference case value is 3.5%.[4]
What alternative approach has the EAG suggested?	The EAG considers that the base-case analysis should adopt a discount rate of 3.5% as recommended by the NICE reference case.[4]
What is the expected effect on the cost effectiveness estimates?	Increasing the discount rate increases the ICER and decreasing the discount rate reduces the ICER. Increasing the discount rate of both costs and effects to 3.5% increased the ICER to £308,960 in the EAG's base-case analysis.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required as this issue can be explored within the CEM.
Abbreviations: CEM, company economic model; CS, company submission; EAG, Evidence Assessment Group; ICER, incremental cost effectiveness ratio; NICE, National Institute of Health and Care Excellence	

Table 1.8: Key issue [7] Uncertainty in extrapolation models used to estimate Wolman related survival

Report section	5.1.11, 7.1.2
Description of issue and why the EAG has identified it as important	Key Issue [7] links to Key Issue [2] and Key Issue [3] The company chose the K-M method to extrapolate Wolman disease-related mortality in the model from the observed model. The CEM also included parametric distributions to extrapolate Wolman disease-related mortality for patients` lifetime. The CS discussed that the best fitted parametric model was not visually fitted with the K-M curve during the trial and the K-M method was selected for extrapolation of Wolman disease-related mortality for a patient's lifetime.
What alternative approach has the EAG suggested?	The EAG agree that the K-M is the best fitted model for Wolman disease-related mortality during the trial follow-up period, but the EAG consider that using the K-M to estimate survival over a patient's lifetime is unrealistic. The EAG suggest an alternative approach of using a combination of K-M method (for the trial follow-up period) and parametric models to estimate survival after the end of the trial follow-up period. In the EAG exploratory scenario analysis which used a K-M distribution for the trial follow-up period (below 5-years) and using the following parametric distributions: exponential, Weibull, Gompertz and log-normal.
What is the expected effect on the cost effectiveness estimates?	The ICER for the EAG base-case analysis which made the same assumptions as the CS and used the K-M approach to estimate Wolman disease-related mortality was £308,960. The ICER for the exponential distribution was: £472,104. The ICER for the Weibull distribution was: £483,062. The ICER for the Gompertz distribution was: £488,590. The ICER for the log-normal distribution was: £446,868.
What additional evidence or analyses might help to resolve this key issue?	Ultimately, analysis is limited by the rarity of the condition. However, better data to estimate survival and the real-world impact of sebelipase alfa require long-term data. The EAG recommends long-term data collection for the efficacy in patients and its use to provide updated estimates of cost effectiveness.
Abbreviations: CEM, company economic model; CS, company submission; EAG, Evidence Assessment Group; ICER, incremental cost effectiveness ratio; K-M, Kaplan-Meier	

Table 1.9: Key issue [8] Assumption of health state values equal to the UK general population health

Report section	5.1.13, 7.1.2
Description of issue and why the EAG has identified it as important	Links to Key Issue [2] and Key Issue [3] The CS has assumed that HRQoL for patient is the same as that of the UK general population. Utility decrements are incorporated for

Report section	5.1.13, 7.1.2
	specific events but longer term HRQoL is taken to be the same as the general population. The evidence for this is sparse, reflecting the very small numbers of patients in studies and the limited follow-up. Alternative data both for clinical events such as the disutility of parental feeding and longer term HRQoL can be drawn from both the literature for sebelipase alfa and related literature. These alternative sources suggest a lower HRQoL than the general population. In the EAG base-case analysis patients were assumed to have a health state value equal to the age and sex adjusted value for the UK general population. This assumption could overestimate HRQoL for patients.
What alternative approach has the EAG suggested?	The EAG has explored alternative HRQoL valuations within the EAG scenario analyses. These include defining a weighting of 0.8 to adjust the utility value at all ages.
What is the expected effect on the cost effectiveness estimates?	The EAG base-case analysis made the same assumption as was made in the CS base-case analysis. The ICER for the EAG base-case analysis was £308,960. When a weighting of 0.8 was applied to the age and sex adjusted general population utilities, the ICER increased to £386,152.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends long-term data collection for the efficacy in patients. This should include incidence of clinical events and survival but also HRQoL. The EAG further recommends that these data are used to provide updated estimates of cost-effectiveness.
Abbreviations: CS, company submission; EAG, Evidence Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost effectiveness ratio; UK, United Kingdom	

Table 1.10: Key issue [9] Uncertainty over life cycle price

Report section	5.1.14, 7.12
Description of issue and why the EAG has identified it as important	The CS used the confidential patient access scheme price in its base-case analysis. The EAG made the same assumption in its base-case analysis. The assumption made is that the current price will not change over the time horizon adopted for the analysis (the estimated patient lifetime). It is possible that both the real price paid by the NHS may change over time, or there may be a cap placed on the cost per patient. The CS submission explored scenarios where a cost cap of [redacted] per patient per annum was introduced and where the cost of sebelipase alfa was reduced by one-third after 10-years. These scenarios were also explored by the EAG. The scenarios are reflective of uncertainty about how the price might behave in the long-term due to, for example, the introduction of a competing technology in the market or expiry of patents. The potential to change the price and cost of sebelipase alfa will affect the ICER.
What alternative approach has the EAG suggested?	The EAG explored the impact on the ICER of changes in market price, and the introduction of a cost cap per patient per annum in scenario analysis.

What is the expected effect on the cost effectiveness estimates?	In the EAG base-case analysis the ICER is £308,960. Introducing a reduction in the price of sebelipase alfa after 10 years to two-thirds of the current price reduced the ICER to £197,048. Introducing a cost cap of [redacted] per patient per annum would reduce the ICER to £266,611.
What additional evidence or analyses might help to resolve this key issue?	It is plausible that price and agreed maximum cost per annum (or indeed other cost containment mechanisms) may occur over time. The EAG recommend revisiting analyses as costs/price mechanisms change or are negotiated.
Abbreviations: CS, company submission; EAG, Evidence Assessment Group; NHS, National Health Service; ICER, incremental cost effectiveness ratio	

Table 1.11: Key issue [10] Uncertainty over feasibility of vial sharing

Report section	5.1.14, 7.1.2
Description of issue and why the EAG has identified it as important	The base-case analysis in the CS and for the EAG make the assumptions that vials of sebelipase alfa are for a single use and any sebelipase alfa not used in a given administration is disposed of. Real world practice is to modulate dose within a 2-week cycle to reduce waste. If the number of vials of sebelipase alfa can be reduced this would, other things being equal, reduce costs and reduce the ICER.
What alternative approach has the EAG suggested?	The EAG attempted scenario analyses where vial sharing is allowed over a 1-week cycle or over a 2-week cycle.
What is the expected effect on the cost effectiveness estimates?	The scenario analyses produced inconsistent results indicating an issue within the CEM. Nevertheless, the EAG would expect these scenario analyses would result in moderate reductions in the ICER.
What additional evidence or analyses might help to resolve this key issue?	Initially, revising the CEM to correct the issue within the model. Longer term, monitoring of real world practice and collection of data on use of vial sharing. Incorporation of these data into a revised economic model.
Abbreviations: CEM, Company economic model; CS, company submission; EAG, Evidence Assessment Group; ICER, incremental cost effectiveness ratio	

1.6 Summary of the EAG's view

The EAG base-case includes the EAG preferred assumptions. For the EAG base-case analysis these are substantially the same as those adopted by the company. The key exception is that in the EAG base-case the EAG has adopted a 3.5% discount rate as the EAG believes that this fits the NICE reference case. Based on the deterministic results the ICER in the EAG base-case was £308,960 for sebelipase alfa compared with BSC. For the probabilistic analysis there was a near 0% chance that sebelipase alfa would be cost-effective at a £300,000 willingness-to-pay (WTP) threshold and a near 100% chance it would be cost-effective at a £320,000 WTP threshold.

Across all the scenarios considered, only one had an ICER below £100,000 (where all patients receive early HSCT). Circumstances that could reduce the ICER included situations where the use or unit cost of sebelipase alfa was reduced (Key Issues 1, 6, 9). These include situations where it was assumed all patients get early HSCT (and hence reduce the need for sebelipase alfa). Other circumstances included reducing the discount rate to 0% (Key Issue 6). Alternative assumptions leading to fewer patients getting early HSCT, health state utilities and methods used to extrapolate Wolman survival increased the ICER.

Of the additional 12 EAG exploratory analyses, 10 resulted in ICERs above £300,000 (all 12 analyses were over the £100,000 threshold). The two remaining scenarios considered vial sharing assumptions for the 1-week count and 2-week count (Key Issue 10). These resulted in ICERs of lower than £300,000 but as noted in the footnotes to Table 7.6 and Table 7.7, there is a fault within the CEM that the EAG has not resolved. Some uncertainty (e.g., Wolman related survival) and HRQoL may be resolved by more data but given the rarity of the condition this would be slow to accrue even where studies were multinational.

Table 1.12: Summary of EAG's base-case results

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Deterministic					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
CS base-case after corrections					
BSC	[redacted]	[redacted]			
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	£239,871
Violation 1 – changing discount rate from 1.5% to 3.5%					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	£308,078
EAG base-case – Deterministic					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	£308,960
EAG base-case - Probabilistic					
BSC	[redacted]	[redacted]			
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	£308,130

Source: Produced by the EAG.

Abbreviations: BSC, best supportive care; CS, company submission; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

2 BACKGROUND

This section presents an overview of rapidly progressive lysosomal acid lipase deficiency (LAL-D), also known as Wolman disease, and its management. The content of this chapter is based on relevant literature, information provided by clinical advisors to the Evidence Assessment Group (EAG) and information presented in the background sections of the company's evidence submission (CS).[2] For additional information on the aetiology, epidemiology, health impact, prognosis, and management, please see the CS, document B, pages 18 to 23.[2]

2.1 Description of health problem

2.1.1 Disease overview

LAL-D is an ultra-rare lysosomal storage disease characterised by a failure to break down cholesteryl esters and triglycerides in the lysosomes, resulting in their build-up in vital organs (particularly the liver and intestine), blood vessels and other tissues with multi-system manifestations.[5] It is caused by a genetic mutation found in the lipase A lysosomal acid (*LIPA*) gene which is located on chromosome 10q23.2-q23.3.[6] Patients with this deficiency experience severe complications such as failure to thrive, malabsorption, systemic inflammation, and liver failure, which if left untreated can lead to multiple organ failure and premature death.

LAL-D can present across the lifespan, from the rapidly progressive infantile onset form to the later onset forms, collectively known as cholesteryl ester storage diseases (CESDs). Wolman disease is the name historically given to the infantile onset, rapidly progressive form of LAL-D. Wolman disease presents within the first few months of life, with symptom onset observed at a median age of one month, followed by rapid disease progression with a median age at death of 3.7 months.[7] The CS identifies [redacted] cases in the UK in the past seven years who have presented with this rapidly progressive type between 6 and 24-months of age.[2]

2.1.2 Epidemiology

The rapidly progressive type of LAL-D is classed as an ultra-rare disease, commonly defined as one which affects fewer than 1 in 50,000 individuals.[8] As with other ultra-rare diseases, there is a lack of available information on the incidence and prevalence of rapidly progressive LAL-D. There is also the potential for mis- or under-diagnosis of the disease due to the rarity and early mortality common in this population which further complicates attempts to establish epidemiological data.

The CS reports the estimated incidence rate for rapidly progressive LAL-D is approximately 1 in 350,000 births and that in England the clinical experience is that on average [redacted] every other year might present with rapidly progressive LAL-D.[2,9]

2.1.3 Aetiology

LAL-D is caused by mutations in the *LIPA* gene located on chromosome 10q23.2-q23.3. Affected individuals are typically either homozygous or compound heterozygous for *LIPA* gene mutations. While the most commonly occurring mutation in later onset LAL-D is the exon splice 8 site mutation, c.894G>A (E8SJM), there are many different mutations that can result in the complete loss of enzyme function in the rapidly progressive LAL-D type. LAL-D is inherited in an autosomal recessive manner, which means each parent of a patient with LAL-D must normally carry at least one defective LAL gene. Children of parents with a defective LAL gene have a 25% chance of inheriting LAL-D with each pregnancy, a 50% chance of being a carrier and a 25% chance of being unaffected by the disease.[10]

2.1.4 Pathogenesis

Lysosomal acid lipase (LAL) is a critical component of lipid metabolism which breaks down low-density lipoprotein (LDL) derived neutral lipids (cholesteryl esters and triglycerides). LDL cholesterol is taken up by hepatocytes. LAL in the lysosomes (cell organelles containing hydrolytic enzymes) breaks down the LDL-cholesterol to free cholesterol and free fatty acids. In rapidly progressive, LAL-D, absent enzyme activity results in an accumulation of cholesteryl esters and triglycerides in the lysosomes, and low levels of intracellular free cholesterol. Low levels of free cholesterol cause upregulation of endogenous cholesterol production by HMG-CoA reductase and of endocytosis via LDL receptors, as well as increased synthesis of apolipoprotein B (ApoB) and markedly increased production of very-low-density lipoprotein cholesterol (VLDL-C).[5]

2.1.5 Clinical features

Rapidly progressive, infantile onset is the most severe form of LAL-D, with sudden and unpredictable symptom onset. Symptoms can present within the first day of life or a few weeks or months after birth. Median onset of symptoms is around one and a half months of age.[11] Patients present with a marked failure to thrive, defined as more than two standard deviations (SDs) below normal height and weight measurements for age.[12] Patients may also experience vomiting, diarrhoea, distended abdomen and steatorrhea. Patients with rapidly progressive LAL-D may also present with hepatomegaly and hepatic injury, as well as increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[5] These infants quickly develop liver fibrosis and cirrhosis due to the large accumulation of cholesteryl esters and triglycerides in the liver. An increase in lipid deposition along the gastrointestinal tract also leads to thickening bowel walls, resulting in malnutrition and wasting.[5]

Furthermore, approximately 50% of infants also have adrenal calcification, which can aid clinicians in distinguishing rapidly progressive LAL-D from other diseases with similar symptoms.[5]

2.1.6 Diagnosis

A diagnosis of rapidly progressive LAL-D can be made by identification of either biallelic pathogenic variants in *LIPA*, or deficient LAL enzyme activity in peripheral blood leukocytes, fibroblasts or dried blood spots.[10] Alternatively, a diagnosis can be established using genetic testing, i.e., the complete sequencing of the coding regions of *LIPA*.[13] While liver biopsy is considered to be the most reliable option to evaluate liver abnormalities, such as the development of fibrosis and cirrhosis, it is an invasive procedure with associated risks and costs, and cannot be used to make a diagnosis of LAL-D.[5] Due to the rarity of the disease, a lack of clinical knowledge can lead to misunderstanding or misdiagnosis of clinical symptoms.[14]

2.1.7 Prognosis

As previously noted, the prognosis for infants with rapidly progressive LAL-D is limited, with death often occurring in the first six-months of life.[15-17] A natural history study of 35 patients with rapidly progressive LAL-D (LAL-1-NH01) reported that only [redacted] patients survived beyond 12-months of age, and all [redacted] of these patients had died before the age of four despite receiving HSCT and/or liver transplantation.[18] Among the subgroup in LAL-1-NH01 who were both untreated and had experienced early growth failure (number of people; N=21), the median age of death was 3.0 months (all patients had died by [redacted]).[7] Kaplan-Meier estimates for probability of survival beyond 12-months of age were 0.038 (95% CI: 0.000, 0.112) for patients with early growth failure and 0.000 (95% CI: 0.000, 0.000) for untreated patients with early growth failure.[7]

2.1.8 Impact on patient health-related quality of life

Due to the rarity of the disease, age and limited survival of untreated patients, information is not available on patients' HRQoL in the trials which form the basis of this submission. The patient organisation submission written by the MPS Society does however provide a detailed overview of patient/carer experiences, including a narrative discussion of quality of life prior, during, and after treatment with sebelipase alfa.[19] Further discussion is presented in section 4.3.1.11. A qualitative study has been carried out however with parents and caregivers of children living with rapidly progressive LAL-D exploring their own quality of life which found that the themes impacting parents were around living with uncertainty, feeling powerless and ultimately accepting a life with LAL-D.[14]

It is recognised that for rapidly progressive LAL-D, improving survival is likely to be a higher priority consideration than HRQoL.

In a treated population, a small study assessed the HRQoL of five patients, by the patients themselves where age appropriate and by parents in all cases. This study reported a high level of HRQoL as perceived by both the children and their caregivers. However, this should be interpreted with care, as parents of one patient scored their child as having 100% scores on all aspects of HRQoL which were much higher than the norm (50 – 80%) for both parent and child reported scores.[20]

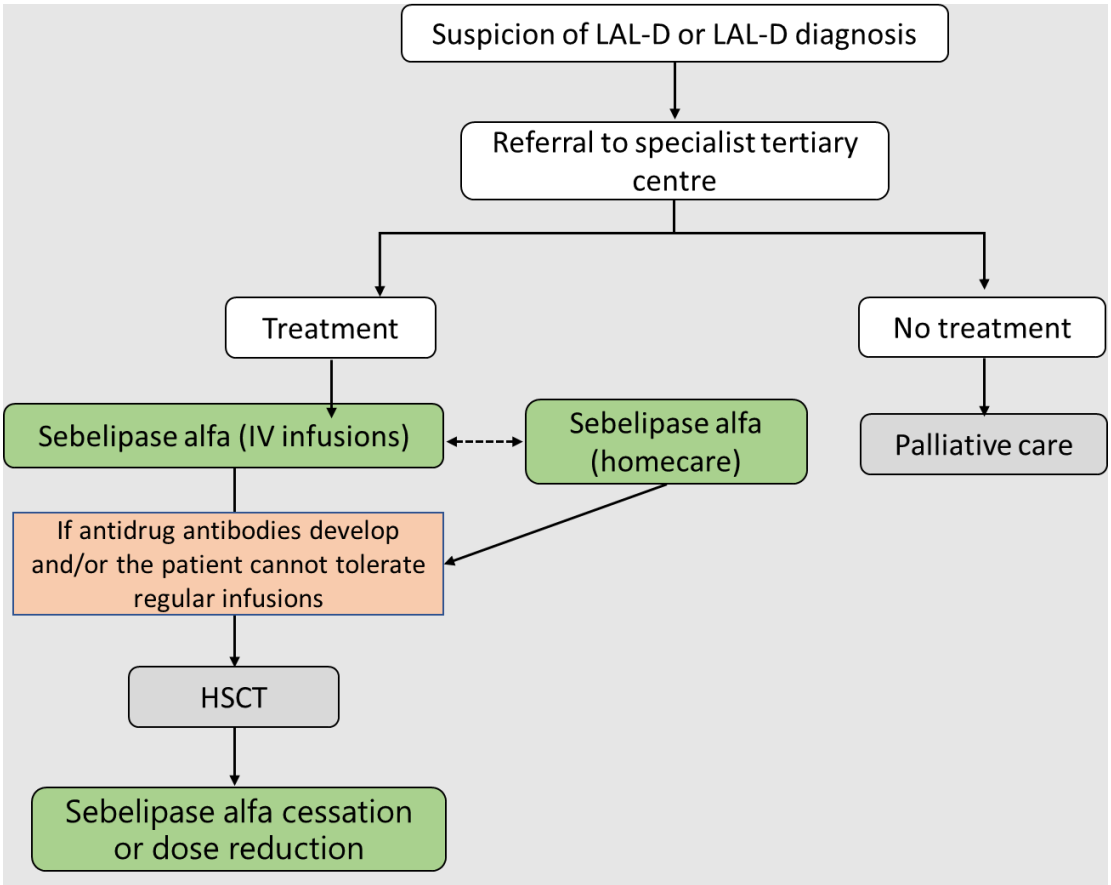
2.1.8.1 Current service provision (critique of company's description)

The CS states that the company is not aware of any published NICE, NHS England, other national or expert clinical guidelines for the diagnosis, treatment or management of rapidly progressive LAL-D.[2] At present there are no UK guidelines relating to rapidly progressive LAL-D. However, international expert consensus on practice has recently been published.[21] Current management options are focussed on supportive care and controlling complications; these include lipid-lowering therapies, vitamin E supplementation, HSCT and liver transplantation.

Sebelipase alfa is provided for compassionate use to patients in the UK via the company's 'Global Access to Medicine' (GATM) programme and the company indicate there are currently [redacted] patients in the UK with rapidly progressive LAL-D who are receiving sebelipase alfa through this route.[2]

The company's proposed treatment pathway is shown in Figure 2.1, and this broadly aligns with what is currently clinical practice via the GATM.

Figure 2.1: Treatment pathway in rapidly progressive LAL-D



Source: Figure 4, page 26, CS[2]
Abbreviations: CS, Company submission; HSCT, haematopoietic stem cell transplantation; IV, intravenous; LAL-D, lysosomal acid lipase deficiency

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM.

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Population	People with Wolman disease	Patients with rapidly progressive LAL-D	The patient population of focus for this submission is patients with rapidly progressive LAL-D, which has historically been referred to as 'Wolman disease' or the 'Wolman phenotype'. LAL-D can present across the lifespan, from the rapidly progressive infantile-onset form where symptom onset is usually up to 6-months of age, to the less-severe later-onset forms, which were historically and collectively known as CESDs. UK clinical experience has shown that, rarely, patients can also present with the rapidly progressive and advanced form of LAL-D between 6 and 24-months of age. The terminology 'rapidly progressive LAL-D' is therefore seen as a more current and clinically accurate description of the target population.	The population, although labelled differently, is broadly in line with the NICE Scope.
Intervention	Sebelipase alfa	As per final scope	NA	The intervention is in line with the NICE scope. With advances in HSCT, the use of sebelipase alfa is increasingly included in a multimodal approach, alongside nutritional support and HSCT.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Comparator(s)	Established clinical practice without sebelipase alfa	As per final scope	NA. However, the budget impact analysis considers the real-world situation in which sebelipase alfa is already established but access is provided under the Alexion Global Access to Medicines (GATM) programme, i.e., where sebelipase alfa is not acquired by the NHS in England.	The comparator is in line with NICE scope. Prior to enzyme replacement therapy (ERT), HSCT or liver transplant may have been used to treat patients. Now, HSCT is used after patients are stabilised with ERT and nutritional support.
Outcomes	The outcome measures to be considered include: 1. Mortality 2. Body weight and nutritional parameters (including growth) 3. Haematological parameters (including serum ferritin, need for blood transfusions) 4. Lipid parameters (including total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides) 5. Liver function (including transaminase level)	The outcome measures to be considered include: Mortality Body weight and nutritional parameters (including growth) Haematological parameters (including serum ferritin, need for blood transfusions) Liver function (including transaminase level) Liver disease progression (including hepatomegaly) Neurological development parameters Anti-drug antibodies	No adrenal gland function evidence was captured in any of the sebelipase alfa clinical trials, so we will not be able to include this outcome as requested in the pre-invitation scope. Clinicians have noted adrenal failure has not been a reported finding, even in long-term follow-up of affected infants receiving treatment.	Aside from adrenal gland function (which was not included in the main trials as an outcome), all other outcomes are in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	6. Liver disease progression (including hepatomegaly) 7. Adrenal gland function (for example, need for adrenal hormone supplementation) 8. Neurological development parameters 9. Cardiovascular events 10. Anti-drug antibodies 11. Adverse effects of treatment (including infusion-associated reactions) 12. Health-related quality of life (for patients and carers)	Adverse effects of treatment (including infusion-associated reactions) Health-related quality of life for patients and carers/family While the following parameters suggested in the final scope are not directly relevant for the rapidly progressive LAL-D population, they may provide valuable information for the long-term follow-up of treated patients who survive beyond infancy and will be discussed in the clinical sections only: 1. Lipid parameters (including total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides) 2. Cardiovascular events 3. Need for liver transplant		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Economic analysis	We plan to provide a full cost–utility analysis comparing sebelipase alfa to the current standard of care without sebelipase alfa	As per final scope	NA	A cost-utility analysis was performed with a full incremental analysis (see section 5.1 below). A budget impact analysis was conducted to calculate the 5-year budget impact for the NHS and PSS in England.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People who have received haematopoietic stem cell transplant • People who have not received HSCT	No subgroup analyses are presented.	Due to the rarity of the condition and the limited patient numbers, no subgroup analyses were planned or conducted for the LAL-CL08 or LAL-CL03 trials. Although no subgroup analyses of the pivotal trials were performed, the efficacy of sebelipase alfa and HSCT as a multimodal therapy in the UK has been explored in a recently published case series (Potter *et al*., 2021[3] N = 5). Results for these five patients with rapidly progressive LAL-D have therefore been provided as part of the evidence base presented in this submission.	No subgroup analysis was undertaken by the company due to limited data. A narrative description is however included.
Special considerations including issues related to equity or equality	NA. No special considerations, including issues related to equity or equality, were stated within the final scope	As per final scope The aim of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between all is aligned with Alexion's principles	NA	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
		on Diversity, Inclusion and Belonging. The decision has been made to focus this appraisal only on the treatment of patients with the most severe form of LAL-D which manifests in very young children, known as rapidly progressive LAL-D. The decision to target this specific population in this appraisal has been justified based on the higher potential for accrual of health benefits over the patients' lifetimes, which results in better cost effectiveness in this population. However, older children, adolescents and adults with LAL-D may be negatively impacted by not having access to treatment with sebelipase alfa, despite evidence of proven clinical efficacy in		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
		these groups. As age is a protected characteristic in UK law, it is possible that excluding these patients from this appraisal could result in equality issues. Later-onset LAL-D (cholesterol ester storage disease) is still being considered within the NICE evaluation of sebelipase alfa for treating LAL-D (ID737). It has been paused while this evaluation for treating rapidly progressive LAL-D is undertaken. We have not identified any other foreseeable exclusions, limitations or adverse effects on protected individuals based on disability, gender reassignment, relationship status, pregnancy and maternity, race, religion or belief, sex, and/or sexual orientation.		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Source: Based on Table 1 pages 9 to 13 of the CS[2] Abbreviations: CESD, Cholesteryl ester storage diseases; CS, Company submission; ERT, enzyme replacement therapy; GATM, (Alexion) Global Access to Medicines programme; HSCT, Haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency; NA, not applicable; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; UK, United Kingdom				

3.1 Population

The population defined in the NICE scope is people with Wolman disease.[1] The population outlined in the CS is *"patients with rapidly progressive LAL-D, which has historically been referred to as 'Wolman disease' or the 'Wolman phenotype'"* (page 7 of the CS).[2] The infantile onset of LAL-D is characterised in the CS by symptom onset usually up to 6-months (although patients can also present with rapidly progressive LAL-D between 6 and 24-months).[2]

The studies included in the CS focus on the following populations:

- Paediatric (≤ 2-years) patients with LAL-D diagnosis and growth failure with onset before 6-months of age: LAL-CL03 (single arm sebelipase alfa study)
- Paediatric (≤ 8-months) patients with LAL-D diagnosis and substantial clinical concerns: LAL-CL08 (single arm sebelipase alfa study)
- LAL-1-NH01 (historical control group)

EAG comment: The EAG consider Wolman disease and rapidly progressive LAL-D to be the same. According to the NORD (National Organization for Rare Disorders), Wolman disease is the most severe expression of LAL deficiency, the symptoms of which usually become apparent shortly after birth.[22] Clinical advice to the EAG has confirmed that symptom onset is typically in the first weeks of life, and most often within 6-months.

The clinical trials included in the CS are broadly in line with this indication. LAL-CL03 includes patients with growth failure with onset before 6-months, and LAL-CL08 includes patients with substantial clinical concerns (which includes marked abdominal distention and hepatomegaly, failure to thrive, disturbance of coagulation, severe anaemia and sibling with a rapidly progressive course of LAL-D).[2] The population for LAL-CL08 encompasses older patients up to 8-months, with a broader range of clinical symptoms compared to LAL-CL03, the vast majority of which are likely to have rapidly progressive LAL-D.[23,24]

The company states that rapidly progressive LAL-D may rarely present up to 24-months,[2] however, a confirmed diagnosis of LAL-D must be accompanied by other clinical features indicative of rapidly progressive onset. In response to the points for clarification (question A1) the company highlights the NICE final scope document to illustrate the alignment of both definitions, for example: '*Wolman disease is a type of LAL deficiency that presents in babies and children under 2-years as rapidly progressing multisystem disease. Wolman disease is characterised by intestinal failure and severe malabsorption, growth failure, hepatosplenomegaly and progressive liver fibrosis and cirrhosis. The condition normally results in death in the first 6-months of life, usually due to multiple organ failure. For the smaller group of children diagnosed slightly later (under 2-years), there is still usually evidence of growth failure in the first 6-months of life'*.[1,25] Clinical advice to the EAG was that a diagnosis at 24-months would not be seen as clinically rapidly progressive in itself. There does appear to be some ambiguity of the 24-month upper age cut-off of rapidly progressive LAL-D. Data held on file by the company identify [redacted] cases in the UK of rapidly progressed and advanced LAL-D in patients aged between 6 and 24-months over the last 7-years. These patients present with severe impairment of liver function (advanced fibrosis) and require treatment intervention with ERT.[2] Given that the company considers that on [redacted] might present with rapidly progressive LAL-D,[2] it is important to consider whether patients presenting aged between 6 and 24-months may represent a sizeable group. In summary, the population in the CS is broadly in line with the NICE

scope,[1] however the EAG acknowledges the ambiguity in the upper age limit, perhaps owing to the rarity of the disease.

3.2 Intervention

The intervention defined in the NICE scope is sebelipase alfa.[1] The intervention outlined within the CS is in line with this.[2] Sebelipase alfa is administered as an intravenous (IV) infusion. For patients with rapidly progressive LAL-D presenting within the first six-months of life, the recommended starting dose is either 1 mg/kg or 3 mg/kg once weekly, depending on the clinical status of the patient (a higher starting dose should be considered based on disease severity and rapid disease progression).[26]

Current clinical practise uses sebelipase alfa alongside nutritional support to control disease progression, however the development of ADAs and the need for central vein access for weekly infusions limits treatment efficacy. More recently, ERT, nutritional support, and HSCT are combined in a multimodal treatment for rapidly progressive LAL-D patients, which has shown to improve long-term gut function, tolerance of a normal diet and quality of life.[3]

EAG comment: The intervention in the CS is in line with the NICE scope,[1] however, increasingly, the treatment pathway typically involves the use of sebelipase alfa and nutritional support prior to HSCT owing to drug/disease-related complications, or [redacted](section **Error! Reference source not found.**). The final evaluation determination document [ID737] for an earlier appraisal of sebelipase alfa (in a broader population), concluded at that time, it was not possible to make a research recommendation for the use of sebelipase alfa as a bridging therapy before HSCT. The rationale was ethical concerns surrounding stopping an effective treatment (sebelipase alfa) and switching to a '*treatment which has not been shown to be effective and carries a high risk of morbidity and mortality*'.[27] However, the evidence-base is growing and research by Potter *et al.,* 2021 identified five patients with Wolman disease and showed that even though ERT efficacy had reduced (due to ADAs), *"it had facilitated [the patients'] 'bridging' to [HSCT] and likely improved their [HSCT] survival"* (page 4).[3] The EAG is mindful that there is considerable uncertainty when HSCT would take place since the use of sebelipase alfa in patients with rapidly progressive LAL-D is still relatively immature (considering the lifetime of patients). Further details are provided in section 4.4.

3.3 Comparators

The comparator defined in the NICE scope is established clinical practice without sebelipase alfa.[1] Data for the comparator were taken from the natural history study (LAL-1-NH01) which included 35 paediatric patients (aged ≤2-years) with LAL deficiency (a subset of 21 patients were identified with rapidly progressive LAL-D who were untreated and experienced early growth failure).[7] Without sebelipase alfa, supportive care was offered to patients, including lipid-lowering therapies.[2] On occasions, liver transplants and HSCT were used, however, clinical expertise to the company suggested that HSCT and/or liver transplant would not currently be recommended without sebelipase alfa.[2]

EAG comment: The comparator in the CS is broadly in line with the NICE scope.[1] The EAG are unaware of any other ERT (aside from sebelipase alfa) which offer a treatment option for patients with rapidly progressive LAL-D. Clinical advice confirmed that the use of HSCT is not considered a viable treatment option on its own.

3.4 Outcomes

The final NICE scope lists 12 outcome measures.[1] All outcomes aside from adrenal gland function and health-related quality of life (which were not measured in sebelipase alfa clinical trials) were included in the CS.[2] Clinical expertise to the company noted *"adrenal failure has not been a reported finding,*

even in long-term follow-up of affected infants receiving treatment" (CS, section B.1.1, Table 1, page 10).[2] The company notes that HRQoL was not included as an outcome measure in LAL-CL03 and LAL-CL08 *"due to the very young age of the patients enrolled and therefore the inability to provide any accurate readings using self-report HRQoL instruments"* (page 8).[25] The CS also notes that lipid parameters, cardiovascular events and the need for liver transplant are outcomes not directly relevant to the rapidly progressive LAL-D population.

EAG comment: Aside from adrenal gland function and HRQoL, all outcomes in the CS are in line with the NICE scope.[1,2] The EAG are satisfied that the lack of adrenal gland function as an outcome measure is a limited cause of concern. The EAG are also understanding of the lack of HRQoL data in the two main clinical trials. There are significant measurement challenges related to HRQoL in neonates, infants and very young children and the validity of parent proxy reports are difficult to assess.[28-31] Consequently, HRQoL measurements are performed infrequently or with instruments not developed or validated for this purpose.[28,32,33] The EAG acknowledges that as there is no valid preference-based HRQoL measure for very young children and infants, the calculation of quality-adjusted life years for economic evaluations is hampered.[28,34] Whilst the assessment of HRQoL both pre- and post-ERT and pre- and post-HSCT would be very informative, the EAG considers this to be an unresolvable issue which has high uncertainty. Aside from adrenal gland function and HRQoL, all other outcomes are in line with the NICE scope.[1]

3.5 Subgroups

The final NICE scope details that if sufficient evidence is available, the following subgroups should be considered:[1]

- People who have received HSCT;
- People who have not received HSCT.

In relation to subgroup analysis, the CS states that: *"due to the rarity of the condition and the limited patient numbers, no subgroup analyses were planned or conducted for the LAL-CL08 or LAL-CL03 trials".*[2] Given the small numbers of patients who had HSCT, it is unsurprising that trial evidence is limited. In response to the Points for Clarification (PfC) (question A11),[25] the company outlined the numbers of patients in the clinical trials who had HSCT or liver transplant. In LAL-CL08, [redacted] patients received HSCT, and no patients received a liver transplant.[24] In LAL-CL03, no patients received a liver transplant or HSCT.[23] It is unclear how many further patients have received HSCT after the trials completed.

Prior to sebelipase alfa, HSCT was used as a 'last resort' treatment option. Now it is used following treatment with sebelipase alfa and nutritional support to improve long-term gut function, tolerance of normal diet and HRQoL.[3] The PfC details this change to the treatment pathway.[25] Specifically, they highlight *"the difference between the way that HSCT has been used historically (i.e. before the availability of sebelipase alfa, and during the early years of its use, such as during the clinical trials) and how it is being used now and planned to be used in the future, as part of a rapidly evolving clinical practice"* (page 18).[25] The response to the PfC provided a narrative summary of patients in the two trial arms who received HSCT.[25] [redacted] patients received HSCT (no patients received a liver transplant) in LAL-CL03.[23] [redacted] underwent transplant following high-titer ADAs (at day [redacted] and day [redacted]), [redacted] due to an inflammatory HLH-type condition and later died at 13.8 months due to sepsis.[3,25] No patients in LAL-CL08 had either a liver transplant or HSCT.[24]

EAG comment: The EAG acknowledges that formal quantitative analysis of subgroups is not feasible given the small patient numbers involved. The EAG is also understanding of the rapid progress in HSCT which has been achieved over recent years and is therefore mindful of how the profile of patients and outcomes post-HSCT are likely to have evolved over time. Further details are provided in section **Error! Reference source not found.**.

3.6 Considerations related to equality

The company provides a discussion concerning why, by focusing on patients with rapidly progressive LAL-D only, equality issues may arise owing to the exclusion of older patients with later-onset LAL-D (detailed in Table 3.1). The CS acknowledges that the decision is justified based on the QALYs gained by infants who would without treatment face an early death.[2]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) of the survival, response, safety, and patient reported outcomes in the infantile presentation of LAL-D.[2] The methods of the SLR are detailed in Appendix D of the CS.[35] The CS reports the most recent SLR undertaken for this current submission, and provides an update (2015 to 2022) to the earlier SLR detailed in the 2015 CS which formed part of ID737 and comprised a broader population, which included patients with LAL-D, Wolman disease and Cholesteryl Ester Storage Disease.[2,36]

The company states the protocol for the SLR, written *a priori*, was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), and was made available to the EAG in response to PfC (question A5).[25]

4.1.1 Searches

An information specialist performed a critical appraisal of the search strategies, presented in CS Appendix D, section D.1,[35] supplemented by additional information supplied by the company in response to question A13 of the PfC letter,[25] for clinical effectiveness studies using the PRESS checklist.[37] The searches conducted in June 2022 for this 2022 SLR were reported to be updated versions of those conducted for the 2015 company submission to NICE (ID737).[2,36] A summary of the resources searched for the company's 2022 SLR of clinical effectiveness studies is given in Table 4.1.

Table 4.1: Resources searched for the clinical effectiveness SLR

Resource - category	Resource	Host Source/Platform	Date Range	Date of search	Search strategy/string/terms reported Y/N	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	Embase	Embase.com	January 2015 to June 2022	08/06/2022	Yes	Yes	Yes[a]
	MEDLINE				Yes		NR
	MEDLINE In-Process, Epub Ahead of Print, and citation status 'publisher'	PubMed		14/06/2022	Yes	Yes	NR
	Cochrane Library • CDSR • CENTRAL[a]	cochranelibrary.com		20/06/2022	Yes	Yes	Yes
Conference proceedings	Society for the Study of Inborn Errors of Metabolism (SSIEM)	NR	2018-2022	NR	NA	NA	Yes
	European Association for the Study of the Liver (EASL)	NR	2018-2022	NR	NA	NA	Yes
	American Association for the Study of Liver Disease (AASLD)	NR	2018-2022	NR	NA	NA	Yes
	North American Society for Paediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN)	NR	2018-2022	NR	NA	NA	Yes

	European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)	NR	2018-2022	NR	NA	NA	Yes
	National Lipid Association (NLA)	NR	2018-2022	NR	NA	NA	Yes
	European Atherosclerosis Society (EAS)	NR	2018-2022	NR	NA	NA	Yes
	Lysosomal Disease Network (LDN)	NR	2018-2022	NR	NA	NA	Yes
Reference lists	"key" systematic reviews and meta-analyses	NA	NA	NR	NA	NA	Yes

Source: CS Appendix D, section D.1[35] and the response to clarification letter question A13[25]
a MEDLINE records were only reported as part of the Embase search
b The company report that any ClinicalTrials.gov records captured by the search of CENTRAL were not included in the SLR and were only used as a method of checking that relevant published studies were captured (there is no mention of any other trial registry records identified in the CENTRAL search), CS Appendix D, section D.1.1[35]
Abbreviations: AASLD, American Association for the Study of Liver Disease; CDSR, Cochrane Database of Systematic Review; CENTRAL, Cochrane Central Register of Controlled Trials; CS, Company submission; EAS, European Atherosclerosis Society; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; LDN, Lysosomal Disease Network; NA, not applicable; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology & Nutrition; NLA, National Lipid Association; NR, Not reported; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; SSIEM, Society for the Study of Inborn Errors of Metabolism.

EAG comment: Whilst the key ideas were captured in the searches, the company did not provide full search details to complete a critical appraisal in the first instance. Dates of coverage for databases searched were not provided, although host sources for the databases searched appear to have been included within the CS Appendix.[35] Furthermore, whilst each line of the search strategy was provided, the number of publications retrieved per line was not; information that is important during a critical appraisal of a search strategy. Search strategies should also include any limitations that were (or were not) imposed upon the search, and updated searches should also include any terms, syntax or limits applied in addition to any date fields that were specifically searched where appropriate. This information was provided by the company in response to question A13 of the PfC letter.[25]

Clinical trials registries were not searched as recommended by the NICE methods guidance (PMG36)[4] and the company report that ClinicalTrials.gov records identified when searching CENTRAL were not included (CS Appendix D, section D.1.1),[35] even though these can be an important source of information about ongoing studies. Furthermore, a search for adverse effects was not conducted.

Search filters have been applied to the searches but were not referenced, as is considered good practice, and are therefore potentially not validated. Boolean operators could have been used more effectively, i.e., combining lysosomal acid lipase deficiency related terms with Wolman disease using 'OR' instead of 'AND'. The current use potentially reduces retrieved documents unnecessarily. Furthermore, all available synonyms, abbreviations or names in free-text search were not utilised. For example, NORD[22] lists LAL-deficiency (Wolman type) as an alternative disease name. In addition, 'Lysosomal acid lipase deficiency', 'LIPA protein', 'Wolman disease' and 'Cholesterol Ester Storage Disease' are searched through MeSH or subject headings, but they are not searched within title, abstract or keyword where applicable. Proximity (adjacency) operators were used to construct the search for PubMed, but this functionality is not present in the PubMed database, this means searches were incorrectly translated across databases. This limits the search unnecessarily. It is possible that there was some incorrect use of quotation marks in the search conducted in PubMed, which would retrieve zero results, but as free-text and subject headings were not presented on separate lines, it is not possible for the EAG to verify this. The potential implication of this being, that records are potentially not being retrieved and missed completely.

4.1.2 Inclusion criteria

The full inclusion criteria for the 2022 SLR are detailed in the CS Appendix (Table 1).[35] Following best practice as outlined by Cochrane,[38] two reviewers independently performed title and abstract screening (Level 1), and full text screening (Level 2) using the inclusion criteria stated below in Table 4.2. Any uncertainty or disagreements were resolved by a third independent reviewer.

Table 4.2: Eligibility criteria used in SLR for RCT and non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Infantile presentation of LAL-D or Wolman disease (newborn infants[a])	Largely consistent with final scope. The reference to newborn infants in the eligibility criteria specifically seems at odds with the broader definition of rapidly progressive LAL-D advocated by the company which encompasses children up to 24-months.[2] However, the population screened at the eligibility stage includes patients under 2-years of age, so this is in keeping with this definition.
• Interventions	No restrictions, but can include: • Stem-cell transplantation • Sebelipase alfa[b] • Enzyme replacement therapy • BSC	The SLR includes the intervention (sebelipase alfa) and comparator (established clinical practice without sebelipase alfa) as defined in the NICE scope.[1] Stem-cell transplantations are included as they were historically used in the treatment of rapidly progressive LAL-D and are now part of a multi-modal approach which includes ERT with dietary substrate reduction.[3]
Comparator	• Placebo • Any other pharmacological intervention	As above.

	Description	Justification
Outcomes	The outcome measures to be considered include: • Mortality • Body weight and nutritional parameters • Haematological parameters (including serum ferritin, need for blood transfusions) • Lipid parameters (including total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides) • Liver function (including transaminase level) • Liver disease progression • Need for liver transplant • Adrenal gland function (for example, need for adrenal hormone supplementation) • Cardiovascular events • Adverse effects of treatment	These outcomes are broadly in line with the NICE scope.[1] Two outcomes included in the scope which were not detailed in the eligibility criteria of the SLR include neurological development parameters and anti-drug antibodies. Anti-drug antibodies are related exclusively to the use of sebelipase alfa. Furthermore, without treatment with ERT, the median age of death is 3-months,[7] so neurological development may not be considered a priority. The need for a liver transplant was also included as an outcome, which is reflective of practice prior to the use of ERT. HRQoL is dealt with separately and is described in section 4.3.1.11
Study design	• Randomised controlled trials • Non-randomised controlled trials • Observational studies • Single arm trials • Qualitative studies • Systematic reviews (to identify relevant unique studies)	All study designs were considered.

Source: Modified from Table 1 of Appendix D from the CS[35]

Footnote: [a] The CS notes that no age-specific restrictions were applied to the search strategy and during the screening of abstracts. In cases where Wolman disease was not specified, studies were included during full-text screening if relevant data are reported for study population (or a subset of study population) below 2-years of age.

[b] The CS notes that studies for sebelipase alfa will only be extracted as per the previous SLR and the comparator data will only be identified but not extracted.

Abbreviations: BSC, best supportive care; CS, company submission; ERT, enzyme replacement therapy; HRQoL, health-related quality of life; LAL-D, lysosomal acid lipase deficiency; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SLR, systematic literature review.

EAG comment: The EAG consider the inclusion criteria to broadly match the NICE decision problem.[1] Neurological development and anti-drug antibodies were not considered, however, given that these are reported in LAL-CL03 and LAL-CL08, this is a limited cause for concern. HRQoL is also not reported but was considered in a separate SLR described in section B.3.4.3 of the CS[2] and in section 4.3.1.11.

The SLR includes the intervention (sebelipase alfa) and comparator (established clinical practice without sebelipase alfa) as defined in the NICE scope.[1] Treatment with HSCT is also considered, and the EAG is in agreement with the company that its use has evolved, from a 'last resort' therapy to part of a multi-modal therapy alongside dietary substrate reduction and ERT.[25]

Figure 1 in the CS[35] details the PRISMA flow diagram. The EAG notes that a single study has been excluded based on language restrictions. Whilst this might risk missing relevant non-English language studies, having checked the list of excludes provided in the CS,[35] the EAG consider that this reference would not meet the other eligibility criteria.

The update and more focused population applied to the SLR ensured relevance to the NICE scope.[1] Only two studies detailed in the 2015 SLR were relevant to the Wolman/rapidly progressive LAL-D population reported in the NICE scope,[36] LAL-1-NH01 and LAL-CL03. These form two of the three pivotal trials used in this submission.

Although the description of methods and reporting of the SLR were of variable quality, the EAG considers these methodological limitations of minimal concern owing to the two key trials sponsored by the company which evaluate sebelipase alfa and also the natural history cohort study (LAL-1-NH01) which describes efficacy data for best supportive care (BSC) without sebelipase alfa.

4.1.3 Data extraction

No information is provided in the CS on their method of data extraction for the SLR. Although eight studies were included in the 2022 SLR, the majority of efficacy data are drawn from LAL-CL03 and LAL-CL08 and compared with standard of care in the absence of sebelipase alfa which was taken from LAL-1-NH01. The company have direct access to these trial data as the sponsors, so this is not a cause of concern.

EAG comment: It is good practice in systematic reviews that every step in the systematic review process is performed by at least two reviewers to minimise bias and to prevent mistakes. Whilst methods of data extraction employed for the SLR relevant to the NICE scope are unclear, and the EAG has no guarantee that the data extraction process was complete, it is unlikely to impact on the validity of the SLR findings and company submission. Alexion Pharmaceuticals is the sponsor of the two sebelipase alfa trials (LAL-CL03 and LAL-CL08) and the natural history cohort (LAL-1-NH01) and therefore had full access to the complete trial data. The EAG therefore finds this approach acceptable.

4.1.4 Quality assessment

The company conducted quality assessment using the Downs and Black checklist which was designed to evaluate methodological quality of both randomised and non-randomised comparative studies.[39] The checklist comprising 27 items is included in Table 7 of the CS Appendices.[35] It is unclear whether the critical appraisal was done by a single reviewer or in duplicate, and no justification for the statement choice ('yes', 'no', 'unclear') is provided.

EAG comment: The quality assessment tool used by the company was considered appropriate by the EAG, although there remains some uncertainty as to the number of people involved in conducting the

critical appraisal. More detailed appraisal of the quality of the LAL-CL03, LAL-CL08 and LAL-1-NH01 studies is presented in section 4.2.2 below.

4.1.5 Evidence synthesis

In the 2015 CS for TA737, 16 records were identified,[36] comprising four clinical trials (population criteria in addition to confirmed LAL-D diagnosis is provided in brackets):

1. LAL-CL03 (growth failure with onset before 6-months, patient up to 24-months)[40,41]
2. LAL-CL02 (patient 4-years and older)[42,43]
3. LAL-CL01 (patient 18 to 65-years)[44,45]
4. LAL-CL04 (patient 18-years and older)[46,47]

In addition, two further studies were identified (LAL-CL06[48,49] and LAL-CL08) but excluded in the CS for TA737,[36] as the studies were not complete and lacked efficacy data. LAL-CL08 forms one of the two key trials in this present CS,[2] and LAL-CL06 (N=31) included patients >8-months of age at the time of dosing.[49] Given the focus on Wolman disease/rapidly progressive LAL-D which reflects the NICE scope for this TA,[1] only patients in LAL-CL03 and LAL-CL08 are relevant. Six patients who met the study inclusion criteria in LAL-CL06 were >8-months and <4-years of age, however, only one had impaired growth so it seems appropriate that this trial was excluded in the updated SLR.[49]

In this CS, comprising an update of studies found between 2015 and 2022, 21 reports comprising eight unique studies were identified.[2] The LAL-CL08 study is complete and included in the submission, alongside LAL-CL03 which was also identified in the earlier SLR. The natural history cohort (LAL-1-NH01) was identified in the CS as the "*only appropriate source of evidence for comparison to the LAL-CL08 and LAL-CL03 trials*" (CS Appendices, page 11).[35] Five other studies were identified.[3,20,50-52] A detailed overview of the clinical effectiveness data of the clinical trials is presented in section 4.3, and evidence derived from the additional study publications is listed where appropriate.

The EAG note that in the CS,[35] two studies relevant to HSCT and nutritional management were not examined. The CS states:[2]

"The SLR identified a further two studies; one presented evidence for treatment with HSCT in the absence of sebelipase alfa,[50] and one reported on clinician experience of nutritional management in patients with rapidly progressive LAL-D.[51] These studies are not directly relevant to the decision problem and have therefore not been considered relevant for inclusion in this dossier." (page 32)

EAG comment: The flow of studies in the SLR conducted in 2015 and updated subsequently in 2022 seems appropriate. The response to the PfC letter gave clarity on this and on how evidence for both reviews was included and cross referenced to the outcomes identified in the NICE scope.[1] Five additional studies were identified in the SLR. Due to the rarity of the condition, these are helpful and provide further data on the developing supportive therapies for patients with rapidly progressive LAL-D, and longer-term follow-up.

The EAG notes the two additional papers, reported as abstracts only, were found to meet the inclusion criteria but were not reported in the CS.[50,51] The EAG considers these are relevant includes which match the eligibility described in Table 4.2. However, the EAG are in agreement with the company that HSCT in the absence of sebelipase alfa would no longer be considered as a viable treatment option, so the Lum *et al.,* 2021 article is unlikely to provide data that would meaningfully impact on the conclusions of this appraisal.[50] The second abstract meeting the SLR eligibility criteria but not deemed relevant, details clinician experience of nutritional management in patients with rapidly progressive LAL-D.[51] Whilst the abstract does provide some useful contextual information detailing the approaches followed to

restrict dietary fat intake, the EAG considers the reference of limited use, given that some/all patients in LAL-CL03 and LAL-CL08 are likely to have received nutritional support alongside ERT as well.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The systematic review conducted by the company identified two non-randomised studies of interventions related to the decision problem of sebelipase alfa treatment in infants with rapid progressive LAL-D (LAL-CL03 and LAL-CL08). Additionally, three studies were identified from the SLR which offer supportive evidence.[3,20,52] Details related to these secondary studies are described when necessary to the effectiveness outcomes reported in section 4.3.

Both clinical studies (LAL-CL03 and LAL-CL08) are part of Alexion's larger clinical development programme to evaluate the safety and efficacy of sebelipase alfa. Data from these two studies focus on the rapid progressive subgroup.

4.2.1 Critique of trials, their analysis and interpretation

Both studies (LAL-CL08 and LAL-CL03) presented in the CS are single-arm, multi-centre and open-label. Findings from the LAL-CL08 study provides the primary clinical evidence, and findings from LAL-CL03 provides supportive evidence for the clinical efficacy and economic model. Considering the lethality of the condition in the rapid progressive cohort and the lack of satisfactory treatment options it was considered unethical to use an internal control arm of placebo plus BSC. To enable comparison between sebelipase alfa and BSC the company incorporated a non-concurrent external control using retrospectively collected chart reviews (LAL-1-NH01) which is also part of Alexion's clinical development programme.[7]

Provided below is a brief overview of both studies with a summary of the methods applied.

4.2.1.1 LAL-CL08

LAL-CL08 is a phase II, multi-centre study conducted between 05 June 2014 and 30 October 2018 with sites in four countries, including the United Kingdom (UK), the United States of America (USA), Italy and Finland. The study comprises ten patients and the final results from a maximum 3-year follow-up (156-weeks) were published in 2021.[53] Compared to the LAL-CL03 population, the eligibility criteria for LAL-CL08 are broader (Table 4.3), including infants who have a laboratory-confirmed diagnosis of LAL-D and have clinical features that require urgent medical care and are indicative of rapidly progressive LAL-D but who may not meet the growth failure criteria. Clinical features include but are not limited to marked abdominal distention and hepatomegaly, failure to thrive, disturbance of coagulation, severe anaemia, and a sibling with an existing diagnosis of rapidly progressive LAL-D (Table 4.3).

Table 4.4 presents the study characteristics of both trials to allow for comparison. With regards to LAL-CL08, [redacted] patients completed the study, [redacted] patients died, and [redacted] received treatment for [redacted] or [redacted] until the sponsored study ceased and patients transitioned onto the licensed therapy. [redacted] of the patients enrolled are based in the UK indicating relevance to the decision problem and the UK.[24] The company submission describes the starting dose as 1 mg/kg once weekly (qw) ([redacted]), dose escalation was permitted to 3 mg/kg qw ([redacted]), if after four doses there was suboptimal response dose was increased again to 5 mg/kg qw ([redacted]). However, we note a protocol amendment to increase dose escalation to 7.5 mg/kg qw where there was evidence of continued disease progression and suboptimal clinical response at 5 mg/kg qw, this applied to [redacted] site.[24] [redacted] patients went on to receive HSCT or bone marrow transplant (BMT) at day [redacted] and [redacted].[24] [redacted] patient received BMT at day [redacted]. Following successful engraftment of HSCT

or BMT two patients had dose reduction and achieved a stable clinical response at the reduced dose of 1mg/kg qw and 3 mg/kg qw. The protocol facilitated a change on dosing regimen to every other week (QOW), however, no patients transitioned to this. Throughout the duration of the trial, doses of 3 mg/kg qw was the most frequently administered with [redacted] administered followed by 5 mg/kg qw ([redacted]), 1 mg/kg qw ([redacted]), and then 7.5 mg/kg qw ([redacted]).

EAG Comment: Clinical advice to the EAG confirmed the clinical manifestations for rapidly progressive LAL-D which usually presents in the first 6-months of life as; distended abdomen, hepatosplenomegaly, liver dysfunction, acute liver failure, gastrointestinal symptoms, failure to thrive, vomiting, poor feeding, diarrhoea and steatorrhoea. Based on this we agree with the company's approach in that the LAL-CL08 cohort are representative of the population defined in the decision problem and broadening the eligibility criteria increases generalisability compared to the LAL-CL03 study (discussed below in section 4.2.1.2). However, the inclusion of participants with unspecified urgent clinical need including those with a sibling with a rapidly progressive course of LAL-D may not meet the criteria for a diagnosis of rapidly progressive LAL-D in current clinical practice. In response to PfC (question A8), the company stated [redacted] ([redacted]) patients had a sibling or cousin with a rapidly progressive course of LAL-D. Most of these patients (if not all) had other clinical concerns, so the EAG considers this to be a limited cause of concern and reflective of anticipated use in the NHS.[25]

No short-term safety concerns were captured at the higher dose of 7.5 mg/kg qw in the [redacted] who received this dose (patient received [redacted] qw).[24] Considering the small patient population (N=10). the requirement for this dose escalation does indicate that doses of 5 mg/kg qw might not always be sufficient to see a clinical improvement and that doses of 7.5 mg/kg qw might be required in clinical practice.

Table 4.3: Eligibility criteria for LAL-CL08, LAL-CL03 and LAL-1-NH01

Category of design	LAL-CL08[a]	LAL-CL03[b]	LAL-1-NH01[c]
Eligibility	Substantial clinical concerns, in the opinion of Investigator and Sponsor, of rapid disease progression requiring urgent medical intervention including, but not restricted to, the following: a. Marked abdominal distension and hepatomegaly b. Failure to thrive as evidenced by: − Weight for height is 2 or more SD below the mean for gender and age − Weight curve had crossed downward by more than 2 major percentile lines on the WHO growth curves (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th) after having previously achieved a stable pattern of growth c. Disturbance of coagulation (e.g., requirement for fresh frozen plasma; 2 values of prothrombin time > 15 sec, or partial thromboplastin time > 40 sec) d. Severe anaemia (e.g., requirement for blood transfusion or haemoglobin < 8 g/dL) e. Sibling with rapidly progressive course of LAL-D Under 8-months of age at first dose	Growth failure* with onset before 6-months of age, as defined by either: • Weight decreasing across at least 2 of the 11 major centiles on a standard WHO WFA chart (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th); • Body weight in kg below the 10th centile on a standard WHO WFA chart AND no weight gain for the 2-weeks prior to screening; • Loss of 5% of birth weight in a child who is older than 2-weeks of age. No prior HSCT or liver transplant or any pre-conditioning treatments	The availability of the following minimum data items in medical records (partial records were accepted): 1. Date of Birth 2. Sex 3. Date of death (or age of death) 4. Weight at birth (or first recorded weight) 5. At least one other weight measurement obtained a minimum of 4-weeks later and prior to the initiation of HSCT or ERT 6. Enzyme of genetic testing date 7. Date of initiation of HSCT or ERT (if applicable)

	No prior haematopoietic stem cell or liver transplantation with pre-treatment (myeloablative) No presence of clinically important concurrent disease or comorbidities		

Source: Modified from Table 4 of the CS,[2] and clinical study reports for LAL-CL03[23] and LAL-CL08[24].

Footnotes:

a Assumes consent and confirmation of documented decreased LAL activity relative to the normal range of the lab performing the assay or a documented result of molecular genetic testing confirming a diagnosis of LAL-D.

b Assumes consent and infant with a documented decreased LAL activity relative to the normal range of the laboratory performing the assay or documented result of molecular genetic testing (2 mutations) confirming a diagnosis of LAL-Deficiency under the age of 24-months.

c Assumes consent and confirmation of documented decreased LAL activity relative to the normal range of the laboratory performing the assay or a documented result of molecular genetic testing confirming a diagnosis of LAL-D within the first two years of life.

* Note from company regarding Inclusion Criterion 3: In the unusual circumstance where a subject had a rapidly progressive course of LAL-D but did not meet the growth failure criteria as defined above, the subject could be enrolled in the study if the investigator had substantial clinical concerns based on evidence of rapid disease progression that required urgent medical intervention. Inclusion under these exceptional circumstances required submission of a written summary of the subject's medical status for review by the Sponsor, and this summary had to be approved by a written confirmation from the Sponsor after consultation with the study safety committee. The subject had to meet all other entry criteria as stated.

Abbreviations: CS, company submission; dL, decilitre; ERT, enzyme replacement therapy; g, grams; HSCT, haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency; SD, standard deviation; WHO, World Health Organization; WFA, weight-for-age.

4.2.1.2 LAL-CL03

LAL-CL03 is a phase II/III multi-centre dose escalation study with eight trial sites in six countries; the UK, USA, France, Ireland, Egypt, and Turkey. The authors applied growth failure to the eligibility criteria as a prognostic factor to differentiate between patients with rapidly progressive LAL-D and less rapidly progressive LAL-D who may also be diagnosed in infancy but would typically have better outcomes and survive beyond six-months of age, unlike the rapidly progressive subgroup (see Table 4.4). Applying growth failure as eligibility criteria facilitated comparability and matching with a subset of patients enrolled onto the LAL-1-NH01 natural history study. [redacted] of [redacted] surviving eligible participants who were screened were ultimately enrolled and allocated to receive intervention with a treatment period up to [redacted] between 04 May 2011 and 03 Jan 2018. [redacted] of the patients are from the UK.

EAG Comment: We note an amendment to the protocol which appears to widen the eligibility to include [redacted] patient, who did not meet the growth failure criteria but where there was clinical evidence of rapidly progressive LAL-D (marked abdominal distention, vomiting, diarrhoea, massive hepatosplenomegaly, anaemia, hypoalbuminemia and elevated AST and lactate dehydrogenase) and who had a diagnosed older sibling. Overall, eight subjects had confirmed growth failure in the first six-months of life. The EAG believes the population enrolled onto LAL-CL03 represents a narrow group of those with rapidly progressive LAL-D who are likely to receive sebelipase alfa in clinical practice.

4.2.1.2.1 Baseline characteristics

Baseline characteristics from people with rapid progressive LAL-D from the two single arm trials (LAL-CL03 and LAL-CL08) and the external control arm (LAL-1-NH01) have been collated into one table (Table 4.5 below) to facilitate comparison.

EAG Comment: We agree the available baseline characteristics presented in Table 4.5 are broadly comparable across all studies and are representative of a patient presenting in England with rapid progressive LAL-D. The population enrolled onto LAL-CL08 appears to be more underweight using weight criteria reported by Vijay *et al.*, 2021[53] (weight for age, WHO percentile and mid-upper arm circumference), indicating a more severe baseline status compared to LAL-CL03. We have some concerns about the completeness of data in the LAL-1-NH01 natural history/control arm, specifically for birthweight. Birthweight (or weight at first record) is listed as a minimum data item required for eligibility in LAL-1-NH01 (Table 4.3). Jones *et al.*, 2016,[7] note that only 20% of the overall population enrolled into LAL-1-NH01 were underweight at birth/first record and this increased to over 50% of the overall population by the time of diagnosis (median age: 2.6 months).

Table 4.4: LAL-CL08, LAL-CL03 and LAL-1-NH01 study characteristics

Category of design	LAL-CL08	LAL-CL03	LAL-1-NH01
Population	Confirmed diagnosis of LAL-D. Under 8-months of age at time of first dosing.	Clinical presentation of LAL-D in infancy with evidence of rapidly progressive disease based on growth failure within first six-months of life.	Patients with a confirmed diagnosis of LAL-D prior to 2 years of age.
Intervention(s)	Repeat IV infusions of sebelipase alfa once weekly with a starting dose of 1 mg/kg, escalated to 3 mg/kg and 5mg/kg if patients met 2/4 pre-specified criteria. Dosing schedule could change to every other week in patients who were stable and had received 96-weeks of treatment.	Repeat IV infusions of sebelipase alfa once weekly with a starting dose of 0.35 mg/kg with escalation to 1 mg/kg, 3mg/kg and then 5 mg/kg based on clinical response and if well tolerated.	Untreated or treated with HSCT and liver transplantation.
Location	Five sites across four countries; UK, USA, Finland, and Italy.	Eight sites in six countries; UK, USA, France, Ireland, Egypt, and Turkey.	Twenty one sites across six countries; UK, USA, Canada, Egypt, France, and Italy.
Trial design	Phase II, open label, multi-centre, non-randomised intervention study.	Phase II/III, open label multi-center, non-randomised intervention study.	Retrospective natural history study.
Duration of study	05 Jun 2014 – 30 Oct 2018.	04 May 2011 – 03 Jan 2018.	30 Sep 2010 – 11 Mar -2013. Chart reviews indicated diagnoses between 1985 –2012.
Primary endpoints (including scoring methods and timings of assessments)	Safety and tolerability.	Proportion of subjects surviving to 12-months of age.	To characterise patient survival and key aspects of the clinical course of LAL-D Wolman phenotype.
Secondary endpoints (including scoring methods and timings of assessments)	Proportion of patients surviving at 12-months of age. Proportion of patient survival past 12-months of age (18, 24 and 36-months). Growth parameters (changes from baseline in percentiles and Z-scores for weight-for-age, weight-for-length or	Safety and tolerability Survival beyond 12-months of age Growth parameters in children Hepatomegaly Splenomegaly Liver function	Secondary objective: Serve as a historical reference for efficacy studies of ERT in patients with LAL-D.

Category of design	LAL-CL08	LAL-CL03	LAL-1-NH01
	height, length or height-for-age, head circumference-for-age, and arm circumference-for-age). Hepatomegaly Splenomegaly Liver function Haematological parameters Characterise the pharmacokinetics (PK) of sebelipase alfa delivered by IV infusion. Exploratory – lipid parameters Development milestones Evaluate potential disease-related bio markers.	Haematological parameters Characterise the PK of sebelipase alfa delivered by IV infusion	

Source: Modified from Table 4 of the CS,[2] and clinical study reports for LAL-1-NH01,[18] LAL-CL03[23] and LAL-CL08.[24]
Footnotes:
*Partial dates were acceptable
Abbreviations: CS, Company submission; ERT, enzyme replacement therapy; IV, intravenous; LAL-D, lysosomal acid lipase deficiency; kg, kilogram; mg, milligram; PK, pharmacokinetics; UK, United Kingdom; USA, United States of America.

Table 4.5: Baseline characteristics of patients in LAL-1-NH01, LAL-CL08, and LAL-CL03

Characteristics	**LAL-1-NH01 (N = 21) Untreated with early growth failure**	**LAL-1-NH01 (N = 35) Overall population**	**LAL-CL08 (N = 10)**	**LAL-CL03 (N = 9)**
Gestational age at birth (weeks)				
N	[redacted]	[redacted]	NR	NR
Mean (SD)	[redacted]	[redacted]	NR	NR
Min, max	[redacted]	[redacted]	NR	NR
Age at first infusion of sebelipase alfa, months, median (range)[a]	NA	NA	2.8 (0.5, 4.1)	3.0 (1.1, 5.8)
Males, n (%)	10 (47.6)	19 (54.3)	5 (50)	5 (56)
Race				
White, n (%)	6 (28.6)	17 (48.6)	1 (10)	4 (44)
Asian, n (%)	8 (38.1)	8 (22.9)	6 (60)	1 (11)
American Indian or Alaska native, n (%)	-	-	1 (10)	0 (0)
Black, n (%)	-	-	0 (0)	1 (11)
Other, n (%)	4 (19.0)	5 (14.3)	2 (20)	0 (0)
Unknown. n (%)	3 (14.3)	5 (14.3)	0 (0)	3 (33)
Birth weight, kg, median (range)	NR	NR	[redacted]	[redacted]
Baseline liver dysfunction				
ALT, U/L, median (range)	[redacted]	[redacted]	37.0 (28, 248)	145.0 (16, 297)
AST, U/L, median (range)	[redacted]	[redacted]	99.5 (56, 441)	125.0 (75, 716)
GGT, U/L, median (range)	[redacted]	[redacted]	95.0 (42, 484)	46.5 (14, 1000)
Total bilirubin, µmol/L, median (range)	[redacted]	[redacted]	12.0 (4.0, 52.0)	29.0 (3, 464)
Albumin, g/L, median (range)	[redacted]	[redacted]	20.0 (18, 29)	29.0 (12.8, 40)
Baseline LLM use, n (%)[e]	NR	NR (NR)	1 (10)	NR
Adrenal calcification at treatment initiation, n (%)	NR	27 (79.4)	5 (50)	9 (100)

Source: reproduced from Table 6, CS Appendix D[35]
Notes: Three patients initiated treatment with sebelipase alfa through the GATM programme and subsequently transitioned to treatment in the LAL-CL08 trial. Informed consent was obtained for each patient before their participation in both the compassionate use programme and in LAL-CL08, and age at informed consent for LAL-CL08 was used for the data presented in this table.
a Calculated based on the age at informed consent for the LAL-CL08 trial.
b Underweight is defined as a measurement at least 2 SD below the median for weight-for-age of a reference population.
c Stunting is defined as a measurement at least 2 SD below the median for length-for-age/height-for-age of a reference population.
d Wasting is defined as a measurement at least 2 SD below the median for weight-for-length/weight-for-height of a reference population.
e Two other patients received transient courses of treatment with lipid-modifying agents, either a 13-day course of atorvastatin for intestinal malabsorption or several brief courses of cholestyramine.
f AST levels in LAL-1-NH01 were recorded at diagnosis for 34 of 35 patients.
g ALT levels in LAL-1-NH01 were recorded at diagnosis for 21 of 35 patients.
h GGT levels in LAL-1-NH01 were recorded at diagnosis for 12 of 35 patients.
i Bilirubin levels in LAL-1-NH01 were recorded at diagnosis for 24 of 35 patients.
j Albumin levels in LAL-1-NH01 were recorded at diagnosis for 22 of 35 patients.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CS, company submission; g, gramme; GATM, (Alexion) Global Access to Medicines programme; GGT, gamma glutamyltransferase; kg, kilogram; L, litre; LLM, lipid-lowering medication; lysosomal acid lipase; N, number of patients; NA, not applicable; NR, not reported; SD, standard deviation; U/L, units per litre; µmol/L, micromole per litre

4.2.2 Quality assessment

The company's critical appraisal of LAL-CL03, LAL-CL08, and LAL-1-NH01 was done using the Downs and Black tool.[39] The checklist is comprised of five core domains, which assess: external validity, study bias, confounding, selection bias, and power of the study. Four response options are possible (yes, no, unclear, not applicable). The company acknowledges that both the LAL-CL08 and LAL-CL03 trials have limitations, consistent with other ultra-rare disease trials.

EAG Comment: A major consideration for non-randomised, open label studies is that they are inherently at higher risk of bias, particularly at the pre-intervention stage due to confounding, bias in selection of participants into the study and bias in classification at intervention. The company have not summarised the extent of bias and its implications. Whilst acknowledging the inherent weaknesses of this type of trial design and adaptive nature of some aspects based on clinical need, overall, we believe both trials appear to be well designed and conducted and judge the risk of bias to be at moderate risk of bias for the primary efficacy outcome measure, survival.

It is unclear what methods the authors have used to identify known or unknown confounders or co-interventions and whether or not this has been informed by a literature review or clinical opinion. Jones *et al.*, 2016[7] have discussed potential confounders in relation to LAL-1-NH01 and this is summarised in section 4.2.3. With regards to the survival outcome the authors have attempted to control for known baseline confounders between LAL-CL03 and LAL-1-NH01 by matching based on strict growth failure within the first six-months of life. In addition, LAL-CL03 and LAL-CL08 exclude participants who have received HSCT and the associated pre-conditioning treatment and liver transplantation.

Co-interventions and other BSC were permitted under the eligibility criteria and included parental and enteral nutrition supplementation, other oral nutritional supplementations, steroids, drugs (antipyretics, antihistamines, corticosteroids), and blood transfusion (red blood cells, plasma, platelets, albumin).

Table 4.3 highlights the differences in trial eligibility criteria between LAL-CL03, LAL-CL08, and LAL-1-NH01. All definitions appear to match the scope of the population provided in the decision problem,[1] however, the narrow eligibility criteria for LAL-CL03, which is restricted to infants who present with growth failure under the age of six-months, may exclude otherwise eligible participants from the wider population of interest as defined by the company in their interpretation of the decision problem. Applying early growth failure to match with infants from the natural history arm increases the internal validity, however, the generalisability to those who are likely to receive the treatment in practice is limited. Although, contrary to expectation, we note the outcome data related to Median Weight-for-Age Z-Scores presented by Vijay *et al.*, 2021[53] indicates a more severe disease status at baseline in LAL-CL08 compared to LAL-CL03. This may be explained by the inclusion of [redacted] patients to LAL-CL08 who were found to have whole *LIPA* gene deletions so are expected to have more severe symptoms of the disease. Other baseline characteristics appear to be comparable. We also note the inclusion of [redacted] infants who received very early diagnosis and did not meet the growth failure criteria but were enrolled based on other clinical criteria. Whilst this is a deviation from protocol it appears to be more representative of the rapidly progressive LAL-D population.

The interventions are clearly defined in both LAL-CL03 and LAL-CL08 in terms of type, setting, dose, and frequency and amendments to protocol are well reported with sound clinical rationale. The protocol and dosing regimen specified in the more recent LAL-CL08 trial reports to be the most representative of current clinical practice. The severity of the condition and use of an objective efficacy measure (survival) means the potential for bias associated with measurement of outcomes is unlikely in both studies. The dosing regimens in both trials are not comparable and we note a protocol amendment so

that [redacted] enrolled in LAL-CL08 received higher doses of sebelipase alfa up to 7.5 mg/kg per week compared to the 5 mg/kg per week initially pre-specified.

The CONSORT diagrams provided in sections D.2.1. and D.2.2. of the CS appendices for LAL-CL08 and LAL-CL03, retrospectively, clearly report the screening and follow-up of patients.[35] [redacted] out of [redacted] subjects completed LAL-CL08; [redacted] participants died, [redacted] due to [redacted] and [redacted] due to [redacted]. [redacted] participants were moved to commercial therapy once sebelipase alfa was given marketing approval in the person's country of residence. Of the [redacted] patients who were enrolled and allocated to receive treatment for LAL-CL03 [redacted] completed, three people died before 12-months of age, due to liver failure (N=1), cardiac arrest (N=1) and peritoneal haemorrhage (N=1) and one person died due to sudden cardiac death at age 15-months.[35,53] No subjects discontinued treatment prior to 12-months of age for reasons other than death giving an indication of the tolerability/acceptability of the therapy. Because of the fatality of the condition participants, their carers, and medical providers are likely to have a higher acceptance of negative side-effects compared to the alternative expected clinical outcome of death. None of the deaths were reportedly attributable to the study drug. Data for all individuals are provided for the primary efficacy outcome measure, proportion of people surviving to 12-months, see section 4.3.1.1. In addition, all pre-specified outcome measures have been reported.

In summary, data provided from LAL-CL08 comprises a treatment period of 156-weeks comparative to a maximum of 260-weeks for LAL-CL03 with a follow-up period of 30 days following the last treatment infusion at study completion. Both trials appear to be well conducted and we judge the risk of bias to be moderate. Owing to the rare nature of the condition, efficacy data are provided from a limited number of patients in the rapidly progressive LAL-D population and whilst the efficacy data does appear to demonstrate an increase in survival and improvement in growth parameters, long-term outcomes are still uncertain.

4.2.3 LAL-1-NH01 Natural History

In the absence of an internal control, comparative data is provided from retrospectively collected medical records from N=35 deceased patients enrolled between 1985 to 2012, although prospective data collection was desirable, no living patients were enrolled onto the natural history study. Of the 35 participants who met the eligibility criteria, data from 21 participants who were untreated with HSCT and liver transplantation and had records of early growth failure were used as comparative data to inform the clinical effectiveness results.[7]

EAG Comments: Given the rare nature of the condition and small population we agree this data source represents the most appropriate available comparative data for this indication and that use of external control in this scenario meets the conditions set out by the International Council for Harmonisation E10: Choice of Control Group and Related Issues Clinical Trials.[54] General considerations given to retrospective studies are the risk of bias, confounding factors and quality of data which can lead to imprecise or biased estimates although the implications here are unclear. In line with pre-specified plans the company did not conduct data imputation.

In the overall population (N=35) participants were enrolled from six countries and [redacted] ([redacted] participant records originated from the UK.[18] All 35 participants had a laboratory confirmed diagnosis of rapidly progressive LAL-D before two-years of age (confirmed by enzymatic activity or *LIPA* gene mutation analysis).[18] However, due to the application of the objective growth failure under six-months of age in the sub group of 21 patients the EAG considers the included participants to represent a narrow group of the LAL-D cohort defined in the decision problem.[1]

There are no available national clinical guidelines for rapidly progressive LAL-D and as confirmed by our clinical expert it is reasonable to say that understanding of the natural history and BSC has evolved since 1985, specifically in terms of nutritional management. It is also likely that techniques for HSCT procedures have improved, although we acknowledge evidence is lacking. Therefore, it is likely that differences exist between the BSC delivered to those in the control arm compared with BSC delivered to patients included in the more recent LAL-CL03 and LAL-CL08 trials. With reference to Jones *et al*., 2016[7] the authors attempt to control for potential confounding factors (sex, country of origin, transplant, blood transfusion, enteral and parenteral supplementation, and steroid therapy) between the treated and untreated groups for patients who meet the early growth failure and separately for the overall population with regards to the survival outcome using multivariate Cox proportional hazard regression. Associations between the following covariates and risk of death were observed in untreated patients who had early growth failure (N=21): [redacted][18] Although the P values suggest slight evidence of statistical significance it is difficult to draw any definitive conclusions about the magnitude of any differences, if they exist, given the small patient population and wide confidence intervals. Based on experiential observations and the limited available data one clinical expert advised that current BSC alone is unlikely to increase survival in the rapidly progressive sub-group beyond that reported by Jones *et al.,* 2016[7] which is a median age of death of 3.5-months (range: 1.4 to 37.3-months) for patients with early growth failure. Therefore, we do not consider these potential confounders a cause for concern in terms of significantly influencing the primary efficacy outcome measure survival. There are however wider considerations to other surrogate outcome measures pertaining to liver function, cardiovascular disease and the lack of available long-term data.

4.2.4 Outcomes and statistical approaches used

Owing to the small patient population no power calculation was conducted to determine a sample size for LAL-CL03 or LAL-CL08. Therefore, the studies are not sufficiently powered to make any statistical inferences of causality and any effect estimates relating to outcomes are subject to uncertainty. However, enrolment was pre-specified and authors planned to recruit approximately 10 patients with at least eight who were under 8-months of age at first therapeutic infusion of sebelipase alfa to meet the primary efficacy endpoint for LAL-CL03.[23] Planned enrolment for LAL-CL08 was up to [redacted] patients.[24] Planned enrolment for LAL-1-NH01 was [redacted] participants.[18]

The authors state no formal inferential statistical testing was planned or performed for both LAL-CL03 and LAL-CL08. All data are presented as individual patient data or using graphs and descriptive summaries. Furthermore, data from all treated patients were included in the final analysis set (N=10 LAL-CL08, N=8 LAL-CL03). The EAG agrees with this approach.

The primary endpoint of LAL-CL08 was safety and tolerability, the secondary efficacy outcome is survival at 12-months. Some of the other remaining outcomes are surrogate endpoints and are incorporated to assess changes in clinically relevant biomarkers associated with disease progression.

EAG Comment: Given the trial is in phase II, the EAG agrees with the choice of the primary outcome measure. We consider the measure of efficacy (survival to 12-months) to be clinically objective and the survival to 12-months to be based on sound rationale. The use of secondary outcomes to capture medium-term survival beyond 12-months strengthens this position.

4.3 Clinical effectiveness results

The following section details the efficacy results in line with the NICE scope.[1] Data are primarily drawn from the two clinical trials (LAL-CL03 and LAL-CL08), alongside the natural history cohort (LAL-1-NH01) and other data collated in the CS as appropriate.[2]

4.3.1 Summary of key trial outcomes

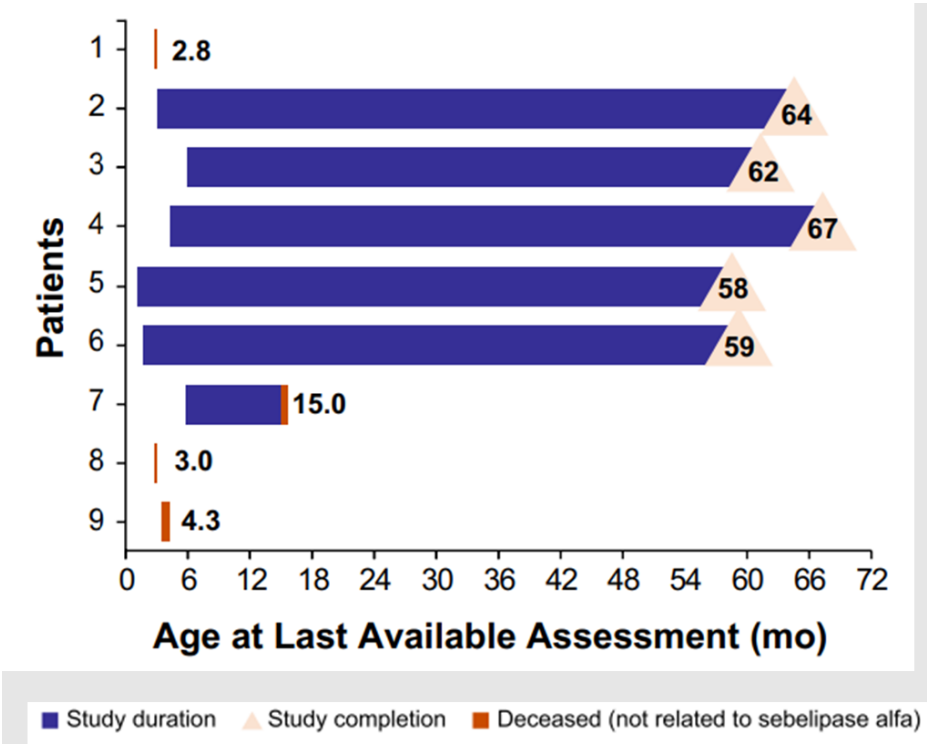
4.3.1.1 Survival

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients in LAL-CL03 and LAL-CL08 with a subset of the historic control cohort which represent untreated infants who presented with growth failure within 6-months.

4.3.1.1.1 LAL-CL03

Patient survival in the LAL-CL03 over the 5-year follow-up period is shown in Figure 4.1. Six of the nine (67%) patients survived beyond 12-months of age, and five (56%) patients survived beyond 18-months.[53] At the last follow-up, the surviving patients were aged between 58.1 and 67.0 months.[24] Four patients died during the trial, these were unrelated or unlikely to be related to study drug.[53] Median age at death was [redacted] months.[24]

Figure 4.1: Patient survival and age at last available assessment for LAL-CL03



Source: Vijay et al., 2021.[53]
Abbreviations: mo, months

A Kaplan-Meier plot detailing survival from birth (Figure 4.2) is shown below. Survival at 12-months of age was 67%.[53]

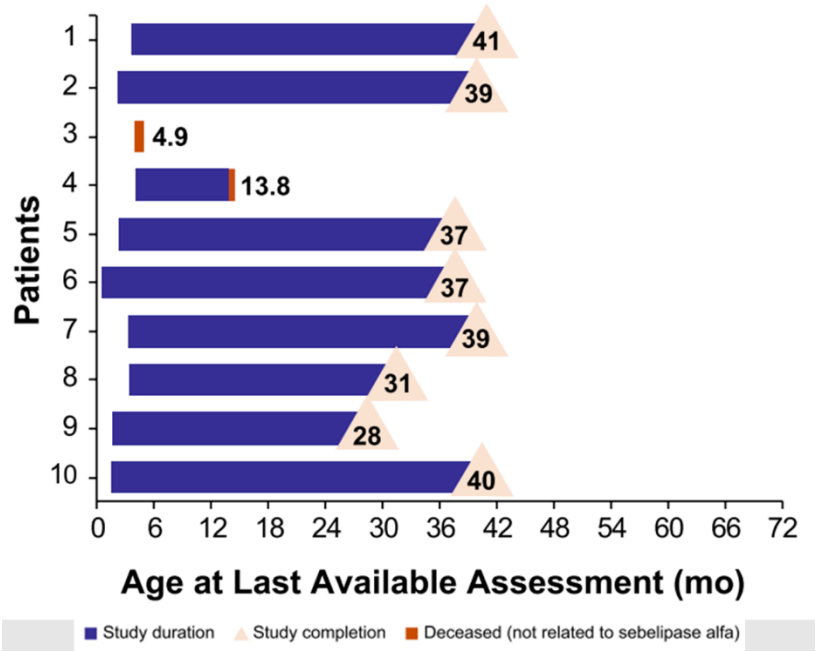
Figure 4.2: Kaplan–Meier plot of survival from birth for LAL-CL03 (PES)

Source: LAL-CL03 clinical study report.[23]
Abbreviations: PES, primary efficacy set.

4.3.1.1.2 LAL-CL08

Patient survival in the LAL-CL08 3-year follow-up period is shown in Figure 4.3. The proportion of patients surviving to 12, 18, 24 and 36-months of age was 90%, 80%, 80% and 75% respectively.[53] At the last follow-up, the surviving patients were aged between 27.8 and 40.6-months.[24] Two patients died during the trial resulting from complications related to disease progression; one patient received four infusions, the second received 41 infusions.[24] Median age at death was [redacted] months.[24]

Figure 4.3: Patient survival and age at last available assessment for LAL-CL08



Source: Vijay *et al*., 2021.[53]
Abbreviations: mo, months.

A Kaplan-Meier plot of survival from birth and survival from the first dose of sebelipase alfa (Figure 4.4) is shown below. Survival at 12-months of age was 90%.[24]

Figure 4.4: Kaplan–Meier plot of survival from birth for LAL-CL08

Source: LAL-CL08 clinical study report.[24]

4.3.1.1.3 LAL-1-NH01

Patient survival for the subset of the natural cohort study (LAL-1-NH01) who were untreated with sebelipase alfa and had rapidly progressive LAL-D with early-onset growth failure are shown in Table 4.6. Compared to 67% and 90% survival at 12-months for LAL-CL03 and LAL-CL08 respectively,[53] no survivors were reported amongst the cohort of 21 patients in LAL-1-NH01.[7] Among patients with early growth failure, median age of death was 3.5 months; estimated probability of survival past age 12-months was 0.038 (95% CI: 0.000-0.112).[7] Nine patients in the full historic cohort had either HSCT (N=9) or liver transplant (N=1), survival was slightly higher (median age of death, 8.6-months).[7]

Table 4.6: Naïve comparison of survival rates for patients with rapidly progressive LAL-D in LAL-CL08, LAL-CL03 and LAL-1-NH01

Study	LAL-CL08	LAL-CL03	LAL-1-NH01
Population	Patients with rapidly progressive LAL-D	Patients with rapidly progressive LAL-D and early-onset growth failure	Patients with untreated rapidly progressive LAL-D with early-onset growth failure
Use of sebelipase alfa	Yes	Yes	No
Survival at 12-months	9/10 (90%) patients	6/9 (67%) patients	0/21 (0%) patients
Survival at 24-months	8/10 (80%) patients	5/9 (56%) patients	0/21 (0%) patients
Survival at 60-months	-	5/9 (56%) patients	0/21 (0%) patients

Source: Vijay *et al*., 2021[53] and Jones *et al*., 2016[7]
Abbreviations: HSCT, haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency

EAG Comment: Survival to 12-months (and 18, 24 and 36-months), or time to death, were key primary or secondary outcome measures in all the clinical trials. Survival at 12-months is broadly consistent across the two trials where sebelipase alfa was in use, 67% for LAL-CL03 and 90% for LAL-CL08.[53] The discrepancy in survival could be attributed to the difference in patient populations, or to the higher starting dose (0.35mg/kg in LAL-CL03 versus 1mg/kg in LAL-CL08), or faster dose escalation of

sebelipase alfa used in LAL-CL08, or related to an improved understanding of disease management, leading to better nutritional management and earlier initiation.[2]

In response to question A11 in the PfC,[25] three patients in LAL-CL08 received HSCT after treatment with sebelipase alfa (no patients received HSCT and/or a liver transplant in LAL-CL03). These were considered as *"a last resort due to a lack of response to treatment due to persistently high ADAs, or as an attempt to keep the patient alive"* (page 19).[25] Previous to the advent of sebelipase alfa, HSCT was occasionally used. Survival in LAL-1-NH01 appeared to be marginally improved among patients who had undergone HSCT.

In recent times, a multi-modal treatment for Wolman disease has been advocated, combining ERT with dietary substrate reduction (a minimal or fat free diet) and HSCT.[3] Four of the five patients described were alive at the time of publication, and disease phenotype and laboratory parameters were shown to be improved compared to when the patients were on ERT. There is also the prospect that in the medium term, ex vivo haematopoietic stem cell gene therapy might be used as a treatment option for Wolman disease with even greater efficacy and a reduction in the risk of Graft versus Host Disease and infection.[3] The EAG consider that new treatment options for rapidly progressive LAL-D which are currently used in clinical practice might further improve patients' outcomes, including survival.

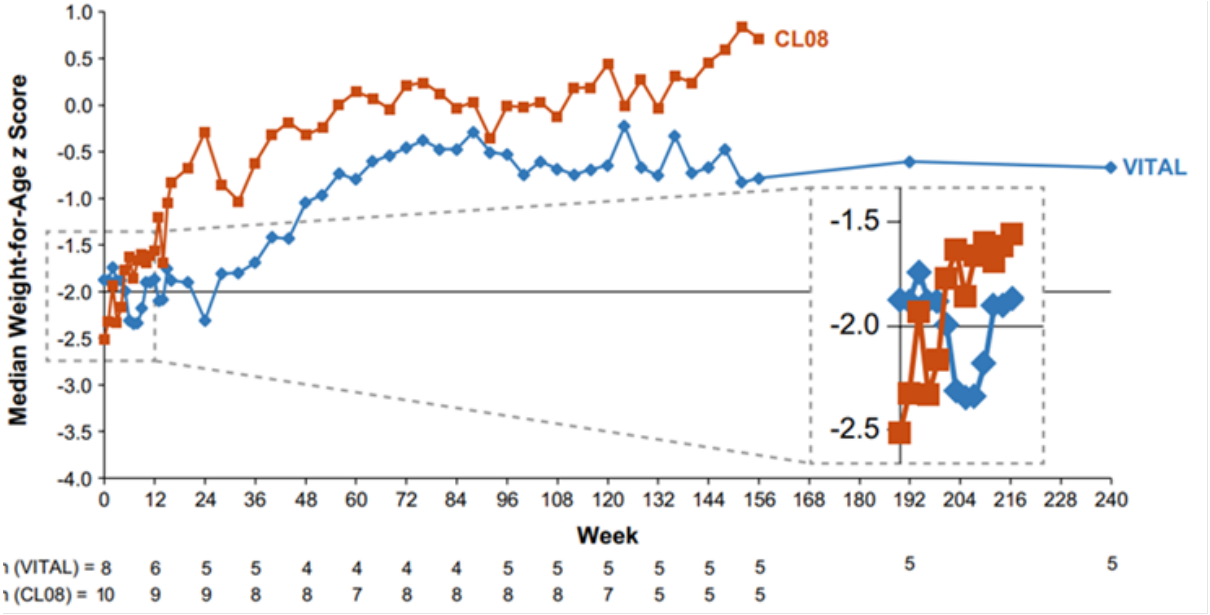
4.3.1.2 Growth and nutritional parameters

The CS describes outcome data in detail for two of five pre-specified outcome measures relating to growth parameters, these are changes in baseline in percentiles and/or Z-scores for weight-for-age and length-for-age. Data from the three other outcome measures; weight-for-length, head circumference-for-age, arm circumference-for-age and body mass index (BMI) for age, are briefly summarised in section L2.3 and L3.3 of the company appendices for LAL-CL08 and LAL-CL03, retrospectively.[35] All growth parameter data are standardised for age and gender.

4.3.1.2.1 Weight-for-age - LAL-CL08 and LAL-CL03

The median weight-for-age Z-scores for LAL-CL08 and LAL-CL03 (labelled as VITAL) are presented in Figure 4.5 from baseline to last assessment at 156-weeks for LAL-CL08 and 240-weeks for LAL-CL03,[2] data are shown against the -2 standard deviation reference line which marks the threshold for being classed as underweight. For LAL-CL08 the median (range) Z-score at baseline was -2.515 (-4.45 to 0.84; N=10) compared to 0.711 (-0.51 to 1.08; N=5) at 156-weeks.[53] For LAL-CL03 the median (range) Z-score at baseline was -1.875 (-4.79 to 0.74; N=8) compared to -0.669 (-1.41 to 1.87; N=5) at 240-weeks.[53]

Figure 4.5: Median weight-for-age Z-scores in LAL-CL08 and LAL-CL03 (VITAL)



Source: Figure 10 from the CS[2]
Footnotes: VITAL refers to LAL-CL03. Abbreviations: CS, Company submission

4.3.1.2.2 Weight-for-age LAL-1-NH01

In the untreated sub-group of the LAL-1-NH01 cohort with early growth failure (N=21) the median (range not reported) weight-for-age Z-scores at first record before diagnosis was -2.55 compared to a median of -2.72 at death.[7] When assessing the overall population of LAL-1-NH01, the percentage of underweight patients over time increased from 20% at birth, 54% at diagnosis and 66% at death.[7]

EAG Comment: The majority of infants have low weight-for-age across all groups at baseline, data from those receiving intervention in LAL-CL03 and LAL-CL08 show an increase in the median age-for-weight Z-scores over the trial period compared to the growth failure sub-group in the external control who experience a median decrease in weight-for-age Z-scores from baseline (before diagnoses (possibly birthweight)) to death.

The outcome data for mid-upper arm circumference-for-age, head circumference-for-age, BMI-for-age and weight-for-length provided in section L.2.3 and L.3.3 of the CS appendices for LAL-CL08 and LAL-CL03 retrospectively, generally support the findings of improved growth.[35] However, as expected due to the small patient numbers they have very wide ranges and uncertainty. For example, the median change from baseline for body mass index-for-age percentiles is (N=[redacted]) [redacted] with a range of [redacted].[35] Long-term data with a median follow-up time of seven-years (range 1-10) from a retrospective cohort including five people, with rapidly progressive LAL-D who received sebelipase alfa[20] reports improved growth parameters in nearly all patients corroborating improvement in growth findings from the LAL-CL03 and LAL-CL08 trials.

4.3.1.2.3 Length-for-age in LAL-CL08 and LAL-CL03

Data from trial LAL-CL03 demonstrate the median (range) length-for-age Z-score increases from -2.29 (-3.91 to 0.87; N=8) at baseline to -0.386 (-1.90 to 1.76; N=5) at week 240. Similarly, in LAL-CL08 the median length-for-age is -1.900 (-3.20 to 0.47; N=9) at baseline, increasing to 0.209 (-1.20 to 0.73; N=5) at week 156 in LAL-CL08.[35]

4.3.1.2.4 Length-for-age in LAL-1-NH01

In LAL-1-NH01 length-for-age was reported as mean (SD) z score of [redacted]; N=14) at first chart record. At diagnosis there was a mean change in Z-score of [redacted]; N=5) and then a mean change in Z-score of [redacted] N=3) at death.[18]

EAG Comment: The findings from LAL-CL08 and LAL-CL03 suggest an improved length-for-age profile in the infants who received sebelipase alfa in both trials up to a maximum of 240-weeks. There are limited comparator data available from the overall natural history cohort of 35 infants but the limited available data shows a decrease in length-for-age from first record to diagnosis and a slight increase from diagnosis to death.

4.3.1.2.5 Nutritional parameters (underweight, wasting and stunting)

Table 4.7 presents the proportion of patients enrolled onto LAL-CL03 and LAL-CL08 who meet three indicators for undernutrition at assessment periods throughout the trials' duration.[23,24] By the end of treatment there was a reduction in the proportion of infants meeting the three indicators. In LAL-CL08, by week 48 [redacted] met the criteria and this was generally maintained for the duration of the trial until week 156. Similarly, the proportion of malnourished patients decreased in LAL-CL03 and by week 96 [redacted] patients were meeting the diagnostic criteria, and this was maintained until the end of the treatment period at week 240.

EAG Comment: Consistent with other growth parameters malnourishment improved in infants receiving sebelipase alfa over the trial duration up to a maximum of 240-weeks.

Table 4.7: Proportion of patients meeting the criteria for underweight, wasting and stunting

	Patients defined as meeting the definition, n/N (%)							
	LAL-CL03†				LAL-CL08‡			
	Stunting[a]	Wasting[b]	Underweight[c]	No stunting, wasting or underweight[d]	Stunting[a]	Wasting[b]	Underweight[c]	No stunting, wasting or underweight
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 4 (month 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 12 (month 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 24 (month 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 48 (month 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 60 (month 15)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 96 (month 24)	[redacted]	[redacted]	[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 144 (month 36)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Week 156 (month 39)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR
Week 192 (month 48)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Week 240 (month 60)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR

	Patients defined as meeting the definition, n/N (%)							
	LAL-CL03†				LAL-CL08‡			
Follow-up/early withdrawal	[redacted]	0[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Last assessment	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR

Source: Clinical study reports for LAL-CL03[23] and LAL-CL08.[24]

Footnotes:

† Primary efficacy set

‡ Full analysis set

a, Stunting defined as at least 2 standard deviations below the median for length-for-age/height-for-age

b, Wasting is defined as wasting at least 2 standard deviations below the median for weight-for-length/weight-for-height.

c, Underweight is defined as at least 2 standard deviations below the median for weight-for-age.

d, Patients who did not meet any of the above criteria. Percentages are calculated based on the number of patients with available data for each parameter (length-for-age/height-for-age, weight-for-length/weight-for-height, and weight-for-age) at a given timepoint.

Abbreviations: n, numerator (number of patients with stunting, wasting or those underweight); N, denominator (total number of patients in cohort); NR, not reported

4.3.1.3 Liver parameters

Hepatomegaly, elevated serum transaminase concentrations, and progressive liver fibrosis and cirrhosis are common features of LAL-D.[55-58] Liver function (including transaminase level) and liver disease progression (including hepatomegaly) were both included in the NICE scope.[1] Changes in serum transaminases (ALT and AST) were a secondary outcome for both LAL-CL03 and LAL-CL08. Transaminases were also recorded for up to 26 of the patients in LAL-1-NH01.[7] Table 4.8 details liver parameters, alongside haematological and lipid effects for LAL-CL03, LAL-CL08 and LAL-1-NH01.

Table 4.8: Liver, hematologic, and lipid effects in LAL-CL03, LAL-CL08 and LAL-1-NH01

Study	LAL-CL03 (N=9)		LAL-CL08 (N=10)		LAL-1-NH01	
	Baseline (N=9), median (range)	End of study[a] (N=4), median (range)	Baseline (N=9), median (range)	End of study[b] (N=4), median (range)	Baseline (diagnosis) (N=35), median (range)	Death or at last measurement median (range)
ALT						
U/L	145.0 (16–297)	26.5 (18–38)	37.0 (28–248)	29.0 (22–106)	56.5[i]	110.5 (13-851)[k]
µkat/L	2.42 (0.3–5.0)	0.44 (0.3–0.6)	0.62 (0.5–4.1)	0.48 (0.4–1.8)	0.94[i]	1.85 (0.22-14.21)[k]
AST						
U/L	125.0 (71–716)	44.5 (41–54)	99.5 (56–441)[c]	44.0 (38–110)	151[j]	283 (35-4,250)[l]
µkat/L	2.09 (1.2–12.0)	0.74 (0.7–0.9)	1.66 (0.9–7.4)[c]	0.73 (0.6–1.8)	2.52 [j]	4.73 (0.58-70.97)[l]
Ferritin						
µg/L (ng/mL)	586.3 (253–48,740)[d]	93.5 (42–123)	1750.5 (481–3020)[e]	62.1 (49–75)	[redacted]	[redacted]
Albumin, g/L	29.0 (13–40)	32.0 (27–37)	20.0 (18–29)	33.0 (20–37)[f]	[redacted]	[redacted]
Haemoglobin, g/L	93.0 (1–103)	115.5 (99–123)	90.0 (81–131)[d]	113.0 (103–129)[f]	[redacted]	[redacted]
Total cholesterol						
mg/dL	139.2 (67–225)[g]	112.1 (93–131)[h]	125.7 (97–1063)[i]	106.3 (85–205)[f]	[redacted]	[redacted]
mmol/L	3.6 (2–6)[g]	2.9 (2–3)[h]	3.3 (3–28)[i]	2.8 (2–5)[f]	2.99 (N=18)	[redacted]
LDL-C						

Study	LAL-CL03 (N=9)		LAL-CL08 (N=10)		LAL-1-NH01	
	Baseline (N=9), median (range)	End of study[a] (N=4), median (range)	Baseline (N=9), median (range)	End of study[b] (N=4), median (range)	Baseline (diagnosis) (N=35), median (range)	Death or at last measurement median (range)
mg/dL	109.4 (19–194)[g]	64.2 (63–75)[h]	119.0 (62–143)[h]	76.6 (53–137)[h]	[redacted]	[redacted]
mmol/L	2.8 (0.5–5)[g]	1.7 (2–2)[h]	3.1 (2–4)[h]	2.0 (1–4)[h]	[redacted]	[redacted]
HDL-C						
mg/dL	8.9 (0–10)[g]	18.9 (13–19)[h]	9.4 (8–12)[f]	13.1 (13–29)[h]	[redacted]	[redacted]
mmol/L	0.2 (0.0–0.3)[g]	0.5 (0.3–0.5)[h]	0.2 (0.2–0.3)[f]	0.3 (0.3–0.8)[h]	[redacted]	[redacted]
Triglycerides						
mg/dL	163.9 (31–218)[g]	99.2 (90–237)[h]	265.7 (71–424)[g]	151.1 (133–195)[h]	[redacted]	[redacted]
mmol/L	1.9 (0.4–3)[g]	1.1 (1–3)[h]	3.0 (0.8–5)[g]	1.7 (2–2)[h]	[redacted]	[redacted]
Liver volume, MN	3.4 (3–4)[h]	1.6 (0.3–3)[h,j]	3.2 (0.1–4)[d]	1.9 (1–2)[e]		
Spleen volume, MN	7.0 (3–11)[e]	2.6 (2–7)[h,j]	5.8 (0.7–15)[c]	4.0 (2–6)[e]		

Source: Vijay *et al*., 2021,[53] Jones *et al*., 2016[7] and Clinical study report, LAL-1-NH01[18]

Key:

a week 240 (month 60; last visit with n > 2); b week 156 (month 39); c n = 8; d n = 7; e n = 2; f n = 4; g n = 5; h n = 3; in = 6; j Week 120 (month 30; last visit with n > 1); i N=24; j N=19; j N=20; k N=26; l N=10; m N=11

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; g/L, grams per litre; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre; mg/dL, milligrams per decilitre; MN, multiples of normal; N, number of participants; ng/mL, nanograms per millilitre; pmol/L, picomoles per litre; U/L, units per litre; µg/L, micrograms per litre; µkat/L, microkatal per litre.

4.3.1.3.1 LAL-CL03

Treatment with sebelipase alfa leads to a reduction in liver injury, evidenced by improvements in serum transaminase levels, including normalisation.[53] Patients undergoing treatment with sebelipase alfa experienced a reduction in median ALT from 145.0 U/L at baseline (N=9) to 26.5 U/L (N=4) in week 240.[53] Over the same period, median AST levels reduced from 125.0 U/L (N=9) at baseline to 44.5 U/L (N=4) at week 240.[53] Rapid reductions in serum transaminases was observed by week 1, with levels remaining stable thereafter.[23]

Figure 4.6 and Figure 4.7 show plots of ALT and AST respectively over the trial period. The results of ALT (Figure 4.6) show levels decreasing rapidly from treatment initiation, a median reduction of [redacted] U/L from baseline was observed by week 1 (0.35mg/kg dose), and then a median reduction of [redacted] U/L from baseline to week 4 (1mg/kg dose), representing a [redacted]% and [redacted]% reduction respectively.[23] Normalisation of ALT levels was achieved in [redacted] patients with elevated baseline ALT (between week 1 and week 6).[23]

Figure 4.6: Plot of ALT levels in individual patients over time (PES)

[redacted]

Source: LAL-CL03 clinical study report[23]
Key: ALT, alanine aminotransferase; PES, primary efficacy set.

Figure 4.7: Plot of AST levels in individual patients over time (PES)

Source: LAL-CL03 clinical study report[23]
Abbreviations: AST, aspartate aminotransferase; PES, primary efficacy set.

The results of AST (Figure 4.7) show levels decreasing rapidly from treatment initiation, a median reduction of [redacted] U/L from baseline was observed by week 1 (0.35mg/kg dose), and then a median reduction of [redacted] U/L from baseline to week 4 (1mg/kg dose).[23] Normalisation of ALT levels was achieved in [redacted] of the [redacted] patients with elevated baseline AST levels.[23] The CS notes that [redacted] patients had transient elevations in serum transaminases that were associated with a switch in dosing regimens qw to qow.[23]

Liver and spleen volume decreased from 3.4 MN (N=3) to 1.6 MN (N=3) and 7.0 MN (N=2) to 2.6 (N=3) respectively.[23,53]

4.3.1.3.2 LAL-CL08

Patients undergoing treatment with sebelipase alfa experienced a reduction in median ALT from 37.0 U/L at baseline (N=9) to 29.0 U/L in week 156.[53] Over the same period, median AST levels reduced from 99.5 U/L (N=9) at baseline to 44.0 U/L (N=5) at week 156.[53]

Figure 4.8 and Figure 4.9: show plots of ALT and AST respectively over the trial period. The results of ALT (Figure 4.8) show variability between patients over time:[23,53]

1. Three patients had elevated ALT levels at baseline, and each achieved normal ALT levels during treatment.
2. Six patients had normal baseline ALT levels, [redacted] experienced an increase in ALT over the trial, [redacted], had fluctuating levels.

Figure 4.8: Plot of ALT levels in individual patients over time (FAS)

Source: LAL-CL08 clinical study report[24]
Abbreviations: ALT, alanine aminotransferase; FAS, full analysis.

Figure 4.9: Plot of AST levels in individual patients over time (FAS)

Source: LAL-CL08 clinical study report[24]
Abbreviations: AST, aspartate aminotransferase; FAS, full analysis set.

The results of AST (Figure 4.9) show a decrease in median AST throughout the trial:[24,53]

- [redacted] patients had elevated AST levels at baseline, normalisation occurred in [redacted] patients.
- [redacted] patients had elevated AST levels throughout the trial (including [redacted] who died)

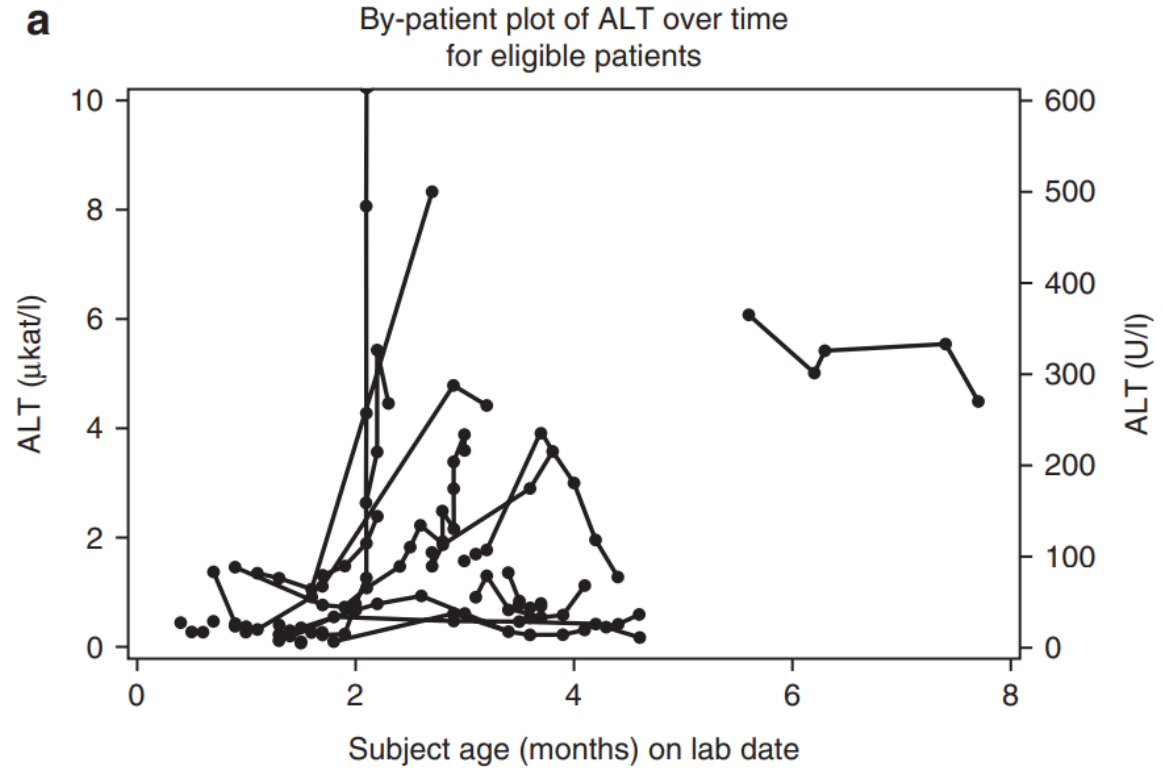
The CS states that [redacted] patients had an overall treatment response in the liver during the trial yet showed transient marked abnormalities in ALT and AST. These patients developed high ADA titers that was associated with diminished clinical effectiveness.[24]

Liver and spleen volume decreased from 3.2 MN (N=7) to 1.9 MN (N=2) and 5.8 MN (N=8) to 4.0 MN (N=2) respectively.[24,53]

4.3.1.3.3 LAL-1-NH01

For the complete cohort of 35 patients in the natural cohort study (including the 21 patients with growth failure), levels of both ALT and AST worsened from diagnosis until death (Figure 4.10). At diagnosis, ALT concentrations were abnormal in 14 of 24 patients and AST concentrations were elevated in 18 of 19 patients.[7] Median ALT increased from 56.5 U/L (N=24) to 110.5 U/L (N=19) and AST increased from 151 U/L to 238 U/L.[7] Total bilirubin concentrations at diagnosis were elevated in 11 patients (52%), and worsening of bilirubin was noted in some patients.[7]

Figure 4.10: Spaghetti plot of (a) ALT and (b) bilirubin changes over time in infants with lysosomal acid lipase deficiency



Source: Figure 1 in Jones *et al*., 2016[7]

Abbreviations: ALT, alanine aminotransferase; U/L, units per litre; µkat/L, microkatal per litre; µmol/L, micromole per litre.

EAG Comment: AST and ALT dropped for those patients who received sebelipase alfa, whereas levels in patients untreated in the natural history cohort increased until death. Elevated transaminase levels (AST and ALT) are key markers of liver cell injury, and the reduction is indicative of a marked improvement in disease symptoms.

Other markers of liver disease progression such as fibrosis or cirrhosis were not included as outcome measures in the clinical trials. Other trials of sebelipase alfa (LAL-CL06) have also included shifts in Child-Pugh status which is used in clinical practice to assess prognosis in individuals with liver disease.[59] The EAG acknowledge however, the overall reduction of transaminase levels is important and is indicative of clinical improvements in liver disease symptoms which is a key area of concern for patients with rapidly progressive LAL-D.

4.3.1.4 Haematological parameters

Haematological abnormalities such as anaemia are frequently observed in infants with LAL-D, and prior to the use of sebelipase alfa, transfusions of whole blood, red blood cells, frozen plasma and/or other components were used.[24]

Two measures of transfusion-free haemoglobin normalisation (TFHN) were summarised in the CS:[23,24]

- Short-term TFHN: patients were required to have haemoglobin levels consistently above the age-adjusted lower limit of normal over a minimum period of 4-weeks (with no transfusions during this period).
- TFHN maintenance: patients were required to have haemoglobin levels consistently above the age-adjusted lower limit of normal beginning at week 8 and continuing for at least 13-weeks (with no transfusions during this period).

4.3.1.4.1 LAL-CL03

Six patients (66.7% of the nine patients in the primary efficacy set (PES) and 100% of the patients in the PES who received sebelipase alfa treatment for at least 4 weeks) achieved short-term TFHN.[23,53] The median time to achieve TFHN was 4-months based on Kaplan-Meier estimates (95% CI: 0.3, 16.6 months).[24,53] Two patients achieved TFHN maintenance, representing 22.2% of the nine patients in the PES, and 33.3% of patients in the PES who received sebelipase alfa for at least 21-weeks.[23,53]

Jones *et al*., 2017[41] lists other key outcomes relating to haematological parameters:

- Haemoglobin levels were abnormal at baseline (N = 9; median 93.0 g/L; range 1.4–103.0 g/L; reported as low in six patients). At > 24-months, haemoglobin had increased in four of the five patients (and remained constant in the remaining patient)
- Albumin had increased in three of the five ongoing patients (and decreased in one patient)
- Median platelet count increased from baseline from 173.0 × 109 /L (N = 9; range 2.6–563.0 × 109 /L)
- Rapid and marked decreases in serum ferratin values post sebelipase alfa initiation. Between baseline and the assessment at week 6, median levels changed by -269 μm (range −11,171 to −215 μg/L; N = 3)

4.3.1.4.2 LAL-CL08

Seven patients (70%) achieved short-term TFHN (one patient died after week 3 so was not evaluable for TFHN).[53] The median time to achieve TFHN was 5.5 months based on Kaplan-Meier estimates.[24,53] TFHN was not attained until after week 8, so no patient met the criteria for TFHN maintenance.[24]

[redacted] patients underwent HSCT and required transfusions during their transplant; [redacted] of these patients achieved TFHN.[24] No patient met the formal criterion for TFHN maintenance.

4.3.1.4.3 LAL-1-NH01

The natural history control cohort did assess haematological parameters,[18] but these were not reported in the CS. In response to the PfC (question A2), the company highlighted that as survival was so poor in this cohort, the data was "*not considered a key focus*" (page 5).[25] Most importantly, 22 patients (63%) received blood transfusions.[25]

4.3.1.5 Neurological development parameters

The Denver Developmental Screening Test II (DENVER II) is a measure of developmental problems in young children (birth to 6-years of age),[60] and has been used in both LAL-CL03 and LAL-CL08. No neurological development data are presented for LAL-1-NH01.

4.3.1.5.1 LAL-CL03

DENVER II was administered for [redacted] patients (33.3%) at screening and [redacted] patients ([redacted]%) at post-baseline assessments only.[23]

For the patients who were administered DENVER II at screening:[23]

- [redacted] patient tested normal for language and fine motor-adaptive skills but was untestable for gross-motor function and personal-social skills (post-dose data were unavailable as [redacted]).
- [redacted] patient tested normal in all four skill areas and continued to test normal for the majority of assessments until week 216.
- [redacted] patient tested suspect in all four skill areas and continued to test suspect through to their last assessments until week 24.

For the patients who were administered DENVER II at post-baseline assessments:[23]

- [redacted] tested normal in all four skill areas and continued to test normal in most assessments through to week 216.
- [redacted] tested normal in all four skill areas at their first assessment at week 40 through to week 72, although fluctuated as suspect in weeks 51 to 120 in certain skill areas (gross motor function, and/or personal-social skills).
- [redacted] tested normal in all four skill areas at their first assessment at week 24 through to their last assessment at week 72, with the exception of their first assessment where they tested as suspect for gross motor function.

4.3.1.5.2 LAL-CL08

[redacted] ([redacted]%) patients who were at least 1 month of age at the date of the assessment were tested using DENVER II.[24] Limited data were available to draw any firm conclusions:[24]

- [redacted] patients tested normal in all four skill areas at baseline, and subsequently alternated between testing normal or suspect.
- [redacted] patients tested suspect in all four skills areas at baseline, and [redacted] continued to test as suspect in all/most assessments. The [redacted] showed an apparent improvement.
- [redacted] was reported as untestable at baseline and subsequently died prior to the next scheduled assessment.

4.3.1.5.3 LAL-1-NH01

No data concerning neurological development was presented for LAL-1-NH01.

EAG Comment: DENVER II is a brief and validated screening tool that assesses the development of pre-school infants and children. There is some doubt with regards to its limited specificity (43%),[61] however, it has a high sensitivity (83%) and has been shown to identify children with development delays.[62] However, in the CS not all patients in the single-arm trials were tested, only 33.3% and 60% in LAL-CL03 and LAL-CL08 respectively, at baseline. Perhaps owing to the small numbers tested, and the considerable noise in data, there doesn't appear to be any clear trends in neurological development post treatment. No neurological development data were presented for the natural history cohort. In summary, the EAG considers there to be great uncertainty about the neurological development data presented in the CS.[2]

4.3.1.6 Serum lipids

The following lipid parameters were issued in the final NICE scope as an outcome measure; low density lipoprotein (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).[1] Both LAL-CL08 and LAL-CL03 pre-specified these lipid parameters as exploratory outcome measures in the clinical study report.[23,24] The CS states that lipid parameters are not directly relevant to the rapidly progressive LAL-D population but may provide information for long-term follow-up in infants who survive beyond infancy.[2] Dyslipidaemia with elevated LDL-C and TG, and low HDL-C is reportedly a common finding in LAL-D children. Subsequently these lipid parameters can be used as surrogate measures to evaluate cardiovascular disease risk and risk of atherosclerosis.[5]

Lipid parameter data from LAL-CL03 and LAL-CL08 is provided in Appendix A of the CS.[35] LAL-CL03 report normalised LDL-C levels in [redacted] patients who had elevated levels at baseline or first assessment which remained stable throughout the treatment period. Conversely a small increase in LDL-C was noted in [redacted] patients at week 1. Data for [redacted] patients that survived beyond four-weeks of treatment was provided for HDL-C levels, all were low at baseline and increased in [redacted] patients, [redacted] achieved fluctuating normal levels and one person's HDL-C levels remained unchanged at last assessment. Triglyceride levels generally decreased in [redacted] surviving patients who were high at baseline.

Limited baseline data are available to assess LDL-C levels and HDL-C in LAL-CL08 enrolled participants, N=3 and N=4 respectively. Decreases in TG were observed during the treatment period.

EAG Comment: Median levels of LDL-C, HDL-C and TG are summarized in Table 4.8. Generally, there appears to be an improvement in lipid profiles for patients treated in both LAL-CL03 and LAL-CL08.[53] However, it is difficult to draw any definitive conclusions and a number of factors should be considered when interpreting the limited available data, the follow-up period of both trials is probably not sufficient in length to detect cardiovascular events and there are several confounding factors. For example, four patients in LAL-CL03 and three patients in LAL-CL08 were receiving lipid modifying medication. Page 118 of the CS report notes a plausible interaction between total parenteral nutrition, and increased triglycerides because blood samples were not always taken in a fasting state.[23] In addition, page 168 of the CS report also notes the influence of concomitant malabsorption and its influence on serum lipid level.[23]

4.3.1.7 Safety and tolerability

4.3.1.7.1 Adverse events

The European public assessment report (EPAR) was updated in 2020 to include safety and efficacy data from LAL-CL03 and LAL-CL08.[63] According to the update the most serious adverse reaction experienced by 3% of patients (19 infants with rapidly progressive LAL-D, 69 children aged between 2 to 18-years of age and 37 adults) included in all clinical trials under Alexion's clinical programme for sebelipase alfa (LAL-CL04, LAL-CL03, LAL-CL06, LAL-CL08 and LAL-CL02) were signs and symptoms consistent with anaphylaxis, such as, chest discomfort, conjunctival infection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.[63]

The European Medicines Agency (EMA) provides incidence and frequency of adverse drug reactions listed by System Organ Class and frequency reported in infants, using pooled data from LAL-CL03 and LAL-CL08, see [63]

Table 4.9.[63] The frequencies are reported according to very common: ≥ 1/10, common: ≥ 1/100 to ≤ 1/10, uncommon: ≥ 1/1000 to ≤ 1/100, rare: ≥ 1/10000 to < 1/1000, very rare: <1/10000.[63]

Table 4.9: Incidence and frequency of adverse drug reactions listed by system organ class and preferred terms in relation to infant population

MedDRA System organ class	MedDRA preferred term	Frequency	Pooled safety set 2 data (N=19) n (%)
Gastrointestinal disorders	Diarrhoea, vomiting	Very common	17 (89.47)
Immune system disorders	Anaphylactic reaction, hypersensitivity	Very common	17 (89.47)
General disorders and administration site condition	Pyrexia, hyperthermia	Very common	15 (78.95)
Cardiac disorders	Tachycardia	Very common	10 (52.63)
Investigations	Body temperature increased, respiratory rate increased, heart rate increased, blood pressure increased, drug specific antibody present, oxygen saturation decreased	Very common	8 (42.11)
Respiratory, thoracic and mediastinal disorders	Respiratory distress	Very common	8 (42.11)
Skin and subcutaneous tissue disorders	Rash, rash maculo-papular	Very common	7 (36.84)
Eye disorders	Eyelid oedema	Very common	3 (15.79)

Source: European Medicines Agency[63]
Notes: Frequency categories are defined as: Very common: ≥ 1/10, Common: ≥ 1/100 to ≤ 1/10, Uncommon: ≥ 1/1000 to ≤ 1/100, Rare: ≥ 1/10000 to < 1/1000, Very Rare: <1/10000.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in each specific category; n, portion or percentage of patients with available data.

All ten patients enrolled onto LAL-CL08 experienced at least one treatment-emergent adverse event (TEAEs), regardless of cause during the trial period.[53]

Table 4.10 presents the most reported TEAEs that were reported by at least four patients, it is unclear why this cut-off was chosen, although justifiable given the small patient population.

Table 4.10: A summary of common treatment-emergent adverse events occurring in four or more patients in LAL-CL08

MedDRA System Organ Class **Preferred Term**	**Patients (N=10)** **n (%)**
General disorders and administration site conditions Pyrexia	[redacted]
Gastrointestinal disorders Diarrhoea Vomiting	[redacted]
Cardiac disorders Tachycardia	[redacted]
Infections and infestations Gastroenteritis	[redacted]
Respiratory, thoracic and mediastinal disorders Respiratory distress	[redacted]
Source: Table 15, CS[2] Abbreviations: CS, company submission; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in each specific category; n, portion or percentage of patients with available data.	

All nine patients who received treatment in LAL-CL03 reported TEAEs, resulting in dose modification for seven (78%) people during one or more trial infusions, this was attributable mostly to infusion associated reactions (IARs) which was reported in five (56%) of patients.[53] No patients discontinued treatment because of TEAEs.[2]

Table 4.11 presents the most commonly reported TEAEs, regardless of cause, that were reported by at least four patients (40%), the frequencies are reported by MedDRA System Organ Class and preferred terms.

Table 4.11: A summary of the most common TEAEs occurring in four or more patients who were enrolled and treated in LAL-CL03

MedDRA System Organ Class Preferred Term	Patients (N=9) n (%)
General disorders and administration site conditions Pyrexia	[redacted]
Gastrointestinal disorders Diarrhoea Vomiting	[redacted]
Cardiac disorders Tachycardia	[redacted]
Infections and infestations Nasopharyngitis Rhinitis	[redacted]
Respiratory, thoracic and mediastinal disorders Cough	[redacted]

Source: Table 18, CS[2]
Abbreviations: CS, company submission; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; n, portion or percentage of patients; TEAE, Treatment emergent adverse events

Six patients died across the two clinical studies, two were enrolled and treated during LAL-CL08, and four were enrolled and treated in LAL-CL03.[53] All fatalities were deemed to be unrelated to treatment and delivery of sebelipase alfa by the study investigators.[53] All deaths occurred after receiving [redacted] or fewer doses of sebelipase alfa with a median age at death of 4.6 months.[2]

Serious adverse events were reported in all nineteen patients. Serious adverse events related or possibly related to sebelipase alfa was reported in a total of six patients; one (11%) patient was treated in LAL-CL03 and five (50%) patients treated in LAL-CL08, these were attributable to infusion associated reactions in all but one patient.[53] Overall, of the 152 infusion associated reactions occurring in 13 (68%) patients across both studies, 94% and 88% were classified as mild to moderate in severity in LAL-CL08 and LAL-CL03 respectively.[2,53] The most common types of serious adverse events reported were LAL-CL03 are pyrexia (33%), urticaria (33%), vomiting (33%), tachycardia (22%) and pallor (22%), comparative to those reported in LAL-CL08, pyrexia (60%), urticaria (40%), tachycardia (70%), irritability (50%) and agitation (50%).[53] Adverse events and its impact on HRQoL are discussed further in section 5.1.12.2.

EAG Comment: In trial LAL-CL08 which presents the most recent and representative clinical care provision, doses starting at 1mg/kg per week up to 5 mg/kg ([redacted]) and 7.5mg/kg per week ([redacted]) are reportedly well tolerated. There were no safety concerns [redacted] who received the highest dose of 7.5 mg/kg per week.[2] Overall considering the current clinical outcomes in those with rapidly progressive LAL-D the balance between the risk and benefit of the condition is positive but long-term outcomes are lacking.

4.3.1.7.2 Loss of venous access

The need for central venous access is critical for the administration of sebelipase alfa and other disease-related treatments including blood transfusions. As the ERT is not curative, weekly (or bi-weekly)

infusions are required. In some patients, central venous access can become increasingly difficult with multiple line infections, and be an indication for treatment with HSCT. This is further discussed in Section B.3.3.3 of the CS.[2] Potter *et al.*, 2021 reported that one patient at aged 25 months was indicated for HSCT on the basis of poor venous central access alongside suboptimal response to treatment with ADAs.[3]

EAG Comment: It is likely that over time, there will be increasing challenges obtaining venous access in patients leading to the necessity of treatment with HSCT. There is insufficient trial evidence, or longer-term follow-up data to understand at what point central venous access becomes problematic for all patients in the trial, and the role HSCT in the treatment pathway. The use of HSCT as a treatment option when central venous access is compromised, is discussed in section 4.4.

4.3.1.8 Anti-drug antibodies

Treatment with sebelipase alfa, like any biological drug, may induce humoral responses, causing the formation of ADA. ADAs may inactivate the drug and cause a loss of targeting and/or an increased clearance of ADA-drug complexes, which may lead to suboptimal exposure and loss of efficacy.[64,65] ADA data are presented for LAL-CL03 and LAL-CL08.

4.3.1.8.1 LAL-CL03

Among the patients (N=7) with post-treatment immunogenicity data, four (57%) developed ADAs for sebelipase alfa during at least one assessment:[53]

- One patient tested positive in week 5;
- Two patients tested positive in week 8;
- One patient tested positive 59.

In these patients, peak titers ranged from 223 to 4,721.[53] For some patients high levels were either for the majority of assessments (N=1), or until weeks 110/208 when the patients were ADA-negative for the remainder of the study (N=2).[53] Finally, one patient had intermittent low-titer levels interspersed with periods during which results were ADA negative.[53]

Of these four patients, three tested positive for neutralising antibodies that inhibited LAL cellular uptake of LAL (two of which also tested positive for neutralising antibodies that inhabited LAL enzyme activity).[53]

4.3.1.8.2 LAL-CL08

Among the patients with post-treatment immunogenicity data, six (60%) developed ADAs for sebelipase alfa:[53]

- One patient tested positive in week 5;
- Two patients tested positive in week 8;
- One patient tested positive in week 12;
- One patient tested positive in week 20;
- One patient tested positive in week 60.

All of these patients tested positive for neutralising antibodies that inhibited LAL enzyme activity and cellular uptake,[53] in three patients, this had an impact on clinical efficacy (including weight-for-age percentile).[2,24] Very-high titers of ADA (ranging from 222,070 to 302,963) were related to whole *LIPA* gene deletions.[2,24] In light of increases in ADA titers, dose escalation followed alongside immunomodulatory therapy (e.g., rituximab or bortezomib).[2] The company notes that improvement

and/or stabilisation of clinical response was observed only when ADA titers decreased after the introduction of immunomodulation therapy or following successful HSCT.[24]

EAG comment: Approximately, 52% of patients (10/19) in LAL-CL03 and LAL-CL08 tested positive for ADAs. In approximately half of these patients, ADAs affected ERT efficacy.[53] The EAG notes that for a sizeable minority of patients, treatment efficacy is limited by ADAs, and dose escalations alongside immunomodulatory therapy would need to be considered.[2]. Analysis by Potter *et al*., 2021[3] describes of the five patients who had HSCT, three patients had significant ADAs as part of their indication for transplant.[53]

The EAG notes there are some important challenges extrapolating the effects of ADAs into the longer term. It is likely that over time, immunity responses to ERT treatment increase so the efficacy of sebelipase alfa to control the progression of LAL-D diminishes. At this stage, the only treatment option is HSCT, and the dose reduction in ERT which follows. There is insufficient trial evidence, or longer-term follow-up data to understand whether ADAs become problematic for all patients in the trial, and the role of immunomodulatory therapy and HSCT in the treatment pathway.

4.3.1.9 Adrenal gland calcification

Adrenal gland function is an outcome listed in the final scope issued by NICE.[1] However, no outcome measures related to adrenal gland function were captured in LAL-CL03 or LAL-CL-08. Adrenal gland calcification has been noted as a clinical feature occurring in approximately 79% (N=34) of patients enrolled in LAL-1-NH01.[7,17] The company states experiential observations from clinicians as "*adrenal gland clinicians have noted adrenal failure has not been a reported finding, even in long-term follow-up of affected infants receiving treatment*".[25]

EAG Comment: The EAG are unable to assess this outcome measure due to lack of data but given reported findings from the natural history study we suggest efforts are made to formally capture and assess the extent and long-term implication of adrenal calcification in infants with rapidly progressive LAL-D.

4.3.1.10 Cardiovascular events

Cardiovascular events are an outcome measure listed in the final scope issued by NICE.[1] The company state; "*the following parameters suggested in the final scope are not directly relevant for the rapidly progressive LAL-D population, they may provide valuable information for the long-term follow-up of treated patients who survive beyond infancy and will be discussed in the clinical sections only.*"[2]

Of the patients enrolled onto LAL-CL08 (N=10) [redacted] experienced tachycardia and 4[redacted] experienced bradycardia as a treatment-emergent adverse event, regardless of cause.[2] Data provided for LAL-CL03 report [redacted] cardiovascular events in [redacted] of patients enrolled (N=9), one patient experienced tachycardia treatment related serious adverse events attributable to intravenous associated reaction.[2] Two patients died due to cardiac arrest and sudden cardiac arrest, but these were unrelated to treatment and arose due to disease progression.[53]

EAG Comment: No patients discontinued treatment due to cardiovascular events and none of the cardiovascular related deaths were related to the study drug. The EAG recommends continuing long-term data collection to monitor the extent and implications of cardiovascular events in this cohort.

4.3.1.11 Health-related quality of life

No health-related quality of life data was recorded for trial participants.

EAG Comment: Given the age of neonates and infants in the trials, the EAG understands that owing to the methodological challenges associated with administering HRQoL to very young children, it is understandable why this information was not reported as an outcome in any of the clinical trials. The patient organisation submission written by the MPS Society provides a detailed overview of patient/carer experiences, including a narrative discussion of quality of life prior, during, and after treatment with sebelipase alfa.[19] The document details the transition of patients *'acutely ill'* at diagnosis to long term survivors having a *'good quality of life with IQ and cognitive function being unaffected'*.[19]

A single paper[20] detailing quality of life in patients with LAL-D was also identified in the effectiveness and health-related quality of life SLRs. Further details are presented in the CS (Appendix D and H)[35] and in section 5.1.13.

4.4 Critique of the technology of interest in the context of a multimodal therapy

Sebelipase alfa is used following diagnosis to prevent disease progression and early mortality. However, the utility of ERT is limited by ADAs and the need for central venous access.[2,3] In recent years, clinical advisors to the EAG confirmed multimodal therapy is used with sebelipase alfa plus nutritional support, followed by HSCT. Potter *et al.,* 2021 reports five patients treated at Royal Manchester Children's Hospital with sebelipase alfa and nutritional support (achieved by minimal or fat-free diet) then HSCT.[3] The indications for HSCT included suboptimal response to treatment, ADAs, poor central venous access, ongoing hemophagocytic lymphohistiocytosis (a severe systematic inflammatory syndrome that can be fatal) or intolerance to ERT anaphylaxis.[3] The paper reports four of the five patients were alive and "*both disease phenotype and laboratory parameters are improved compared to when they were on ERT alone*".[3] The CS reports that as of [redacted].[2]

In response to clarification (question A11),[25] the company reported that three patients in LAL-CL08 received HSCT (no patients in LAL-CL03 received transplant).[23,24]

EAG comment: The EAG acknowledge that treatment for rapidly progressive LAL-D is evolving, particularly with newer approaches such as the use of HSCT after sebelipase alfa and nutritional support. In the trials, three people (out of 19 across both trials) had HSCT ([redacted]). The Potter *et al*., 2021 paper is helpful to show clinical outcomes in patients for whom had HSCT owing to either suboptimal responses to sebelipase alfa, including ADAs, and other disease-related complications.[3] Although there is now over a decade of data relating to the use of sebelipase alfa in rapidly progressive LAL-D populations, longer-term data which includes the transition to adulthood and beyond is not available. There is therefore uncertainty in the longer-term outcomes related to the treatment with sebelipase alfa and the timing of HSCT and survival post transplant. This is problematic as the Markov model detailed in the CS includes a heath state (HS5) which is characterised by HSCT, and this is described and critiqued in sections 5.2.2.

4.5 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was performed. The CS states that a "*naïve comparison of outcomes has been conducted for sebelipase alfa compared with standard of care in the absence of sebelipase alfa. Jones et al., 2016[7] (LAL-1-NH01) was considered the only appropriate source of evidence for comparison to the LAL-CL08 and LAL-CL03 trials*" (page 11).[35]

EAG comment: No indirect comparison was required. The EAG agrees that LAL-1-NH01 provides the closest comparison for patients with rapidly progressive LAL-D detailed in LAL-CL03 and LAL-CL08.

4.6 Additional work on clinical effectiveness undertaken by the EAG

No additional analysis was completed by the EAG.

4.7 Conclusions of the clinical effectiveness section

A SLR was conducted to identify literature relevant to the NICE scope.[1] This comprised of a SLR undertaken for the CS which formed part of the ID737 technology appraisal in 2015,[36] and an update to this review which focused exclusively on those patients with rapidly progressive disease which is the focus of the current NICE scope.[1] LAL-CL03, LAL-CL08, and LAL-1-NH01 were identified alongside five supporting studies. The trial evidence centres on results from two non-randomised intervention studies (LAL-CL03 and LAL-CL08) and one historical control (LAL-1-NH01) to facilitate comparability of survival and other outcome measures with patients not treated with ERT.[2]

Kaplan-Meier estimates of survival to 12-months of age in the combined population including both LAL-CL-03 and LAL-CL-08 participants (N=19) was 79%.[53] In LAL-CL03, six of nine infants treated with sebelipase alfa survived beyond 12-months (67% 12-month survival, 95% CI: 30% to 93%).[2,53] The proportion of patients surviving to 12-months in LAL-CL08 is 90% (95% CI: [redacted]% to [redacted]%).[24,53] This can be compared to the natural history cohort where median age of death in patients with early growth failure (N=26) was 3.5 months and none of the 21 untreated patients who had early growth failure survived beyond 12-months of age.[7] Nine patients in the full historic cohort had either HSCT (N=9) or liver transplant (N=1), in these patients survival was slightly higher (median age of death, 8.6 months).[7]

Other key outcomes showed a positive intervention effect, median age-for-weight Z-scores improved (with an associated reduction in the proportion of infants meeting the criteria for stunting, wasting and underweight), key liver parameters (AST and ALT) decreased and lipid profiles for treated patients improved.[2] Although the trials had small sample sizes, and there was considerable variability within the data, the EAG consider that treatment with sebelipase alfa resulted in clinically meaningful outcomes, which slowed disease progression.

The age of symptom onset (under 6-months vs 6-24-months) in Wolman disease/rapidly progressive LAL-D was a substantial source of uncertainty (Key issue 1, section 1). This may have implications for how many people are treated in the UK if the technology is recommended. An additional source of uncertainty regarding generalisability to the UK was the eligibility criteria for the LAL-CL03 trial which focused only on the rapidly progressive LAL-D population (Key issue 4, section 1). Therefore, these data may not generalise to those who do not exhibit rapidly progressive clinical features. The EAG notes this an unresolvable issue. Specifically, the eligibility criteria were restricted to patients who met strict growth failure criteria so they could be matched to patients in the external control arm. This was done to increase internal validity.

The long-term effectiveness of sebelipase alfa, and the role of HSCT in the treatment pathway, are also substantial sources of uncertainty (Key issue 3, section 1). Although, sebelipase alfa was generally well tolerated and negative side effects are offset against the significant improvement in survival in patients who received sebelipase alfa. The median (range) age of surviving patients at end of study was 5.2 (4.8-5.6) years in LAL-CL03 and 3.2 (2.3-3.5) years in LAL-CL08.[53] Although trial duration was considerable, there are many uncertainties which relate to longer-term follow-up and outcomes in patients as they transition to adolescence and adulthood.

Of particular concern is the presence and impact of ADAs which is associated with diminished treatment efficacy and loss of venous access which hinders the delivery of sebelipase alfa and blood transfusions. Consequently, sebelipase alfa, nutritional support and HSCT are combined in a multimodal treatment for rapidly progressive LAL-D patients who have sub-optimal response to ERT alone, or have other disease-related complications (Key issue 2, section 1). However, the long-term effectiveness and adverse effects of HSCT are unknown both in LAL-D patients and other conditions. Therefore, extrapolating data across the lifespan of these patients is difficult.

5 COST EFFECTIVENESS

5.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

5.1.2 Searches for cost effectiveness analysis review

The company reported in the current CS that as no relevant studies were found by their searches in June 2015, for their CS for NICE [ID737], their search for cost effectiveness studies was a 'targeted search'.[2,36] No further information was provided in the CS as regards the sources searched or the search methods (CS Document B, section B.3.1, p. 109).[2,36] In response to the PfC letter, question A6, the company supplied additional information.[25] The company reported that the targeted search was conducted to supplement existing evidence: "*Given sebelipase alfa is the only active treatment available for rapidly progressive LAL-D; has previously been assessed by NICE and is already in use within UK clinical practice the findings of any literature review of economic evaluations were considered likely to be of limited use.*"[25] The company's targeted search, of PubMed and Ovid MEDLINE ("*using terms such as, 'enzyme replacement therapy', 'LAL-D', 'Wolman disease' 'cost effectiveness model OR economic model' and 'economic evaluation'*")[25] identified one SLR (Katsigianni *et al.*, 2022)[66] and "*the company concluded that the Katsigianni SLR would provide decision makers with the relevant information required over and above the previous appraisal.*"

EAG comment: The EAG do not agree with the company's reasoning for not updating their June 2015 searches;[36] not finding relevant studies in 2015 does not mean that no studies will have been published during the period from June 2015 to September 2022. The only way to be certain of this is to update the 2015 searches. The one SLR that the company suggest would be helpful to decision makers, Katsigianni *et al*., 2022,[66] was published online on 19 September 2022 and on 6 December 2022 the journal made corrections to the online article as the journal had not incorporated proofing corrections made by the SLR authors.[67] The full search strategies were not available online for the Katsigianni *et al.*, 2022 SLR;[66] although the SLR authors report searching a reasonable range of databases. The search terms reported in the text are limited to a small number of MeSH terms and would not be considered extensive enough to meet minimum standards for conduct of an SLR.[66] It remains a concern to the EAG that the company did not run a fully updated search and conduct a full SLR themselves.

5.1.3 Searches for model inputs

5.1.3.1 Searches for HRQoL

Regarding the search for health-related quality of life studies (reported in CS Appendix H),[35] key ideas were captured in the searches; however, the company did not provide full search details to complete a critical appraisal in the first instance. In response to the PfC (question A13) the company provided full search details including the search strategies with the numbers of records retrieved per line for all but

one (Evidence-based medicine (EBM) Reviews HTA) of the databases searched.[25] A summary of the resources searched is presented in Table 5.1 below.

EAG comment: The search of the CENTRAL database is narrow and contains lines used from the search for clinical effectiveness studies, it is unclear as to why caregiver-related terms are used within a randomised controlled trials database. It has been documented that the electronic searches updated existing information from 2015 onwards, however, no new records have been added to the NHS Economic Evaluation Database (NHS EED) database from 1 January 2015 onwards; an updated search would produce no new publications (since the company's June 2015 search). Furthermore, regarding the use of the HTA database, new records were added to the Centre for Reviews and Dissemination (CRD) HTA database up to 31 March 2018, limiting to 2015 would have missed new records added between 2015 and 31 March 2018. To access the most up-to-date version of the HTA database information the company could have searched the freely available International Network of Agencies for Health Technology Assessment database as an alternative, which is freely available and covers all available years up to the present. The EAG do not have access to the EBM Reviews Health Technology Assessment database, but the EAG understands that the HTA content is the same as that on CRD.

As the basic structure of the utility SLR search is very similar to the search for clinical effectiveness studies, many identified issues have been duplicated i.e., narrow search for disease terms. However, a few more issues specific to this search have been identified as outlined. Searching In-process records means that only a subset will have MeSH terms, therefore these terms would need to be supplemented with title, abstracts or keywords to ensure all records can be retrieved. The use of "AND" instead of "OR" in combining lysosomal acid lipase with Wolman disease in conjunction with the lack of search within title, abstract and keywords potentially narrows down the search too much. Using incorrect syntax in PubMed when attempting to search for Economics and Value of life MeSH terms increases the number of irrelevant publications retrieved. Furthermore, incorrect use of adjacency operators in PubMed i.e., "Life adj3 Quality", in addition to not specifying any search fields where applicable, e.g., "HRQoL", "Absenteeism" OR "Presenteeism" means these terms could have been translated in several ways potentially leading to high amounts of irrelevant records being retrieved.

Table 5.1: Resources searched for the HRQoL SLR

Resource - category	Resource	Host Source/Platform	Date Range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	MEDLINE	Embase.com	January 2015 to June 2022	14/06/2022	Yes	Yes	Yes[a]
	Embase				Yes		Yes
	MEDLINE In-Process	PubMed			Yes		Yes
	EconLit	EBSCOhost		20/06/2022	Yes		Yes
	Centre for Reviews and Dissemination (CRD)[b] • HTA • NHS EED	CRD	Archived records to 2015[b]		Yes		Yes
	Evidence-based medicine (EBM) Reviews HTA	NR	January 2015 to June 2022	NR	NR	NR	NR
	Cochrane Library[c]	cochranelibrary.com		20 June 2022	Yes	NR	Yes
Conference proceedings	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	NR	2018-2022	NR	NR	NR	Yes
	Society for the Study of Inborn Errors of Metabolism (SSIEM)	NR	2018, 2019, 2021	NR	NR	NR	Yes

Resource - category	Resource	Host Source/Platform	Date Range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart
	European Association for the Study of the Liver (EASL)	NR	2018-2022	NR	NR	NR	Yes
	American Association for the Study of Liver Disease (AASLD)	NR	2018-2021	NR	NR	NR	Yes
	North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN)	NR	2018-2021	NR	NR	NR	Yes
	European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)	NR	2018, 2019, 2022	NR	NR	NR	Yes
	National Lipid Association (NLA)	NR	2021	NR	NR	NR	Yes
	European Atherosclerosis Society (EAS)	NR	2018-2021	NR	NR	NR	Yes
	Lysosomal Disease Network (LDN)	NR	2018-2022	NR	NR	NA	Yes
HTAs[c]	1 NICE 2 SMC 3 AWMSG 4 'Other European HTAs' 5 CADTH 6 PBAC	NR	NR	NR	NA	NA	Yes

Resource - category	Resource	Host Source/Platform	Date Range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart
"Bibliographies"	NA	NA	NA	NR	NA	NA	Yes

Source: CS Appendix H[35] and the response to PfC letter Question A13[25]

a Reported as part of the Embase search

b The search was limited to 'archived records until 2015'

c No further details were given

Abbreviations: AASLD, American Association for the Study of Liver Disease; AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CRD, Centre for Reviews and Dissemination; CS, Company submission; EAS, European Atherosclerosis Society; EASL, European Association for the Study of the Liver; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; HTA, health technology assessment; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; LDN, Lysosomal Disease Network; NA, not applicable; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology & Nutrition; NHS EED, NHS Economic Evaluation Database; NLA, National Lipid Association; NR, Not reported; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; SMC, Scottish Medicines Consortium; SSIEM, Society for the Study of Inborn Errors of Metabolism

5.1.3.2 Searches for cost and resource use

The company report (in CS Appendix I) that a literature search was not undertaken to identify cost and resource use information.[35] Instead resource use data were sought by clinical expert elicitation and costs were source from the National Schedule of NHS Costs 2020/21.[68]

EAG comment: The EAG are concerned that relevant references could have been missed because no search was conducted for this information, for example, the 2018 publication by Guest *et al.*, 2018 giving information about healthcare costs and resource use in children and adults with LAL-D does not appear in the CS.[2,69]

5.1.4 Inclusion/exclusion criteria

The company stated in their 2022 CS (CS Document B, section B.3.1, page 109) that their systematic literature search, reported as part of the 2015 CS for technology appraisal of sebelipase alfa for the treatment of LAL-D, did not identify any economics studies (TA737).[2,36] The inclusion/exclusion criteria for this 2015 search are set out in the CS for this appraisal and are not reproduced in detail in the 2015 Evidence Review Group (ERG) Report.[13,36] However, in 2015 the ERG did not flag any serious concerns about the inclusion and exclusion criteria.[13] The company went on to state that they were unaware of any independent economic evidence that had been published since their search on 1st June 2015.[2] The company reported conducting a new targeted search (details of inclusion/exclusion criteria were not reported).[2] This search identified a systematic review of economic evaluations of ERT in lysosomal storage diseases.[66] They report that only one relevant study was identified which reported on the economic analysis of sebelipase alfa for all patients with LAL-D.[70] This analysis was based on that submitted to NICE in 2015 for TA737.[71]

5.1.5 Conclusions of the cost effectiveness review

The identified studies were sought to help inform the CEM. Neither economic evaluation was directly relevant to the scope of the current decision problem (they did not focus on rapidly progressive LAL-D). The cost effectiveness review was a targeted update of the search conducted in 2015. The ERG when commenting on the CS for TA737 did raise some issues about this review but none of these were critical.[71] The EAG are of the view that although the company has sought to identify all relevant economics evaluations, it cannot be definitively said that there are no further data. Issues identified in the searches suggest that there is the possibility that relevant publications may have been missed.[2]

With respect to the cost effectiveness evidence, both identified economic evaluations compared sebelipase alfa against BSC over a lifetime time horizon for patients with LAL-D. In the CS submitted as part of TA737 the reported incremental cost per QALY gained was approaching £1million[36] and was in excess of 2.5m Euros for the Irish national assessment of sebelipase alfa for treating LAL-D.[70] However, as these relate to a different patient population they are not further considered.

5.1.6 NICE reference case checklist

The EAG appraised the company's economic evaluation by assessing the extent to which the evaluation meets the NICE reference case checklist.[4] The summary of this appraisal can be found in Table 5.2.

Table 5.2: NICE reference case checklist

Elements of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	The scope of the economic analysis is in line with the scope developed by NICE and deviations were justified. The company decided to target only the population with rapidly progressive LAL-D and justified this in their submission (see section 3). The company did not perform any subgroup analysis and justified this due to the rarity of the condition (see CS sections B.1.1, B.3.2)[2]
Comparator (s)	Listed in NICE scope	Sebelipase alfa is compared with BSC (See CS section B.3.2 and sections 3.3 and 5.1.9)[2]
Perspective on costs	NHS (and PSS)	A partial NHS perspective in the model (a NHS and PSS perspective is stated as being adopted in the budget impact model although the same costs components as those reported in the CS and CEM were included) (see CS sections B.3.2.2 and B.3.15 and section 5.1.6, 5.1.10 and 5.1.14)[2]
Perspective on outcomes	All health effects for patients, and carers if relevant	Only health effects for patients were included in the model (see CS section B.3.4.5 and section 3.4 and 5.1.12).[2] Although impacts of a child's death on parents/carers were included in a scenario analysis
Type of economic evaluation	Cost–utility analysis with fully incremental analysis Cost-comparison analysis	A cost-utility analysis was performed with a full incremental analysis (see CS sections B.3.2 and B.3.9.1 and section 5.1.6 and 5.1.7)[2]
Time horizon	Sufficiently long to capture differences in cost and outcomes	A lifetime horizon was considered (see CS section B.3.2.2 see section 5.1.6 and 5.1.7)[2]
Synthesis of evidence on health effects	Based on systematic review	A systematic literature review of HRQoL was conducted (see CS section B.3.4.3)[2]
Measuring and valuing of health effects	Health effects must be expressed in quality-adjusted life years (QALYs). The EQ-5D is the recommended	Health outcomes were valued in terms of life years and QALYs gained using the EQ-5D-3L (See CS section B.3.4.5.1 and section 5.1.13)[2]

Elements of health technology assessment	Reference case	EAG comment on company's submission
	measure of health-related quality of life	
Sources of data for measurement HRQoL	Reported direct by patients and/or carers or both	Impacts on HRQoL as measured by the EQ-5D-3L were inferred from a report by Demaret *et al.*, 2021, which reported a French nationwide retrospective study in 5 patients with Wolman disease over a median follow-up of 7-years.[20] This study used the Pediatric Quality of Life Inventory. Based upon these data the CS assumed near normal development and HRQoL. Consequently, it was assumed that the utility of patients could be derived using the UK general population. The model uses the age-adjusted utility norms reported by Hernández Alava *et al*., 2022 using the EQ-5D-3L[72] (See CS sections B.3.4.3 and B.3.4.5.1).[2] Further parenteral nutrition utility values came from Ballinger *et al*., 2018, assuming that the lowest utility value for short bowel syndrome was assigned for those who received seven cumulative days of parenteral nutrition.[73] The duration of nutrition was informed by clinical expert opinion. A utility decrement for HSCT was used only in scenario analysis. This utility decrement and the duration of its application were taken from the ERG report for NICE TA554.[74] A spillover decrement to carers/family members due to the death of an infant was included in a scenario analysis. This utility decrement was extracted from Song *et al*., 2010 (see CS section B.3.4.5.1)[2,75] The EAG was concerned about the lack of HRQoL as the Demaret *et al*., 2021 study presents data on neurological development and the effect of HSCT on HRQoL.[20] This means the EAG has uncertainty about HRQoL
Source of preference data for valuation of change in HRQoL	Representative sample of the public in the UK (United Kingdom)	The sources of preference data were Hernández Alava *et al*., 2022.[72] As noted above alternative sources were used for key events and Ward *et al*., 2007 and Szende *et al*., 2015 were used as alternative general population health state utility values.[76,77]

Elements of health technology assessment	Reference case	EAG comment on company's submission
Discount rate	An annual rate 3.5% on both cost and health effects	The company used a 1.5% discount rate for the future costs and benefits in their base-case analysis. The company justified their choice of discount rate on the basis that "*treatment with sebelipase alfa restores people who would otherwise die to full or near full health, and this is sustained over a very long period.*" A sensitivity analysis was conducted where a 3.5% discount rate was applied, in line with the NICE reference case[4] (See CS section B.3.2.2)[2]
Equity weighting	QALYs gained are of equal weight irrespective of patient characteristics	Age and gender utilities were provided and there was no indication of unequal weighting (See CS section B.3.4.5.1)[2]

Source: Section B.1.1, B.3.2, 2, B.3.2.22, B.3.1.5, B.3.4.5.1, B.3.2.2, B.3.4.5.1, B. 3.4.5 B.3.9.1, B.4.2.1 B.4. 2..5 B.4.2.6, B.4.2.9 of CS,[2,20,73] NICE reference case,[4] NICE TA554[72,74,75,77]

Abbreviations: BSC, best supportive care; CEM, company economic model; CS, Company submission; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PSS, personal social services; QALYs, quality-adjusted life years; UK, United Kingdom.

EAG comment: With respect to costs the EAG notes that the CS adopted a partial NHS perspective, meaning that most costs are confined to cost of administration of sebelipase alfa and the delivery of tertiary care associated with the investigation and monitoring of Wolman disease (see section 5.1.14). With respect to measuring and valuing health effects, though EQ-5D-3L health state utilities were used to estimate QALYs (see section 5.1.13) the justification given was based upon very sparse data. A scenario analysis was conducted with a 10% reduction in HRQoL for all ages. In the CS, it was concluded that the ICER is insensitive to modifications to health-related quality of life. In the PfC (question B3), the company mentioned that the adjusting multiplier of 0.9 was an arbitrary value used to assess the sensitivity of ICER to lower utility values. The company stated that this reduction had low to moderate impact on of the ICER.[25]

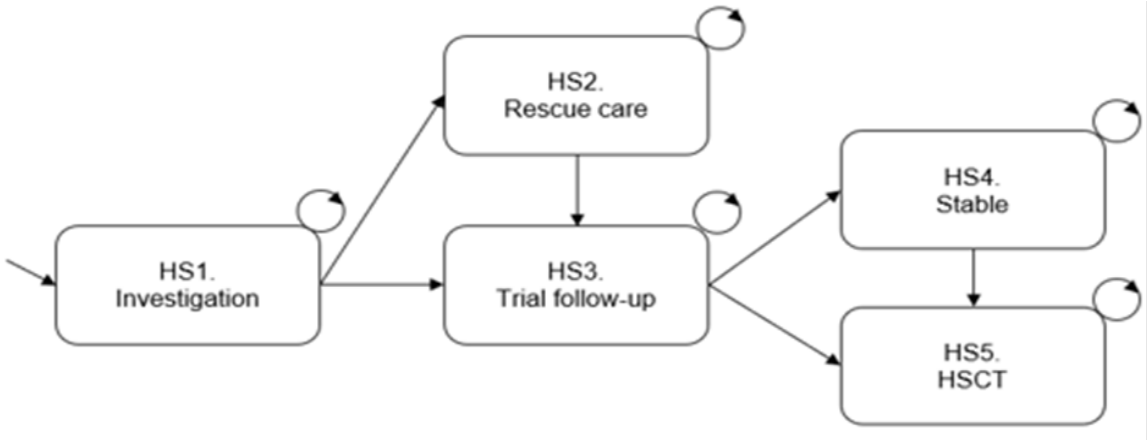
In the base-case analysis, the company assumed a 1.5% discount rate for future costs and effects. Whilst it is appreciated that the start of the CEM is at birth, the justification that the intervention restores people to near full health over a long period does not differentiate why this condition is any different to any other condition with long-term impacts. A scenario analysis was conducted where the NICE reference case value of 3.5% was adopted.[4] The EAG considers that the base-case analysis should adopt a 3.5% discount rate.

5.1.7 Health states and transitions (model structure)

The company developed a Markov model which is used to assess the cost effectiveness of sebelipase alfa compared with BSC and has been operationalised in Microsoft Excel. The dose requirements of sebelipase alfa were modelled using a decision tree.

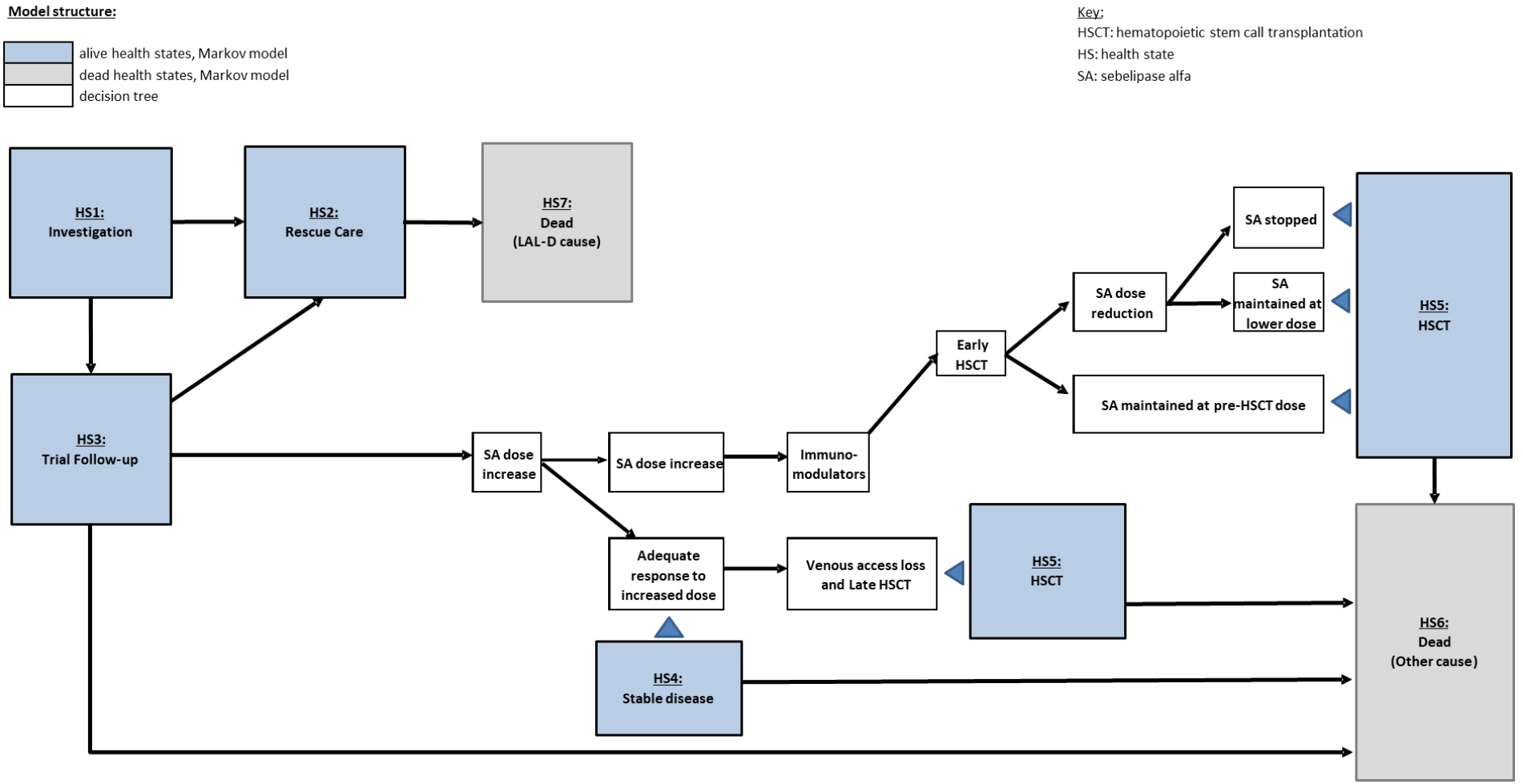
The structure of the model is depicted in Figure 5.1 and Figure 5.2. Figure 5.1 is a reproduction of Figure 20 from the CS[2] and Figure 5.2 is taken from the CEM. The key distinctions between the two are that Figure 5.2 included transitions to death states (general UK population death and Wolman cause disease death). Figure 5.2 also shows how the decision tree is integrated into the Markov model. The CEM links related mortality risk and resource consumption related outcomes to health states as shown in Figure 5.2. The cycle length for the model was monthly, and a lifetime time horizon was adopted.

Figure 5.1: Health state diagram as shown in the company submission



Source: Reproduction of Figure B20 from the CS[2]
Notes: Rectangles represent living health states. Mortality is a risk from every health state (Other cause mortality from age 5 = HS4 and 5). Straight arrows represent allowable transition and direction between health states, curly arrows indicate residency, unattached arrow shows point of model entry.
Abbreviations: HS, health state; HSCT; haematopoietic stem cell transplant

Figure 5.2: Model structure as described in the CEM



Source: Reproduced from "Overview" sheet in the CEM
Abbreviations: CEM, company economic model; HS, health state; HSCT, haematopoietic stem cell transplant; SA, sebelipase alfa

The health states in the economic model are defined in Table 5.3 (reproduced from Table 25 in the CS).[2] According to the CS within the BSC arm at the start of the model, newborn children with rapidly progressive LAL-D enter the model in the Diagnostic investigation (HS1). They can stay in this state for up to 4 cycles (i.e., 4-months). During that period, some infants transition to rescue care (HS2). Here infants receive one-month of neonatal critical care (although the model structure suggests they may stay in this state for multiple cycles). Thereafter, the infant moves to state H7; death due to LAL-D. Infants who do not transition to HS2 directly move to HS3 (Trial follow-up) where they are monitored. However, all infants are expected to transition to state HS2 in the first year. By the eighth month, every infant in BSC has transitioned to (HS7) death caused by Wolman disease. In the CS, patients that die due to Wolman disease transition to (HS6) instead of (HS7).

Table 5.3: Health states included in the model

Name	Representation	Use of sebelipase alfa
HS1. Investigation	Hospital-based neonatal care including IV parenteral nutrition. Trial based Wolman-related mortality risk.	Sebelipase alfa from birth, infused in the hospital setting.
HS2. Rescue care	One-month of neonatal critical care preceding a LAL-D death.	Sebelipase alfa until death, infused in the hospital setting.
HS3. Trial follow-up	Physician and dietician monitoring for up to 5-years, with LAL-D related mortality risk as observed in trials unless transition to HSCT. Specialist nutrition included.	Sebelipase alfa administered by the Alexion homecare service.
HS4. Stable	Physician and dietician monitoring from 5-years until loss of venous access and consequent transition to HSCT as rescue (late HSCT). No LAL-D related mortality. Specialist nutrition included.	Sebelipase alfa administered by the Alexion funded homecare service.
HS5. HSCT	Period characterised initially by immunomodulation and HSCT and remaining natural life. Entry via early or late HSCT, both carrying mortality risk from the procedure. Physician and dietician monitoring continues post HSCT. Specialist nutrition included.	Sebelipase alfa is discontinued 18-months after HSCT.
HS6/HS7. Dead	Mortality from Wolman-related, HSCT-related, or other cause.	NA

Source: Table 25 in the CS[2]
Abbreviations: CS, Company submission; HS, health state; IV, intravenous; HSCT, haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency; NA, not applicable.

For infants receiving sebelipase alfa, newborns start the model in the diagnostic investigation state (HS1). From the second month, some newborns treated with sebelipase alfa transition to rescue care (HS2) before transitioning to death by Wolman disease. In the BSC arm all patients transition to HS6 during the first year (all patients will die after 217 days by Wolman disease).

The remaining infants transition to trial follow-up (HS3), which lasts up to five-years. After five-years, patients treated with sebelipase alfa transition to a stable health state (HS4); clinicians monitor these patients until loss of venous access and transition to HSCT (HS5). In the base-case, this transition can happen as early as 24-months of age primarily due to loss of response to sebelipase alfa. This is known as (early life HSCT), and it was informed based on clinical experience, with [redacted] of infants transitioning to early life HSCT. Remaining surviving patients are expected to transition to HS5 due to loss of venous access (late transition to HSCT). In the CEM all surviving patients in the sebelipase alfa group transition from HS4 to HSCT (HS5) by the time they are [redacted]-years old. Whenever, an individual transfers to HSCT there is a one-off risk of death from the procedure. Whilst in state HS5 patients undergo immunomodulation therapy and HSCT. They then remain in this state for the rest of their life. A patient in the sebelipase alfa arm can transition to (HS6) mortality that is not caused by Wolman disease and the transition probability to this state has been defined by the UK population lifetable.[78] In the CS, the presentation is simplified in that patients treated with sebelipase alfa who die are transitioned to (HS6) irrespective of whether mortality was due to Woman disease or any other cause.

The final section of the decision model, the decision tree, applied only to those treated with sebelipase alfa. The company used this decision tree to model the dose distribution within the sebelipase alfa arm (Figure 5.3). The dosage of sebelipase alfa varies over time and is dependent on body weight and whether the patient is in state HS5 (HSCT). In this state sebelipase alfa is discontinued 18-months after HSCT. The decision tree allows response dosing reviews to occur at multiple time points (see Figure 5.3 reproduced from Figure 21 in the CS).[2]

The CS also defined how treatment with sebelipase alfa changed over time. To do this six treatment phases were defined. The length of treatment phases (Table 5.4 adapted from CS Table 34) and related dosing levels (

Table 5.5 adapted from the CS Table 33) were based on expert opinion except for the first phase.[2] This phase covered the period from birth to 3-months. The duration of the phase came from Vijay *et al*., 2021.[53] The dosing level (L1 in

Table 5.5, adapted from the CS Table 33) was based on expert opinion as were all other dosing levels.[2] The duration of the subsequent phases was based on expert opinion.

The second phase considered a dose change that occurred between the ages of 3-9-months (Dosing level L2 in Table 5.5). The third phase which covered the ages 9-30-months, included a dose decrease for those that received early HSCT at 24-months (Dosing level L4) and for those whose dosage was not increased in phase 2 a dose increase (Dosing level L3). In phase 4, for those that received early HSCT the dosage is reduced over the next 12-months such that it stopped by age [redacted]-months. In phase 5, which covers the ages [redacted]-months to 18-years dosage can be maintained (Dosing level L3), reduced (Dosing levels L4, L5 and L6) or stopped. In the final phase, from age 18-years to age [redacted]-years when loss of venous access is assumed to occur and all surviving patients receive HSCT, patients' dosage can be maintained (Dosing level L3), reduced (Dosing levels L4, L5 and L6) or stopped.

Table 5.4: Treatment phases

Phase	Sequential treatment phase [bounding milestones/nodes]*	Length of phase	Source
I	Initial [Initiation to first increase]	Age 0–3-months	Vijay *et al.*, 2021, Table 4[53]
II	Stable [First increase to second increase]	Age 3–9-months	Clinical expert interview
III	Multi-modal reduction [Second increase, early HSCT reduction]	Age 9–30-months	
IV	Discontinue [Reduction to stop]	Age 30–[redacted]-months	
V	To adult [Stop to adult]	Age [redacted]-months to 18-years	
VI	Adult adjusted [Adult to loss of venous access]	Age 18 to [redacted]years	

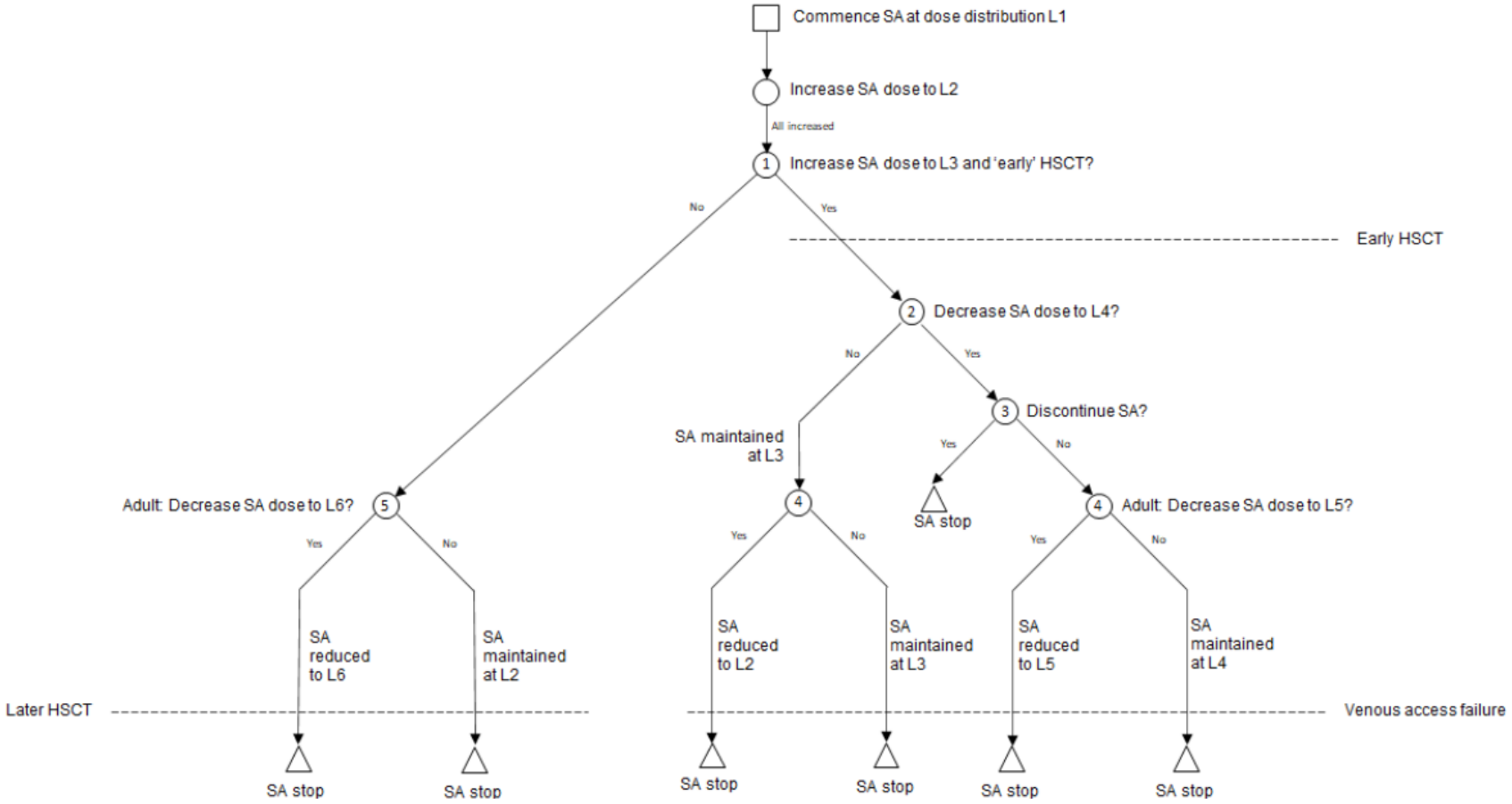
Source: Table 34 from the CS[2]
Notes: Phases may not be sequential. Sebelipase alfa dose is unchanged between phases C1 and C2, but C1 includes adjunct therapy. * The CS defined this as steps in the decision tree embedded in the model. The decision points in the decision tree were defined based on duration of dosage for each level.
Abbreviations: CS, Company submission; HSCT, haematopoietic stem cell transplant

Table 5.5: Treatment milestone and dose distribution

Treatment milestone	Dosing levels	Dose	Proportion of patients	Source/note
Treatment initiation	L1	3 mg/kg QW	100%	Expert clinical opinion
1st dose increase, following initial exploratory dose	L2	3 mg/kg QW	50%	
		5 mg/kg QW	50%	
2nd dose increase and initiation of immunomodulators and HSCT (multi-modal treatment)	L3	5 mg/kg QW	100%	
Dose decrease post early HSCT	L4	3 mg/kg QW	100%	
Dose decrease with adulthood post early HSCT	L5	1 mg/kg QW	50%	
		3 mg/kg QW	50%	
Dose decrease with adulthood (without early HSCT)	L6	3 mg/kg QW	50%	
		5 mg/kg QW	50%	

Source: Table 33 from the CS[2]
Abbreviations: CS, company submission; HSCT, haematopoietic stem cell transplant; kg, kilogram; mg, milligram; QW, once weekly.

Figure 5.3: Decision Tree of sebelipase alfa dosing copied from the company submission



Source: Reproduced from Figure 21 in the CS[2]

Abbreviations: CS, company submission; HSCT, haematopoietic stem cell transplant; SA, sebelipase alfa

Notes: The box is a decision node and represents the decision to use sebelipase alfa or not (BSC). Circles numbered 1 -5 are chance nodes and represent clinical decisions beyond the payer's control. Codes L1-L6 are sebelipase alfa dose distribution 'levels'. Triangles are terminal nodes, representing alternative dosing pathways. Dashed lines are illustrative indications of the time of period when HSCT is possible. Venous access failure is an assured risk and therefore not a represented by a decision node: subsequent late rescue HSCT is allowed only in those without previous early HSCT.

EAG comment: The EAG considered some inconsistencies in the model structure of the CS and CEM.[2] However, the company explained the typographical error in the model structure as the arrow between health states (HS) 2 and 3 should be pointed in the opposite direction, allowing transition from HS3 to HS2.[25] HS2 is effectively a tunnel state for residency prior to mortality from rapidly progressive LAL-D. Therefore, transition is only from HS3 to HS2. The company also mentioned in a scenario (non-base-case) in which people receiving early HSCT do not discontinue sebelipase alfa, transition from HS5 to HS2 becomes possible (LAL-D death due to loss of venous access and no second HSCT).

The model as displayed and described in the CS (see Figure 5.1) and CEM (see Figure 5.2) are not identical.[2] Some of this is because the CS has simplified the presentation of the model. For example, the CS describes six health states but the CEM has seven because the CEM death is split according to whether the death was caused by LAL-D (HS7) or other causes (HS6). The CS combines these two states. Similarly, according to the CS (pages 111-112): "*All infants in the BSC strategy will transition through Rescue care to LAL-D death within the first year, some experiencing outpatient management on the way (HS3)*".[2] So, whilst transition from HS2 to HS3 is allowed this is not depicted in Figure 20 of the CS (reproduced as Figure 5.1 above).[2]

In terms of extrapolation over trial data to patients` lifetime, the EAG considered that the company fitted several parametric models and finally decided to choose a non-parametric Kaplan-Meier approach for the base-case analysis as parametric models are not fitted via visual inspection. Though, the gamma and exponential distributions were chosen as the best fit for the sebelipase alfa, and multi-modal (sebelipase alfa + HSCT) based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC) measures. The EAG agree that the Kaplan-Meier is the best fitted model for the trial follow-up, however, using a more flexible parametric modelling approach (NICE DSU 21)[79] including best fitted model over trial follow-up could be more relevant to fit the model for patients` lifetime in this analysis.

The EAG considered that ERT cessation post-HSCT as implemented in the CS occurring at level 3 sebelipase alfa dosage (2nd dose increase and initiation of immunomodulators and HSCT) for 6-months after early HSCT for patients at 24-months old was reasonable. However, for the late HSCT as modelled in the CEM, which occurs when patients are 30-years old, the cessation of sebelipase alfa was also assumed at the same time and the immediate stop of ERT after HSCT is not a reasonable assumption. The EAG clinical expert also advised "*the cessation of ERT post HSCT is a much longer process and continues for a period post HSCT (undefined at present) and may possibly alternate weekly after again an undefined period. But does not stop immediately after HSCT*".

The EAG considers the description of the relationship between the treatment phases listed in Table 5.4 and treatment milestone and dose distribution in Table 5.5 provided in the CS to be unclear.[2] For example, the CS does not describe how the two tables relate to each other.[2] These tables detail the dose according to pre-defined treatment milestones which are used in Figure 5.3 and incorporated into the CEM and as such should be described in greater detail.

The CS also assumed the general UK population life expectancy for patients receiving (early/late) HSCT. This point was also checked with the EAG clinical expert, and they agreed with this assumption as mentioned: "*patients with Wolman who survive the early period and establish ERT can survive into long term, from my experience, 10 years.*" However, given that no person with rapidly progressive LAL-D has yet survived to adulthood there remains significant uncertainty.

5.1.8 Population

The population considered in the cost effectiveness model, although labelled differently, is broadly in line with the NICE scope (see section 3.1).[1] The CEM population was based on the trials that informed the effectiveness evidence. The study characteristics of this population are summarised in Table 5.6.

Table 5.6: Key baseline patient characteristics used in the economic model

	Mean	Source	Comment
Age of patients	0.00-years	[80]	Patients are included from birth.
Proportion of patients that are male	52.6%	[23] [24]	EAG has concerns about why the company did not use the England or UK national average for this value.

Source: CS and CEM.[23]
Abbreviations: EAG, External Assessment Group; UK, United Kingdom.

EAG comment: The EAG checked the population included within both the NICE scope and this CS with our clinical expert.[1] It was concluded that the definition provided by the company means the population identified by the company is the same as the population proposed in the NICE scope.[1,2] Please see section 3.1 for more details.

5.1.9 Interventions and comparators

The cost effectiveness of sebelipase alfa was compared with established clinical practice without sebelipase alfa, which is described as BSC within the CS. The intervention and comparator are in line with the decision problem and NICE final scope.[1] Sebelipase alfa, a weight-dependent drug, is indicated for long-term enzyme replacement therapy for patients of all ages with LAL-D and is administered intravenously. The company mentioned that the recommended dose for patients aged < 6-months presenting with rapidly progressive LAL-D is either 1mg/kg or 3mg /kg QW, depending on clinical status. Patients younger than six-months who do not present with rapidly progressive LAL-D, receive a dose of 1mg/kg Q2W via IV. As mentioned in the EAG comment for section 5.1.7, the CS does not provide clarity on how the treatment milestone and dose distributions shown in CS Table 33 relate to treatment phase found in CS Table 34.[2]

The comparator used in the CEM was established clinical practice which was also referred to as BSC in the CS.[2] BSC does not prevent disease progression and mortality. The comparator used in the CS is within the NICE scope.[1] According to the CEM patients in the base-case die due to Wolman disease by 8-months after birth.

The comparator used in the CEM was established clinical practice which was also referred to as BSC in the CS.[2] BSC is a form of palliative care and does not prevent disease progression and mortality as at the time of the submission there are no alternative treatment for the population of interest. The comparator used in the CS is within the NICE scope.[1] According to the CEM patients in the base-case die due to Wolman disease by 8-months after birth. As discussed in section 5.2.2 a significant proportion of patients in the BSC arm transition from the Investigation state (HS1) to the Rescue Care health state (HS2) before transitioning to mortality caused by Wolman disease (HS7), while a smaller proportion transition to the Trial Follow-up health state, HS3 before transitioning (HS7) via (HS2) HSCT was

assumed not to be a rescue therapy for patients in BSC. The company used Potter *et al*., 2021, to justify this assumption.[3]

Further details about the model's intervention and comparator can be found in sections 3.2 and 3.3 of this EAG report.

EAG comment: The CS provides brief information about the comparator which provides a degree of ambiguity for the EAG about what the comparator entails. The EAG agree with the assumption that HSCT would not be used as a rescue therapy in BSC as it is unlikely to be effective in the more severe stages of untreated LAL-D.

5.1.10 Perspective, time horizon and discounting

The company's economic evaluation was carried out from the NHS perspective for costs and from a patient perspective for QALYs. A broader perspective considering the impact of bereavement on parents/carers was adopted as a scenario analysis.

Time horizon adopted for the analysis was the lifetime of the child, which was taken to be a maximum of 100-years. Costs were reported in 2022 UK pounds Sterling and in the base-case future costs and benefits were discounted at an annual rate of 1.5%. The justification given in the CS was that treatment with sebelipase alfa "*restores the lives of people who would otherwise be dead to full or near full of near full health*".[2] Sensitivity analysis considered a discount rate of 3.5% in line with the NICE reference case.[4]

EAG comment: The company stated that the base-case analysis is in alignment with the NICE reference case, taking the payer perspective of the UK NHS setting (section B.3.22 Page 109).[2,4] However, the EAG notes that only a partial NHS perspective was used, meaning that most costs are confined to cost of administration of sebelipase alfa and the delivery of tertiary care associated with the investigation and monitoring of Wolman disease (see section 4.2.10).

Costs falling on PSS were stated as being included in the analysis, however, the company has only referenced the costs for a community nurse average of Band 8A-D to deliver the home administration of sebelipase alfa included in the sensitivity analysis (Table 60, scenario 16).[2] No other PSS cost were included.

The EAG notes that the inclusion of the broader impact on QALYs of parents and carers following the death of a relative/carer is not common, although this was included in a scenario analysis only.

The choice of discount rate in the base-case analysis is not in line with the NICE reference case and the EAG do not consider the use of a lower discount rate appropriate for the base-case analysis.[4]

5.1.11 Treatment effectiveness and extrapolation

The CS assumed three distinct causes to inform the economic model to extrapolate life expectancies (overall survival) of patients in both intervention and control groups including Wolman-related mortality within the first five-years of life, the natural/background mortality of all ages (UK general population life expectancies) and (early) HSCT-related mortality in the first five-years post procedure.

Of these only the first is relevant to BSC due to the very high expected mortality caused by Wolman disease as all patients died during the first year. All three causes will now be discussed in turn below.

5.1.11.1 Wolman-related mortality within the first 5-years

For Wolman-related mortality within the first 5-years patient data were taken from LAL-CL03, LAL-CL08, LAL-1-NH01, and Potter *et al*., 2021 and used to derive K-M estimates for those treated with sebelipase alfa (N=19) and those receiving BSC (N=21).[3] The available data from two studies which had a 5-year follow-up was that there were no deaths in the final 3-years of follow-up (Vijay *et al*., 2021 and Potter *et al*., 2021).[3,53] This latter observation along with clinical expert opinion is the basis of the assumption made in the CS that mortality beyond 5-years was the same as natural/background mortality of all ages for the UK population.[2] Therefore, in the base-case analysis Wolman-related mortality was based on the K-M estimates.

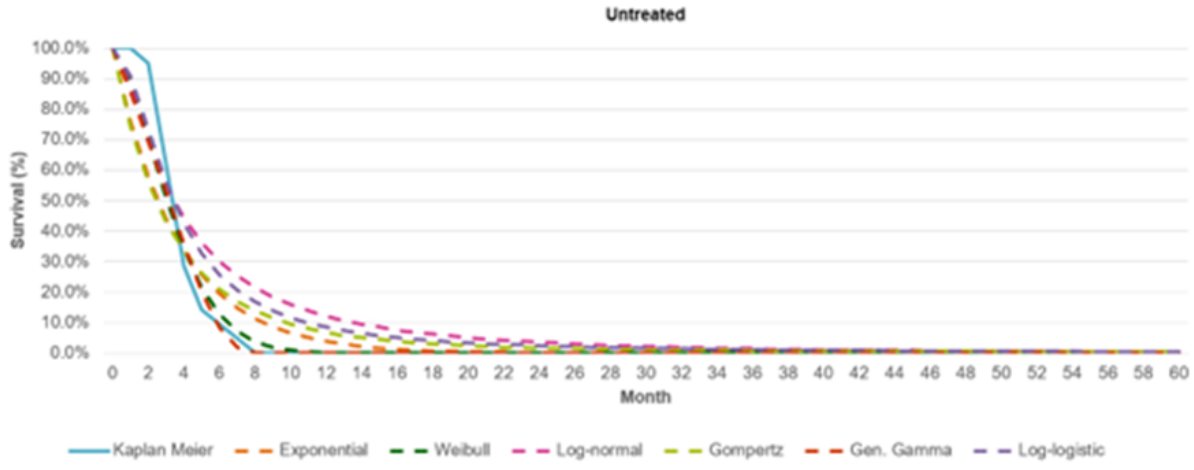
In the sensitivity analysis, the company explored fitting alternative parametric survival models to the survival data. The company explored six approaches to estimate survival curves: exponential, Gompertz, Weibull, log-logistic, log-normal, and generalized gamma distributions. Model fit and plausibility were assessed by AIC and BIC in combination with a visual inspection of the estimated survival curves against the K-M curves produced. Figure 5.4 and Figure 5.5 (reproduced from Figures 24 and 25 in the CS) show the parametric survival curves and K-M data for BSC and sebelipase alfa treatment respectively.[2] Table 5.7 shows the summary statistics by treatment arm on which survival and K-M curves have been estimated. For the economic evaluation, data were pooled across treatment arms and a single model fitted to both or all treatment arms, were considered under the assumption of proportional hazards.

Table 5.7: Summary statistics for overall survival by treatment arm

Treatment	n	Events	Restricted mean (days)	Restricted mean (SE)	Median	95% CI
BSC (untreated)	21	21	110.86	9.15	93	(86,148)
SA (treated)	18	5	1522.50	196.68	NR	NR

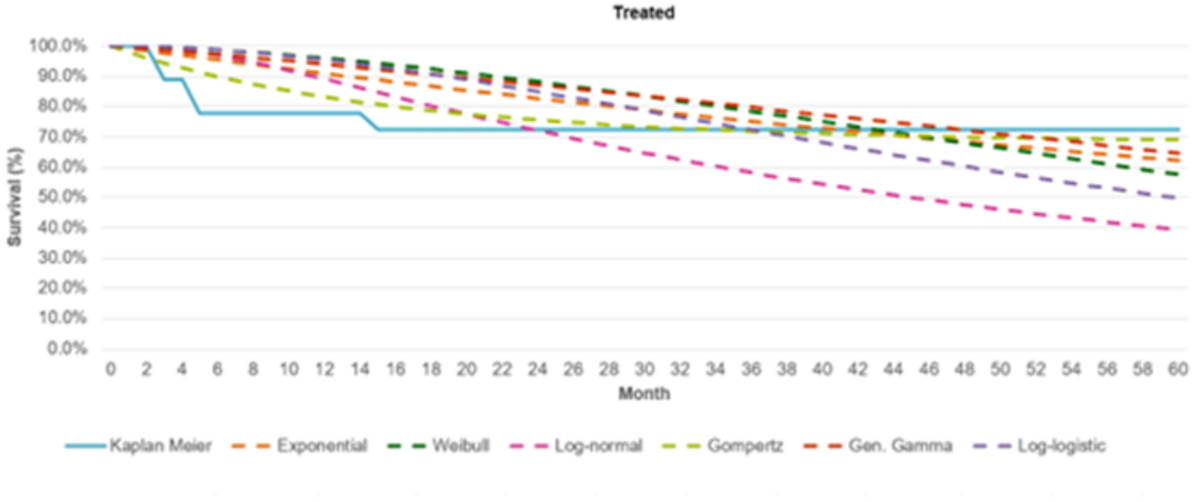
Source: Table 28 from the CS[2]
Abbreviations: BSC, best supportive care; CI, confidence interval; CS, Company submission; n, number of people; NR, not reported; SA, sebelipase alfa; SE, standard error.

Figure 5.4: Parametric curves and Kaplan-Meier data for best supportive care



Source: Figure 24 of CS[2]
Abbreviation: CS, company submission; Gen Gamma, generalised gamma

Figure 5.5: Parametric curves and K-M data for sebelipase alfa treatment



Source: Figure 25 of CS[2]
Abbreviation: CS, Company submission; Gen Gamma, generalised gamma.

EAG comment: The K-M survival data are based upon the pooled patient level data from numerous sources. The EAG note, as reported in section 4.3.1.1 that these data are not pooled to provide an overall estimate in efficacy. The potential reasons for this are that there are differences in dosing between studies and differences in the patient population (for example, in LAL-CL03 used a narrow definition of rapidly progressive LAL-D, whereas LAL-CL08 used a broader definition rapidly progressive LAL-D. This heterogeneity between studies has likely introduced a further level of uncertainty in the estimation of Wolman-related mortality at 5-years and in subsequent model fitting of survival curves. Ultimately this uncertainty is not addressable without more data which will be difficult to obtain.

With respect to the fitted survival functions, the approach described in CS for model fitting for each arm seems reasonable.[2] The decision to pool the data from arms and include a treatment effect (under an assumption of proportional hazard) is perhaps less clear as the data available is still very sparse and for those receiving sebelipase alfa as Figure 5.5 illustrates none of the curves visually looked to be good fit for the K-M survival data. The fits for the survival models for BSC are visually more similar to the patient level data. This is understandable as the observed period of the patient level data includes the entire duration of survival of those receiving BSC.

The key issue however is the assumption, based upon relatively sparse data, that mortality for those receiving sebelipase alfa is very low (effectively zero from month 16). It is possible that with a larger data set a different pattern of survival might emerge but this cannot be addressed without continued follow-up and monitoring of those who have received sebelipase alfa for rapidly progressive LAL-D.

5.1.11.2 Natural background mortality

Given that no deaths occurred in the final 36-months of follow-up in Vijay *et al.*, 2021 or Potter *et al.*, 2021 it was assumed in the CS, and supported by the expert clinical opinion sought by the company that survival following 60-months could be based on UK general population mortality.[2,3,53]

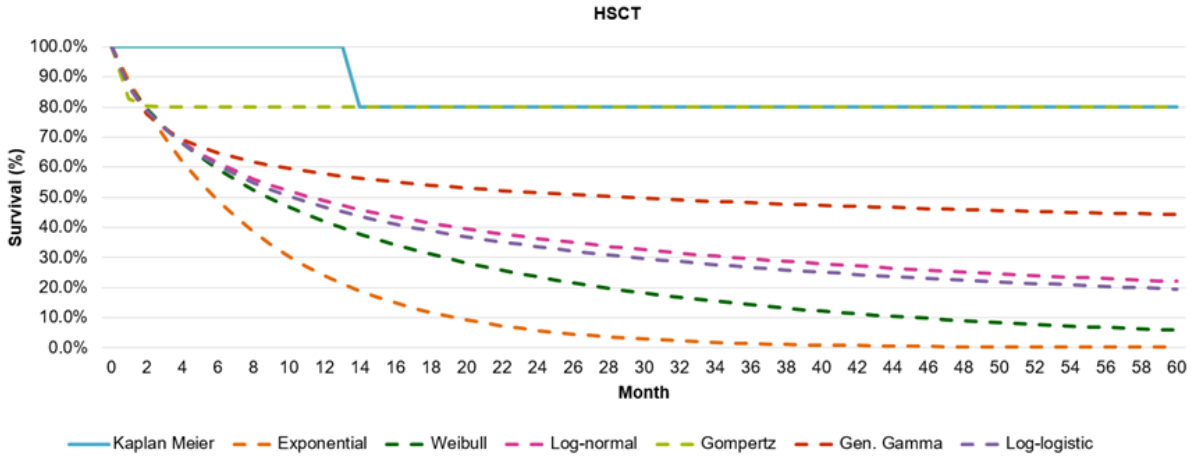
EAG comment: The EAG note the sparse data on which this is based. As Table 5.7 shows it relates to the experience of 18 children. It is possible that further data could change (or confirm) this assumption.

The EAG has conducted an exploratory analysis to explore the impact of long-term mortality that is 5% higher than the UK general population. Five percent has been chosen as a small but illustrative change.

5.1.11.3 HSCT-related mortality in the first five-years post procedure

The company used the same approach to estimate survival for HSCT treatment as they use to estimate survival for best supportive care and treatment with sebelipase alfa. Here the source of data was Potter *et al.*, 2021 (N=5).[3] The participants in Potter *et al.*, 2021 received both HSCT and sebelipase alfa.[3] Figure 5.6 shows the parametric curves and K-M survival data, and Table 5.8 shows the summary statistics. These show that only one death occurred out of the five participants over the 60-month follow-up.

Figure 5.6: Parametric curves and K-M survival data: sebelipase alfa + HSCT



Source: Figure 26 of CS[2]
Abbreviations: CS, company submission; Gen Gamma, generalised gamma; HSCT, haematopoietic stem cell transplant

Table 5.8: Summary statistic for overall survival of HSCT-treated patients

Treatment	n	Events	Restricted mean (days)	Restricted mean (SE)	Median	95% CI
SA + HSCT	5	1	50.52	8.48	NR	NR

Source: Table 29 from CS[2]
Abbreviations: CI, confidence interval; CS, Company submission; HSCT, haematopoietic stem cell transplant; n, number of patients; NR, not reported; SA, sebelipase alfa; SE, standard error.

ERG comment: The data for survival following initiation of HSCT is based upon exceedingly sparse data and hence the estimates provided must be treated cautiously. Given the sparse data it is unsurprising that none of the survival curves visually looked like they were a good predictor. The closest was the Gompertz model but this appeared to predict an earlier mortality than shown by the K-M data.

5.1.12 Adverse events

5.1.12.1 Incidence of AEs

The CS provided a summary of adverse reactions in the LAL-CL08 and LAL-CL03 trials, including the extent of exposure to sebelipase alfa, details are summarised in the clinical effectiveness section 4.3.1.7. A summary of adverse events, anti-drug antibodies and deaths by overall and different time intervals. Table 5.9 shows the adverse reactions in the overall duration of trials (adapted from CS Tables 13, 14, 16, 17, 19, and sections B2.10.1.3, B2.10.1.4, B2.10.2.1, B2.10.2.4 of the CS).[2]

Table 5.9: Summary of adverse reactions in the LAL-CL08 and LAL-CL03 trials

Study	**LAL-CL08**		**LAL-CL03**	
Patients	Overall ([redacted])		Overall ([redacted])	
Median number of weeks on treatment (all doses)	[redacted]		[redacted]	
Number of infusions administered	[redacted]		[redacted]	
Any TEAE	10 (100)		9 (100)	
Most common TEAES	*Pyrexia*	[redacted]	*Diarrhoea*	[redacted]
	Diarrhoea	[redacted]	*Vomiting*	[redacted]
	Vomiting	[redacted]	*Cough*	[redacted]
	Tachycardia	[redacted]	*Nasopharyngitis*	[redacted]
	Gastroenteritis	[redacted]	*Pyrexia*	[redacted]
	Respiratory distress	[redacted]	*Rhinitis*	[redacted]
Any treatment-related TEAE	8 (80)		6 (67)	
Most common treatment-related TEAE (LAL-CL08)	*Tachycardia*	[redacted]	*Pyrexia*	[redacted]
	Pyrexia	[redacted]	*Vomiting*	[redacted]
Any infusion-associated reactions (LAL-CL03)	*Irritability*	[redacted]	*Urticaria*	[redacted]
	Agitation	[redacted]	*Tachycardia*	[redacted]
	Urticaria	[redacted]	*Pallor*	[redacted]
Any serious TEAE[a]	10 (100)		9 (100)	
Any related serious TEAE			1 (11)	
Any severe TEAE[a]	7 (70)			
Any IAR[b]	8 (80)		5 (56)[c]	
ADAs	6 (60)		4 (57)	
Dose modification due to a TEAE[d]	7 (70)		7 (78)	
Treatment withheld or permanently discontinued due to a TEAE[e]	[redacted]		0 (0)	
Death (%)	2 (20)		4 (44)	

Source: Adapted from CS Tables 13, 14, 16, 17, 19, and sections B2.10.1.3, B2.10.1.4, B2.10.2.1, B2.10.2.4 of the CS[2]
Notes:

[a] TEAEs included events with an onset at or following the start of treatment with sebelipase alfa or events whose severity; worsened or relationship at or following the start of treatment and occurring up to 30 days after the last infusion of sebelipase alfa. Related TEAEs include any event assessed by the Investigator as related or possibly related to the trial drug.

[b] IARs include any event with an onset during the trial drug infusion or within 4 hours after the trial drug infusion, where the event was assessed by the Investigator as related or possibly related to the trial drug.
[c] Non-serious TEAE data were unavailable for one patient from Week 0 to Week 39.
[d] Dose modifications include dose decreased, dose interrupted and drug permanently discontinued per the AE electronic CRF page.
[e] Includes trial drug withheld or trial drug permanently discontinued per the AE CRF page.
Abbreviations: ADA, anti-drug antibody; AE, adverse event; CRF, case report form; CS, Company submission; IAR, infusion-associated reaction; TEAE, treatment-emergent adverse event

According to the CS, in both trials, 100% of patients experienced TEAEs and SAEs.[2] It is stated that most SAEs were related to LAL-D complications and comorbidities. In LAL-CL08, 50% of patients undergoing SAEs, were classified as IARs. Overall IARs occurred in 80% and 56% of patients in LAL-CL08 and LAL-CL03, respectively.

The frequency of TEAE and treatment-related TEAE and IARs were presented by the company by system organ class and preferred terms. The most common TEAES were pyrexia, diarrhoea and vomiting in LAL-CL08 and diarrhoea, vomiting and cough in LAL-CL03. In LAL-CL08 and LAL-CL03, 70% and 78% of patients received dose modification, respectively. No patients were reported as having received permanent dose reduction or discontinued from either trial due to TEAE. ADAs to sebelipase alfa were reported in 60% and 57% of patients in LAL-CL08 and LAL-CL03, respectively.

According to the CS in LAL-CL08, two (20%) deaths occurred.[2] One patient died due to pericardial effusion and another due to sepsis at 4.9 and 13.8-months of age. These deaths were deemed unrelated to the study drug. Four (44%) deaths were reported in LAL-CL03, two approximately at the age of 3-months, and the remaining at the age of 4.3 and 15-months. Hepatic failure, haemorrhage, cardiac arrest and sudden cardiac death were the causes of death.

As real-world evidence, sebelipase alfa exposure, AEs and death data from the safety population of ALX-LALD-501 are also provided in the CS.[2] The safety population includes UK (7) and non-UK (20) patients. It is stated in the CS that the AEs aligned with those reported in LAL-CL08 and LAL-CL08. The company mentioned that the UK patient population enrolled in the LAL-D registry largely overlaps with LAL-CL08 and LAL-CL03 trials. In ALX-LALD-501, the company reported [redacted] deaths in the safety population. [redacted] patient died at enrolment, and the [redacted] died at [redacted] years of age due to liver cirrhosis/failure.

5.1.12.2 Impact of AEs on HRQoL

AEs and the healthcare resources associated with their management were not explicitly included in the economic evaluation model.

The CS stated that AEs temporarily impact HRQoL and in most cases are managed by infusion adjustments and treatment (by infusion interruption/discontinuation, infusion-rate reduction and/or conventional treatment with antihistamines, corticosteroids, analgesics or antipyretics). It was mentioned that the majority of TEAEs were non-serious, mild or moderate and unrelated to treatment with sebelipase alfa.[2]

For adverse drug reactions, which were related to the formation of ADAs, the company assumed that it was implicitly considered in the model by inclusion of HSCT and capturing the associated resources for inpatient admissions due to complications of the disease.

EAG comment: The TEAEs are reported by the number of events and patients experienced events. The company stated that most TEAEs were mild or moderate but provided no definition for serious and severe TEAEs.

In the model, health utilities were adjusted for increasing age but disutilities due to AEs were not included. The exception to this is HSCT but as described below disutilities for this were only applied in a scenario analysis and not the base-case.

The EAG also requested further details for this at the clarification step and the company`s reply was "*Change in utility from treatment-emergent adverse events (TEAEs) with sebelipase alpha was not included in the model due to insensitivity of the ICER.*" The company justification was that in the scenario analysis of changes in HRQoL, a 10% reduction in HRQoL of all ages has an 11% increase (low to moderate) on the base-case ICER.[25] "*Note that imaging and investigational resource consumption was included through the time horizon, accounting for some resources relating to disease and treatment complications*".[25]

5.1.13 Health-related quality of life data identified in the review

5.1.13.1 Primary evidence (clinical trials)

The primary evidence sources for cost effectiveness analysis of sebelipase alfa are the patient-level data from two open-label multicentre studies (LAL-CL03 and LAL-CL08). These trials did not measure the HRQoL of patients with rapidly progressive LAL-D. To identify HRQoL studies in patients with LAL-D, the company conducted an updated SLR on 26 June 2022. Of 140 identified records in the updated search reported in the CS,[2] Demaret *et al*., 2021 was the only study included.[20] This SLR is an update of the one conducted in 2015 for NICE HST ID737, which found no eligible studies for inclusion.[36]

Demaret *et al*., 2021, is a retrospective cohort study that enrolled five patients with Wolman disease who received sebelipase alfa in France.[20] Participants were followed up for 1-10-years with a median follow-up of 7-years. The Pediatric Quality of Life Inventory questionnaire (PedsQL 4.0) was employed to measure the patients' HRQoL. The PedsQL includes four multidimensional scales of physical functioning, emotional functioning, social functioning and school functioning. The study reported the HRQoL of the patients at the patients' last follow-up, which varied between 14 and 120-months. The item scores on the questionnaire range from 0 (better) to 4 (poorer) were converted to a scale from 0 (poorer = 4) to 100 (better = 0). Responses were provided by both the child and parent participants (Table 37 of the CS). As can be seen from Table 5.10, there was variation between child and parent. Global scores varied from 61-80 for the child responses and 51-100 for parent responses.

Table 5.10: Results for each child based on both child and parent responses on the PedsQL

	Patient 1 (%)	Patient 2 (%)	Patient 3 (%)	Patient 4 (%)	Patient 5 (%)
Age at diagnosis (months)	2	0	0	0	2
Follow-up (months)	120	83	37	84	14
Patient evaluation	71	61	NA	80	NA
Physical functioning (8 items)	75	56	NA	88	NA
Emotional functioning (5 items)	60	60	NA	90	NA
Social functioning (5 items)	70	70	NA	70	NA
School functioning (3 or 5 items)	75	60	NA	70	NA
Parental evaluation	82	51	85	85	100
Physical functioning (8 items)	75	47	84	91	100
Emotional functioning (5 items)	80	75	70	80	100
Social functioning (5 items)	85	45	100	100	100
School functioning (3 or 5 items)	90	40	NA	65	NA

Source: Table adapted from Table 37 in the CS[2] with additional data on age at diagnosis and follow-up (months) from Demaret *et al*., 2021.[20] Patient 2 and Patient 4 were one year older than ages mentioned in the CS[20]
Note it is not explicitly explained in the CS why some responses are not applicable, but this occurs when the child is pre-school age and most likely unable to provide a response of the PedsQL themselves.
Abbreviations: CS, Company submission; NA, not applicable; PedsQL, Pediatric Quality of Life Inventory questionnaire

In the CS, it is stated that both parents and patients (when available) reported acceptable or high HRQoL globally and in all 4-dimensional scales.[2] They go on to state the further results from Demaret *et al*., 2021, that cognitive development was normal, and no patient had special educational needs.[20] Demaret *et al*., 2021, concluded that sebelipase alfa allowed 100% survival of five patients with Wolman disease with near-normal bio-clinical and growth parameters follow-up, up to 10-years.[2,20]

5.1.13.2 Utility value sources

The cost effectiveness model provided by the company considered six health states, including investigation, rescue care, trial follow-up, stable, HSCT, and dead. The CS stated that the utility values for defined health states had to be modelled in the absence of evidence on HRQoL for people with rapidly progressive LAL-D.[2] Demaret *et al*., 2021, was not used directly in the modelling but was used just to justify the company's assumption of the near-normal life of patients with established ERT.[20] Consequently, in the base-case analysis it was assumed the utility of both treated and untreated patients could be derived using age-specific and sex-specific UK general population norms for the EQ-5D-3L

(see Table 5.11).[72] These utilities begin at age 16-years, so the model assumes that general utility for those aged 16-years also applies to all children under age 16-years.

Table 5.11: Utilities used in the CEM for the base-case analysis by 5-year increment

Age (years)	Gender weighted utility
0	0.929
5	0.929
10	0.929
15	0.929
20	0.927
25	0.922
30	0.915
35	0.906
40	0.896
45	0.884
50	0.870
55	0.855
60	0.838
65	0.820
70	0.800
75	0.779
80	0.755
85	0.730
90	0.704
95	0.675
100	0.646
Source: Reproduced from Table 38 in the CS[2] Abbreviations: CEM, company economic model; CS, Company submission.	

Within the CEM ('Inputs & Outputs' sheet and 'HU norms' sheet), two other sources of utility values were also reported and could be used as the basis of scenario analyses (Ward *et al*., 2007 and Szende *et al., 2014)*.[76,77] The Ward *et al*., 2007 study is a systematic review and economic evaluation study which evaluated the clinical effectiveness and cost effectiveness of statins for the primary and secondary prevention of cardiovascular events in adults with, or at risk of, coronary heart disease (CHD).[76] No justification was given by the company for using this source of utility values. It was just provided in the CEM. The Szende *et al*., 2014 study reported EQ-5D data for individuals older than 18-years of age in 24 countries including UK and England.[77] The source of utility values are the age-adjusted EQ-5D index based on the European VAS value set, and country-specific TTO value sets (including those for the UK).[77] For the Szende *et al*., 2014 study there is an error in the labelling of the data source of VAS and TTO-adjusted utility values in the CEM (column D&F, 'HU norm' sheet).[77] In the formula in the CEM the VAS value set was used for estimating age-adjusted TTO utility and vice versa. This error was corrected before the EAG analyses.

EAG comment: According to the NICE manual [PMG36] on measuring and valuing health effects in cost-utility analyses, HRQoL should be measured directly by patients.[4] If it is not possible, measuring it through close relatives (carer) is preferable.[4] The company uses utility values estimated from the Hernández Alava *et al*., 2022 study using the standard EQ-5D-3L.[72] Although the EQ-5D is a valid generic tool to measure HRQoL and the preferred measure by NICE due to consistency across evaluations, it is not appropriate for use in children aged under 12-years of age population.

The one source of HRQoL data reported in the CS is the study by Demaret *et al*., 2021. The number of patients in the Demaret *et al*., 2021 study is however very small (responses available for three children and 5 parents).[20] The study employed PedsQL to measure and report HRQoL in the form of child self-report and parent proxy-report. Two of the child participants were pre-school age and unable to give a response. Parents may not be perfect proxies for their children and in Demaret *et al*., 2021 there were variations between child and parent responses – see Table 5.10.

The CS made the assumption based on Demaret *et al*., 2021 that the HRQoL of patients would be the same as the UK general population. As Table 5.10 shows that responses are not uniformly 100% and, in some cases, substantially below this. Global scores varied from 61-80 for the child responses (mean 73, median 75) and 51-100 for parent responses (mean 81, median 85). This suggests that an assumption of HRQoL being equal to the age and sex adjusted population health may result in utility values for those treated with sebelipase alfa to be slightly too high. Based upon this, the EAG consider that the scenario analysis where a weight of 0.8 hazard rate was applied may be more appropriate (see section 7.1.2.1). In the CS, it was mentioned they used 0.8 hazard ratio as an alternative scenario in adjusting HRQol values.[2] However, in the PfC response letter, the company stated that the correct hazard ratio is 0.9, which is applied in scenarios 28 (for a 10% reduction in HRQoL at all ages) and 29 (for a 10% reduction in HRQoL at all ages and a 20% hazard rate on other cause mortality). The PfC response to question B2b provided revised estimates to these two scenarios and reported that the ICER increased from £239,608 in the CS base-case to £266,223 and £268,687 for scenarios 28 and 29 respectively.

The adoption of a multiplier of 0.8 may also be supported by Kanters *et al.*, 2011.[81] This study assessed the burden of illness in Pompe patients in the Netherlands.[81] It reported that HRQoL of patients with Pompe disease is lower than the utility value of the general population. In this study, the average EQ-5D utility score of the patients on supportive care was estimated at 0.72, which was 17% lower than the Dutch general population.[81]

The frequency of infusion by sebelipase alfa may also affect a patient's quality of life. Sebelipase alfa, as indicated in the CS, is a long-term ERT, is recommended weekly, should be administered over approximately 2-hours, and in the cases of suboptimal clinical response, there may be dose escalation. The impact of the frequency of infusion on a childs HRQoL may be inferred from the CS. As mentioned in section B.2.12 of the CS, one child was referred for HSCT because of the patient's desire to reduce the frequency of infusions.[2] The study by Simon *et al.*, 2019.[82] also investigated health utilities for three rare diseases in childhood and adulthood using the time-trade off approach. Two of the 18 health states valued were ERT conditions in 8 and ≥18-years old. The estimated health utilities for ERT treatment were (0.48, 95% CI: 0.42–0.53) and (0.67, 95% CI: 0.62–0.72), for child and adults respectively. Both the studies by Kanters *et al.*, 2011 and Simon *et al.*, 2019 suggest that assuming that a patient's health is the same as the UK general population may overestimate HRQoL for this condition.[81,82]

5.1.13.3 Disutility values sources

Within the CS utility decrements are applied. These can be split into those that affect the child and those that affect the parent/carer (which are used only in a scenario analysis). These decrements are summarised in Table 5.12 and are further described below.

Table 5.12: Utility decrements applied in the base-case and scenario analyses

Health state applied	Utility description	Utility value	Decrement duration	Source
HS1 Base-case	Parenteral nutrition utility (7 days per week)	0.26 (absolute)	3.22 months (duration of initial hospitalization period)	Ballinger *et al.*, 2018[73] Duration is informed by expert clinical opinion[2]
HS5 Scenario	HSCT decrement	[redacted]	[redacted]	EAG report in TA554 committee papers[74]
Decrement per patient death (Scenario)	Monthly family grieving decrement per parent/carer	0.04 per caregiver (decrement)	65-years; 2 caregivers	Song *et al.*, 2010[75]

Source: Reproduced from CS Table 39.[2]
Abbreviations: CS, company submission; EAG, Evidence Assessment Group; HS1-5, health state 1-5; HSCT, haematopoietic stem cell transplant

5.1.13.3.1 Patients' disutilities

Parenteral nutrition

The data for the disutility related to parenteral nutrition was taken from Ballinger *et al*., 2018, which estimated utilities associated with parenteral support requirement in patients with short bowel syndrome and Intestinal Failure. The lowest utility value (0.26) for seven cumulative days of parenteral nutrition was considered in the CEM base-case analysis.[73] Expert clinical opinion was used to estimate the total parenteral nutrition duration for their initial hospitalization, post-diagnosis, and was estimated as 3.2 months (98 days).[83]

Haematopoietic stem cell transplant

The disutility data for patients who underwent HSCT was taken from NICE TA554 for tisagenlecleucel for HSCT when treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25-years.[74] Two time points were considered: early HSCT at 24-months old and late HSCT at 30-years old. The utility values considered in the CEM are [redacted] for HSCT follow-up for a period of [redacted] around the HSCT procedure and [redacted] for HSCT recovery for a further [redacted]. These decrements were not used in the base-case analysis but only in a scenario analyses.

No decrement was considered for initial hospitalization in the CS. Wolman disease patients receive care in a hospital setting for 3.2-months from birth when they are in the investigation health state (HS1) and for one-month in the rescue care health state before death (HS2). For patients in HS1, the utility decrement due to parenteral nutrition was considered and this could also reflect the disutility of the initial hospitalisation. For patients in HS2, the patients' health utility was assumed to be the same as those in other health states, such as the stable state. However, this quality of life would be expected to be lower for patients who are in their last month of life. Adjusting the CEM for a lower health state utility would be expected to change the ICER. However, given this only applies to a very short period of time out of the total life course for those treated with sebelipase alfa the impact on the ICER would be small and hence the EAG will not make any adjustments for this. The EAG explored the effect of including a utitlty decrement for the rescue care heath state in the EAG sensitivity analysis. (See section 7.1.2.1)

5.1.13.3.2 Caregivers' disutilities

The data for the disutility related to the effect of infant death on caregivers/family members was obtained from Song *et al.*, 2010 which examined the long-term impact of child death on bereaved parents' HRQoL.[75] In a scenario analysis only, a utility decrement of 0.04 for family bereavement for a period of 65-years was included.

EAG comment: The majority of adverse reactions experienced are assumed to be minor and of short durations and so are not assigned any disutilities. No disutilities are assigned due to the burden of continuous care, although these may be reflected in the global HRQoL scores if these are considered to be less than the age and sex adjusted values for the general population, which is not the case for the CS base-case.

In Ballinger *et al*., 2018, eight health state vignettes were developed to value the number of days per week – from 0 to 7-days – on parenteral support in patients with short bowel syndrome and intestinal failure.[73] The longest duration on parenteral support is seven-days with a mean utility (SD) value of 0.26 (18) and was used in the CS.[2] Should parenteral support be needed for longer than this Ballinger *et al*., 2018 noted that more days on parenteral nutrition is associated with an increasingly negative impact on HRQoL.[73] This raises the question as to whether it is appropriate to use this value when children would receive parenteral nutrition for 98 days. This likely introduces a small bias against BSC, although it is unlikely to substantially affect the overall results.

A further concern is that as part of the costs component of the model it is possible to incur costs for either nasogastric tube feeding (NGT) or percutaneous endoscopic gastrostomy (PEG). However, no corresponding disutility is defined should these events occur either in the company base-case or scenario analyses.

Enteral tube feeding could impact patients' and caregivers' quality of life, particularly in the long-term. From the patient's perspective, physical functioning may be the most affected dimension. For instance,

a study by McFarland *et al.,* (2017), which investigated the cost-utility of a clinical algorithm for nasogastric tube placement confirmation in adults.[84] This study reported the health utility values associated with NGT when there were: no, mild, moderate, and severe complications. It revealed that nasogastric tube insertion had an impact on perceived health state values, even when no complication occurred.[84] According to CS, patients would have dietary restrictions, even with ERT. It was assumed that for the duration of 60-months feeding would be by NGT or PEG and that for 3.2 of months, patients would be hospitalised and receive parenteral nutrition. There is no evidence on the level of complication for this type of feeding in the CS. The EAG considered a utility decrement associated with nasogastric feeding for patients in states HS3 and HS4 in the EAG scenario analysis (see section 7.1.2.1). A scenario analysis reported in the CS included the impact of bereavement on parents/caregivers' HRQoL. The EAG consider this only a partial consideration of the spillover effects of disease on parents/caregivers' HRQoL as it does not include the impact of supporting a child with a serious chronic condition. The EAG consider that the inclusion of bereavement disutility and the exclusion of other impacts on parents/caregivers' HRQoL is likely a bias against BSC (see section 7.1.2.1). Disutility associated with parental spillover due to childhood conditions was obtained from Simon *et al.*, 2019 which estimated spillover disutility for having a child on ERT.[82]

5.1.14 Resources and costs

The CS has provided information on the identification, measurement and valuation of costs and healthcare resource use under section B.3.5 of the CS.[2] The information is summarized by each of the health states included in the model. The company also outlined whether these costs were applied to the comparator group (BSC); intervention group (sebelipase alfa) or both.

5.1.14.1 Intervention and comparator drug costs

Intervention costs:

The company included information about the full and patient access scheme (PAS) discounted cost associated with a single pack of sebelipase alfa (one 20 mg vial) (B.3.5.1.1.1, Table 40).[2] The PAS discounted cost was included in the economic model. The undiscounted pack cost was [redacted] and the PAS discounted cost was [redacted]. The company also included the cost for the administration of the drug at an outpatient setting based on the the cost of an outpatient appointment with a Paediatric Metabolic Disease Specialist sourced from the National Schedule of NHS Costs 2020/21 (Service code 261, currency code WF01A).[68]

A homecare service funded by the Company is provided to patients at four months after discharge from hospital admission. As this will not be an NHS incurred cost, the cost of delivering this service was not provided and it was not added to the base-case economic model.

The CS base-case analysis assumes that vials are for single use only irrespective of the proportion of the vial that may be wasted after administration. In order to reflect real-world practice the company conducted a sensitivity analysis that allows for a 2-week round-up vial consumption (Table B60 of CS, scenario 15).[2] Under this scenario the ICER decreased from £239,608 to £224,458.

EAG comment: The company stated that the homecare service funded by Alexion for the administration of sebelipase alfa will continue to be provided to patients once they have been discharged from hospital (B.3.5.1.1.2 of the CS).[2] The company affirmed that the potential re-imbursement of sebelipase alfa would have no impact on the configuration of their homecare service (B.3.5.4 of the CS).[2] The rationale for the exclusion of this cost from the economic model is that the cost for this service will be absorbed by Alexion and will not fall on the payer/NHS. The EAG requested details for inclusion

of the homecare service cost of sebelipase alfa administration as funded by the company and not included in the analysis. In response to question B5 in the PfC[25] the company stated that "*there is no plan to withdraw this service*" and provide homecare for all patients receiving their specialist products (e.g., NICE HST1, eculizumab for treating atypical haemolytic uraemic syndrome).[25]

The company provided a scenario analysis exploring the effect on the cost-effectiveness results of switching the provision of their homecare service to the NHS (B.3.10.3 of the CS).[2] In this case, the homecare service would be provided by a community nurse costed for one hour of patient-related work, including qualifications (HST for Gaucher Type 1) mid-point Band 8AD. The results of this scenario analysis are outlined in Table B60 of CS (scenario16).[2] Under this scenario the ICER increased from £239,608 in the CS base-case analysis to £242,560. The EAG considers this is a reasonable assumption. The EAG has included the provision of homecare service "*no homecare service*" scenario on this basis as part of their base-case analysis (section 7.1.2.1).

The EAG notes that the company's base-case analysis includes the use of single-dose vials with an additional sensitivity analysis which takes into account a 2-week round up vial consumption (Table B60 of CS scenario 15). As the company acknowledges that "*real-world practice is to modulate dose within a two-week cycle in order to reduce waste and the vial requirement*" (Section B.3.5.1.1.2 of CS),[2] the EAG has included the 2-week round-up vial consumption option as part of their scenario analysis (section 7.1.2.1).

Healthcare resource use associated with each health state:

Health state 1 - Investigation: The first health state included in the model incorporates the costs associated with the investigation and initial care of infants with Wolman disease from birth. The company assumed that patients would have received a total of 10-weeks of Neonatal Critical Care, see Table 5.13 (4-weeks in the intensive care unit (ICU); 4-weeks in a high dependency unit (HDU) and 6-weeks in the General Ward) (B.3.5.2, Table 42 of the CS).[2] The costs for in-patient stays at each ward (see Table 5.14) has been sourced from the National Schedule of NHS costs 2020/21 (Table 41 in the CS).[68] No other costs have been added to this health state.

Table 5.13: Unit cost of neonatal critical care

Resource	HRG currency code	Unit cost, 2020/21	Unit cost, 2022
Neonatal Critical Care, Intensive Care [ICU day]	XA01Z	£1,816.33	£1,853.86
Neonatal Critical Care, High Dependency [HDU day]	XA02Z	£1,243.00	£1,268.68
Neonatal Critical Care, Normal Care [General ward day]	XA05Z	£769.19	£785.08

Source: Table 41 from the CS[2]
Notes: Sourced from the National Schedule of NHS Costs 2020/21.[68] The 2022 unit cost is an inflation from the source cost using the CPIH Index 06: Health 2015 = 100 (Multiplier 1.02).[85]
Abbreviations: CPIH, Consumer Prices Index including owner occupiers' housing costs; CS, company submission; HDU, high dependency unit; HRG, Healthcare Resource Groups; ICU, intensive care unit; NHS, National Health Service.

Table 5.14: Duration of neo-natal critical care

Resource	Duration (weeks)	Source

Neonatal Critical Care, Intensive Care [ICU day]	4	Clinical expert opinion
Neonatal Critical Care, High Dependency [HDU day]	4	
Neonatal Critical Care, Normal Care [General ward day]	6	

Source: Table 42 from the CS[2]
Abbreviations: CS, company submission; ICU, intensive care unit; HDU, high dependency unit; NHS, National Health Service.

Health state 2 – Rescue Care: This stage includes costs associated with end-of-life care provided for a month prior to Wolman-related death. This is equivalent to a one-month stay (30.44-days) at the Neonatal ICU (XA01Z – weighted average – neonatal critical care stays in ICU). This cost was sourced from the National Schedule of NHS costs 2020/21 (see Table 5.13).[68] No other costs have been added to this health state.

Health state 3 – Trial follow-up: The Company provided a table (Table 43 in the CS) outlining the healthcare resource use associated with physician and dietician monitoring for this population group for the first 5-years (see Table 5.15).[2] These costs included blood tests, dietician visits, magnetic resonance imaging (MRI), ultrasound, and neonatal critical care. Specialist nutrition has been added to this stage. The costs associated with the out-patient administration of sebelipase alfa stops at month 3 in the CEM. From this point on, sebelipase alfa is administered by the Alexion homecare service with no costs incurred by the NHS. Table 5.15 – Rate of resource consumption in the first 5-years (Table 43 from CS).[2]

Table 5.15: Rate of resource consumption in the first 5-years

Resource per cycle	Proportion	Age 0–1	Age 1–2	Age 2–3	Age 3–5
Paediatric metabolic physician monitoring	1	0[a]	0[a]	0.29	0.29
Dietician visits	1	2	1	1	1
Laboratory tests	1	0.33	0.33	0.33	0.33
Abdominal magnetic resonance imaging	0.5	0.08	0.08	0.08	0.08
Abdominal ultrasound	0.5	0.08	0.08	0.08	0.08
Admission (5-days)	1	0.17	0.17	0.17	0

Source: Table 43 from CS[2] including clinical expert opinion[83]
Note: a, Metabolic monitoring is part of sebelipase alfa administration in the first 2-years, so is not applied again here.
Abbreviations: CS, company submission.

Health state 4 – Stable: At this stage, physician and dietician monitoring continues from 5-years until loss of venous access occurs. The rate of resource consumption is outlined in Table 45 of the CS (see Table 5.16).[2] Loss of venous access would lead to a transition to HSCT as rescue (late HSCT). Costs for specialist nutrition have been added to this stage. Specialist nutrition may be consumed orally, parentally, by nasogastric tube or gastrostomy. The company states that information on costs relating to specialist nutrition has been provided by The Birmingham Women's and Children's NHS Foundation Trust dietetic service.[2] Unit costs for specialist nutrition has been provided by the company (Table 48 of the CS).[2] The EAG has not been able to verify the accuracy of this costing information. Sebelipase

alfa is administered by the Alexion homecare service with no costs incurred by the NHS. See Table 5.17, below.

Table 5.16: Rate of resource consumption after the first 5-years

Resource per cycle	Proportion	Age 5+ years
Paediatric metabolic physician monitoring	1	0.29
Dietician visits	1	1
Laboratory tests	1	0.17
Abdominal magnetic resonance imaging.	0.5	0.08
Abdominal ultrasound	0.5	0.08
Source: Table 45 from CS[2] including clinical expert opinion[83] Abbreviations: CS, company submission.		

Table 5.17: Cost of specialist nutrition

Route of administration and period of administration	Unit cost per day	Proportion requiring specialist nutrition	Duration
Parenteral IV infusion	£43.45	100%	3.22 months
Nasogastric tube (NGT) or gastrostomy (PEG)			
First year	£42.44	100%	60-months
Second year	£38.33	100%	
Subsequent years	£45.17	100%	
Oral	£43.81		Life
Source: Table 48 from CS[2] Notes: a, The UK Stem Cell Strategy Oversight Committee report estimates costs in 2012/2013 GPB so these costs have been calculated in 2022 GBP using the CPIH index[85] Abbreviations: CPIH, Consumer Prices Index including owner occupiers' housing costs; CS, company submission; GBP, Great British Pounds; HSCT, haematopoietic stem cell transplant; IV, intravenous; NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy			

EAG Comment: The costs for specialist nutrition have been provided by the company (Table 5.17 of this report and table 48 of the CS).[2] In their CS, the company stated that the cost of modular nutrition when parentally administered was advised by Birmingham Women's and Children's NHS Foundation Trust dietetic service. Per day costs were applied as presented in Table 48 of CS. The EAG notes that the reference provided by the company in Table 5.17 does not agree with the source quoted in the CS (Section B.3.5.2). The EAG has not been able to verify the accuracy of this costing information. The EAG notes that the company explored the uncertainty surrounding the cost of specialist nutrition in their scenario analysis (Table B60, scenario 33). Under this scenario the ICER decreased from £239,608 in the CS base-case analysis to £221,273.

Health state 4 – Stable: Only those in the sebelipase alfa cohort transition to HS4. This stage begins at month 61 in the CEM. Resource cost categories remain the same to those outlined for patients aged 3-5-years during health state 3 until loss of venous access prompts a transition to HSCT (health state 5). Changes in the rate of consumption of these resources decreases during this stage leading to a lower cost associated with resource use overall.

Health state 5 – HSCT: The company states that patients transitioning to this stage will be in receipt of two periods of 2-month courses of immunomodulation therapy followed by allogeneic HSCT. Discontinuation of sebelipase alfa is assumed to happen 18-months after HSCT. The company applied follow-up costs for 24-months. Information for these costs was gathered from UK Stem Cell Strategy Oversight Committee report[86] from November 2014 and inflated to 2022 GBP using the CPIH. The consumption of healthcare professional time (physician and dietician monitoring), laboratory and radiological tests and specialist nutrition, continued during this stage.

All costs variables included in the company's base-case analysis are outlined in Table 5.18.

Table 5.18: Cost variables used in base-case with unit cost sources

Variables used in the base-case	Value (£)	Unit cost source	EAG Comments
Cost per day of initial hospitalization: ICU	1816	National Schedule of NHS Costs 2020/21 (XA01Z)	Unit costs checked
Cost per day of initial hospitalization: HDU	1243	National Schedule of NHS Costs 2020/21 (XA02Z)	Unit costs checked
Cost per day of initial hospitalization: General ward	769	National Schedule of NHS Costs 2020/21 (XA05Z)	Unit costs checked
Cost per day of intensive care	1816	National Schedule of NHS Costs 2020/21 (XA01Z)	Unit costs checked
Cost per visit of paediatric metabolic disease physician	566	National Schedule of NHS Costs 2020-2021 (Service code 261, currency code WF01A)	EAG found discrepancy in unit cost; it should read "Unit costs is £625.24"
Cost per visit of dietician	79	National Schedule of NHS Costs 2020-2021 (WF02A)	Unit costs checked
Cost per day of parenteral nutrition	43.45	Birmingham Women's and Children's NHS Foundation Trust dietetic service	EAG unable to verify costs
Cost per day of nasogastric feeding, year 1	42.44	Birmingham Women's and Children's NHS Foundation Trust dietetic service	EAG unable to verify costs
Cost per day of nasogastric feeding, year 2	38.33	Birmingham Women's and Children's NHS Foundation Trust dietetic service	EAG unable to verify costs
Cost per day of nasogastric feeding, year 3 onwards	45.17	Birmingham Women's and Children's NHS Foundation Trust dietetic service	EAG unable to verify costs
Cost per day of oral nutrition	43.81	Birmingham Women's and Children's NHS Foundation Trust dietetic service	EAG unable to verify costs
Cost of HSCT	139123	National Schedule of NHS Costs 2020-2021 (SA20B; SA21B; SA22B; SA23B; SA38B; SA39B; SA40Z; SA18Z and SA34Z)	Unit costs checked. Weighted average cost of HSCT using codes:(SA20B; SA21B; SA22B; SA23B; SA38B; SA39B; SA40Z; SA18Z and SA34Z)

Cost of Bone Marrow Transplant, Allogeneic Graft (Sibling), 18-years and under	89628	National Schedule of NHS Costs 2020-2021 (SA20B)	Unit costs checked
Cost of Bone Marrow Transplant, Allogeneic Graft (Volunteer Unrelated Donor), 18-years and under	111945	National Schedule of NHS Costs 2020-2021 (SA21B)	Unit costs checked
Cost of Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 18-years and under	142066	National Schedule of NHS Costs 2020-2021 (SA22B)	Unit costs checked
Cost of Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18-years and under	58854	National Schedule of NHS Costs 2020-2021 (SA23B)	Unit costs checked
Cost of Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 18-years and under	77209	National Schedule of NHS Costs 2020-2021 (SA38B)	Unit costs checked
Cost of Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 18-years and under	101474	National Schedule of NHS Costs 2020-2021 (SA39B)	Unit costs checked
Cost of Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified)	62931	National Schedule of NHS Costs 2020-2021 (SA40Z)	Unit costs checked
Cost of Bone Marrow Harvest	4774	National Schedule of NHS Costs 2020-2021 (SA18Z)	Unit costs checked
Cost of Peripheral Blood Stem Cell Harvest	7545	National Schedule of NHS Costs 2020-2021 (SA34Z)	Unit costs checked
Cost of 0–6-months follow-up post HSCT	25551	UK Stem Cell Strategy Oversight Committee report	EAG unable to verify costs as not enough details on the methodology applied by the UK Stem Cell Strategy Oversight Committee are included in the report
Cost of 6–12-months follow-up post HSCT	9361	UK Stem Cell Strategy Oversight Committee report	EAG unable to verify costs as not enough details on the methodology applied by the UK Stem Cell Strategy Oversight Committee are included in the report
Cost of 12–24-months follow-up post HSCT	4363	UK Stem Cell Strategy Oversight Committee report	EAG unable to verify costs as not enough details on the methodology

			applied by the UK Stem Cell Strategy Oversight Committee are included in the report
Cost of Magnetic Resonance Imaging Scan of One Area, without Contrast, 19-years and over	246	National Schedule of NHS Costs 2020-2021 (RD01A)	Unit costs checked
Cost of Magnetic Resonance Imaging Scan of One Area, without Contrast, between 6 and 18-years	268	National Schedule of NHS Costs 2020-2021 (RD01B)	Unit costs checked
Cost of Magnetic Resonance Imaging Scan of One Area, without Contrast, 5-years and under	276	National Schedule of NHS Costs 2020-2021 (RD01C)	Unit costs checked
Cost of Magnetic Resonance Imaging Scan of Two or Three Areas, without Contrast	221	National Schedule of NHS Costs 2020-2021 (RD04C)	Unit costs checked
Cost of Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning	313	National Schedule of NHS Costs 2020-2021 (RD07C)	Unit costs checked
Cost of Ultrasound Scan with duration of less than 20-minutes, without Contrast	70	National Schedule of NHS Costs 2020-2021 (RD40Z)	Unit costs checked
Cost of Ultrasound Scan with duration of less than 20-minutes, with Contrast	131	National Schedule of NHS Costs 2020-2021 (RD50Z)	Unit costs checked
Cost of blood test, haematology	4	National Schedule of NHS Costs 2020-2021 (DAPS05)	Unit costs checked
Cost of blood test, clinical biochemistry	2	National Schedule of NHS Costs 2020-2021 (DAPS05)	Unit costs checked

Source: Table B51 of CS (amended to show CS unit costs and EAG comments)[2]

References: National Schedule of NHS Costs 2020-2021;[68] UK Stem Cell Strategy Oversight Committee report[86]

Abbreviations: CS, Company Submission; EAG; Evidence Assessment Group, HDU, high dependency unit; HSCT, Haematopoietic stem cell transplant; ICU, Intensive care unit; NHS, National Health Service

EAG comment: The company states that the base-case analysis is in alignment with the NICE reference case, taking the payer perspective of the UK NHS setting (section B.3.22 Page 109).[2,4] However, the EAG notes the following issues:

The resource use included in the company model seems to be largely restricted to the tertiary setting. Healthcare services received in the community or a primary care setting have not been considered as part of the CEM except for the sensitivity analysis (Table B60 of CS – scenario 16)[2] which includes the home administration of sebelipase alfa by a community nurse (Band 8A-D). The EAG notes that the company could consider the potential costs incurred by the NHS in all settings (primary & community care, secondary care, tertiary care). However, the company's response to the EAG question B6 in PfC about the exclusion of resource use of care services received in a primary care setting and personal social service care costs was that the cost relating to sebelipase alfa treatment in people with rapidly progressive LAL-D come from specialised NHS service and were not expected to spill into primary care or social care.[25] The EAG checked with a clinical expert who confirmed that this patient group may use primary care on occasions but would usually be tertiary care as first point of call and secondary in an emergency. The clinical expert added that access to education and any extra help may also be required. Consequently, the EAG notes that it is reasonable to assume that patients affected by Wolman disease may also need to access primary and social care services and this could have been explored further by the company in order to fully meet the requirement to take an NHS and PSS perspective set in the scope.[1]

The company assumed that the cost of sebelipase alfa administration in the outpatient setting was equal to the cost of a paediatric metabolic disease specialist. When the EAG consulted a clinical expert to determine whether or not this assumption was reasonable, our clinical expert disagreed with this assumption. According to our clinical expert, administration costs will include the cost day case bed with a doctor or senior nurse who will be present during infusion within the first few months of starting and establishing infusion rates and drug reactions, which will be considerably more expensive than the metabolic disease specialist. The EAG has explored the impact of this in its sensitivity analyses (see section 7.1.2.1).

Adverse events and other outcomes measures are listed in the CS (see section B.3.2.2.3 of the CS) but not considered by the company in the economic model.[2] For example, liver disease; liver transplant; impaired liver and adrenal gland function; and cardiovascular events may have a significant impact in the level of healthcare resource for this patient group over their lifetime. The EAG required further clarification in the PfC (question B5) on why the costs relating to other healthcare use and concomitant medication use associated with any adverse events or co-morbidities typical of this population group had not been included in the company's model. The company responded that "*Resources described in CS section B.3.5 do include costs relating to specialised care for co-morbidities, as part of disease management (CS section B.3.5.2 Table 43 before age 5, Table 45 after age 5). Furthermore, the cost of specialist nutrition is included in the base-case, an indirect cost consequent to the life-sustaining treatment of sebelipase alpha*".[25] The EAG notes the following:

- Although the costs described in Tables 43 and 45 of the CS[2] cover some of the costs associated with Wolman disease, these are confined to physician and dietetic monitoring, blood tests, magnetic resonance imaging (MRI), ultrasound, and neonatal critical care. Costs associated with the potential adverse events/co-morbidities such as those mentioned by the EAG and included in the NICE scope[1] remain excluded.
- There is evidence that patients (infants and adults) with less rapidly progressive presentation of LAL-D, often referred to as Cholesteryl Ester Storage Disease (CESD) are affected by co-morbidities such as hepatomegaly, splenomegaly, liver fibrosis, liver cirrhosis, liver transplant, premature atherosclerosis, premature cardiac events.[69] The EAG notes that 1) the economic model should have considered the probability of these outcomes affecting the population with

Wolman disease (included in this evaluation) and 2) the costs associated with the management of these outcomes.

The company also provided further commentary on their response to question B5 in PfC. The exclusion of adverse events was further justified by the insensitivity of ICER for the change in utility from treatment adverse events (TEAEs) with sebelipase alfa.[25] In response to EAG clarification point the company reported that "*Most IARs are understood to have only a very temporary impact on HRQoL and are successfully managed by infusion interruption/discontinuation, infusion-rate reduction and/or conventional treatment with antihistamines, corticosteroids, analgesics or antipyretics.*".[25] However, the EAG believes the impact of TEAE on costs (as well as utilities) should have been included at least in sensitivity analyses.

The company has provided details of the HSCT follow-up costs applied for 24-months (Table 47 from CS and Table 5.18 in this report).[2] The costs have been gathered from a UK Stem Cell Strategy Oversight Committee report from November 2014. The EAG notes that:

- The UK Stem Cell Strategy Oversight Committee report[86] does not offer enough detail about their methodology to enable us to replicate the results
- The committee's figures are based on a study which includes Dutch adult patients receiving a stem cell transplant in the Netherlands between 1994 and 1999[87]
- The patients from the study have acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) and they do not include patients with LAL deficiency or Wolman disease
- The company has explored the uncertainty surrounding HSCT costs in their sensitivity analysis (Table B60 of CS)[2] by including a scenario which increases all HSCT costs (including follow-up) up by 20%. Under this scenario the ICER increased from £239,608 in the CS base-case analysis to £240,531.

5.1.15 Summary of company assumptions applied in base-case analysis

Table 5.19 shows a summary of the key assumptions used in the CEM base-case analysis.

Table 5.19: Company economic model assumptions

Assumption	Justification
HRQoL is assumed equal to general-population quality of life; and for ages 0-15-years this is approximated to age 16-years.	There is a lack of evidence to inform population specific values. However, some support for general population HRQoL comes from the single study identified in a systematic search.[20] This ten-year follow-up of 5 cases in France evaluated paediatric HRQoL using the PedsQL inventory questionnaire. Scores were acceptable or high globally and across all four-dimensional scales. Further, authors concluded that sebelipase alfa allowed near normal bio-clinical and growth parameters.
No long-term LAL-D related mortality. After the 5-year follow-up period of LAL-CL03 and LAL-CL08, there could be no LAL-D related mortality.	LAL-D related survival in the model is informed by the LAL-CL03 and LAL-CL08 trials of sebelipase alfa, within which the last recorded LAL-D attributed death was before age 18-months. The larger ALX-LAL-D-5001 global registry (N=29; 7 UK patients) recorded a total of two deaths over up to 11-years follow-up. The second event occurred at 3.5-years from sebelipase alfa treatment initiation. Expert clinical opinion supported the assumption of no LAL-D related mortality after 5-years.

Assumption	Justification
Sebelipase alfa dosing is based on expert clinical opinion.	Survival in the model was based on the LAL-CL03 and LAL-CL08 trials, however, their design had a dose finding element, follow-up was limited to 5-years, and they completed in 2018. The expert opinion of clinicians with experience of these trials and with cases since is the favoured source for informing dose requirement, both for the age range included in trials as well as older ages.
HSCT is not a rescue therapy in BSC (untreated patients).	Based on Potter *et al.*, 2021, HSCT is unlikely to be successful in the highly morbid states associated with untreated rapidly progressive LAL-D.[3]
HSCT cannot be received twice.	Expert clinical opinion.
Loss of venous access in early life recipients of HSCT results in LAL-D-related death.	Demaret *et al.*, 2021[20] report challenging venous access in a participant of LAL-CL-03, who required 6 central venous access devices because of device infection or failure. Expert clinical opinion from the UK supports the use of HSCT for cases of venous access difficulty, reporting an example of rescue HSCT for this reason.
HSCT is the rescue option for loss of venous access in later life. Sebelipase alfa is discontinued thereafter, and mortality is unaffected.	This is a predicted challenge for patients with rapidly progressive LAL-D who have been administered ERT every week since birth. Over 1,500 infusions are anticipated by the 30th birthday. The assumption of serious difficulty with venous access which would interfere with ERT administration is supported by expert clinical opinion. Presently the only clinical option when faced with potential disruption of treatment is HSCT. No patient with rapidly progressive LAL-D has yet reached teenage years so no direct evidence exists to support his assumption, nor is there existing equivalent QW IV administered ERT treatment from which long-term experience can be taken.
HSCT in later life is modelled as occurring at a fixed time for all eligible patients; age 30-years.	In the absence of evidence from which an age at IV loss (treatment duration until IV loss) can be estimated, expert clinical opinion is the preferred source.

Source: Table B52 in the CS[2]

Abbreviations: BSC, best supportive care; CS, company submission; ERT, enzyme replacement therapy; HRQoL, health related quality of life; HSCT, haematopoietic stem cell transplant; IV, intravenous; LAL-D, lysosomal acid lipase deficiency; PedsQL, Pediatric Quality of Life Inventory questionnaire; QW, once a week; UK, United Kingdom

6 COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

The company base-case results are summarised with the PAS discount in Table 6.1. The company discounted future benefits and costs at 1.5% in their base-case analysis. Sebelipase alfa accrued [redacted] extra QALYs compared to BSC at an additional cost of [redacted]. This corresponds to an incremental cost per QALY gained of £239,608. Also reported in Table 6.1 is the impact of discounting costs and QALYs at 3.5% per annum. Sebelipase alfa gained [redacted] incremental QALYs compared to BSC at an additional cost of [redacted] which corresponds to an incremental cost per QALY gained of £308,078. The impact of adopting a 0% discount rate is also shown in Table 6.1. Here sebelipase alfa incurred an additional cost of [redacted] and provided [redacted] more QALYs, which corresponded to an incremental cost per QALY gained of £180,397.

The company also comment on the calculation and application of the decision modifier. They state that the undiscounted QALY gain of [redacted] was greater than 30 QALYs gained per patient using the lifetime horizon and as such a weight of 3.0 should apply increasing the willingness-to-pay (WTP) threshold to £300,000 per QALY gained for a highly specialised technology.

EAG comment: The results presented in Table 6.1, illustrate the very low costs and QALYs associated with BSC. In the CS base-case analysis, the life-time costs associated with BSC are just [redacted]% of the lifetime costs of sebelipase alfa. The corresponding figure for QALYs is [redacted]%. Increasing the discount rate increased the ICER and decreasing the discount rate reduced the ICER. This illustrates the comparatively greater effect changes in QALYs has relative to changes in cost on the ICER. The EAG consider it a matter of judgement as to whether the disease modifier of 3.0 should be applied (and hence the WTP threshold per QALY should be £300,000 or the standard £100,000). The EAG explore alternative scenarios in section 7 and comment further there on their finding relative to the different WTP thresholds and the gain in QALYs.

Table 6.1: Base-case results (deterministic) discounted at 1.5% and alternative assumptions about the discount rate

Analysis	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base-case analysis (discount rate 1.5%[a]	BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
	Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
Costs and QALYs discounted at 3.5%[b]	BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
	Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,078
Cost and QALYs undiscounted[c]	BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
	Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180,397

a Source: Table 53 in CS[2]
b Source: CS Table 55[2]
c Source: Table 57 in the CS[2]
Abbreviations: BSC, best supportive care; CS, company submission; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.

6.2 Company`s sensitivity analysis

The company used both probabilistic and deterministic sensitivity analyses to characterise and explore parameter and structural uncertainty in their analyses.

6.2.1 Probabilistic sensitivity analysis

The company's probabilistic sensitivity analysis (PSA) was based on sampling 1000 times from individual probability density functions. When the company could not establish standard errors from the data source used it was assumed that the standard error was equal to 20%.

The base-case probabilistic results using the PAS cost sebelipase alfa are shown in Table 6.2 with their accompanying 95% credible intervals. Sebelipase alfa was more costly with an additional cost of [redacted] (95% CI [redacted]). This additional cost was accompanied by additional QALYs with sebelipase alfa gaining [redacted] QALYs compared with BSC (95% CI [redacted]). The company reported the incremental cost per QALY gained to be £239,518 (95% CI £233,289 to £246,466).

Table 6.2: Base-case probabilistic results discounted at 1.5%

Technologies	Total costs (£) [95% CI]	Total QALYs [95% CI]	Incremental costs (£) [95% CI]	Incremental QALYs [95% CI]	ICER versus baseline (£/QALY) [95% CI]
BSC	[redacted]	[redacted]	-	-	-
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,518 [£233,289 to £246,466]

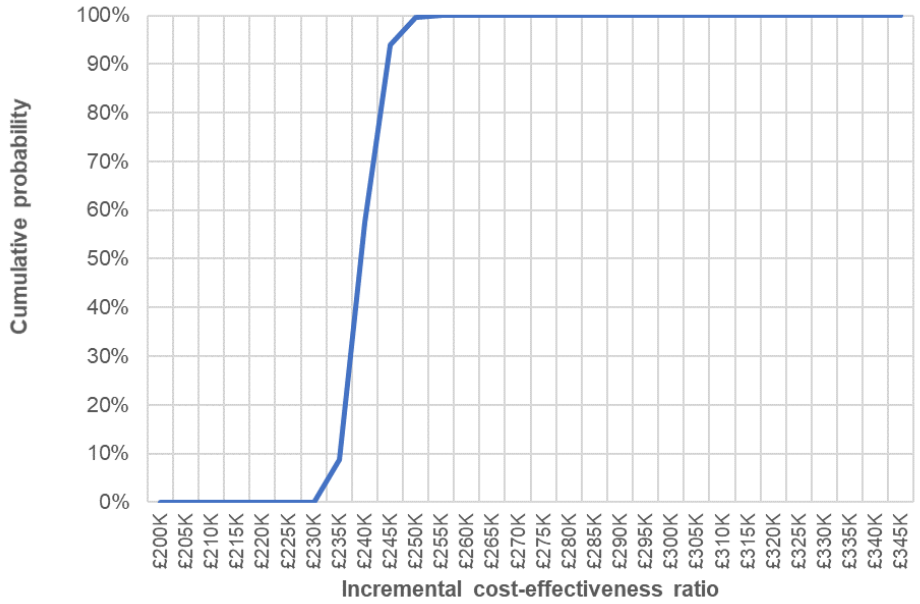
Source: Table 53 from the CS[2]
Note: Costs and QALYs are discounted at 1.5% per annum.
Abbreviations: BSC, best supportive care; CI, confidence interval; CS, Company submission: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

The accompanying cost effectiveness plane is shown in Figure 6.1 and the corresponding cost effectiveness acceptability curve is shown in Figure 6.2. As Figure 6.2 shows, sebelipase alfa has a 0% probability of being cost effective below an ICER of approximately £230,000. Thereafter, its probability rises to 100% once the ICER is approximately £250,000.

Figure 6.1: Cost effectiveness plane

Source: Figure 28 from the CS[2]
Abbreviations: CS, company submission; GBP, Great British Pounds; QALYs, quality adjusted life years.

Figure 6.2: Cost effectiveness acceptability curve



Source: Figure 29 from the CS[2]
Abbreviations: CS, company submission.

EAG comment: The result of the probabilistic analysis are similar to the base-case results reported in Table 6.1. The costs of BSC reduce slightly and the QALYs slightly increase. There is a similar pattern for sebelipase alfa with the net effect being that the ICER is virtually unchanged.

6.2.2 Deterministic analysis

The company decided not to conduct a one-way deterministic sensitivity analysis. The company justified this decision because the ICER was more sensitive to known parameters and assumptions. Therefore, the company felt it more important to assess the impact of these on the ICER in scenario analyses (Table 6.3 and the Tornado diagram depicted in Figure 6.3).

6.2.2.1 Alternative use of HSCT

The company conducted several analyses to assess the impact of alternative use of HSCT on the cost effectiveness results. In the scenario analysis, the company varied the use of HSCT by altering the following:

- The proportion of people receiving early HSCT (scenarios 9-11, Table 6.3)
- The proportion of people receiving dose reduction after HSCT (scenarios 26, Table 6.3)
- The proportion of people who discontinue sebelipase alfa treatment after HSCT (scenario 12, Table 6.3)

In the CS base-case analysis it was assumed that [redacted] of patients treated with sebelipase alfa would receive HSCT at 24-months, six months later, the dosage of the intervention will decrease, and treatment of sebelipase alfa will be discontinued at 42-months. When the proportion of patients receiving HSCT at 24-months was reduced to 50% (scenario 9), QALYs slightly decreased compared to the base-case analysis but costs substantially increased due to more people receiving sebelipase alfa for a longer period and consequently the ICER increased to £394,538. Correspondingly, a much larger increase in the ICER was observed when no patients had early HSCT (scenario 11). Here the ICER was £656,664. When it was assumed that all patients received early HSCT (scenario 10) the ICER reduced to £63,794. When it was assumed that only 50% of patients discontinued sebelipase alfa after HSCT (the CS base-case analysis assumed 100%) the ICER increased to £562,225.

Changing the proportion of patients that receive a dose reduction after starting HSCT was explored in scenario analysis (scenario 26). In the CS base-case analysis, 100% of patients had a dose reduction after early HSCT. Halving the proportion of patients who had a dose reduction after early HSCT increases costs considerably compared to the base-case due to more people receiving a higher dose sebelipase alfa whilst QALYs decreased slightly resulting in an increased ICER of £686,352.

In the CS base-case analysis patients did not have a dose reduction of sebelipase alfa at the age of 18-years. When the company assumed that 20% of patients had a dose reduction at age 18-years, (scenario 25), the QALYs did not change in comparison to the base-case. In this scenario, the costs increased compared to the base-case resulting in an increased ICER of £271,516.

The ICER was sensitive to venous access in later life. The age at which late HSCT would be required because of venous access failure was also explored with ages of 20 and 40-years explored (scenarios 24 and 23, respectively) and venous access never failing (scenario 13). Reducing the age of venous access failure reduced the ICER to £187,641 and increasing the age increased the ICER to £284,115. When it was assumed that venous access never failed the ICER increased to £408,641.

6.2.2.2 Alternative parametric overall survival models

Parametric distributions for the overall survival extrapolation were explored. The company explored the exponential, Weibull, Gompertz, and log-normal models in scenario analyses (scenarios 2-5). All the parametric distributions resulted in higher ICERs than the base-case analysis (Table 6.3). The log-normal model was the parametric distribution which resulted in the highest ICER (£335,369). The

ICERs were approximately £25,000-30,000 higher than the base-case analysis when the exponential, Weibull and Gompertz distributions were used. However, when these distributions were used both the incremental costs and QALYs were notably much lower than the base-case analysis.

The log-logistic and the Gamma model were not included in the scenario analysis despite Gamma having the highest AIC Rank and BIC Rank compared to the other parametric distributions. The company did not justify this.

6.2.2.3 Alternative acquisition costs of sebelipase alfa

The CS reports that the ICER was sensitive to changing alternative scenarios that impacted the total cost of acquiring sebelipase alfa through the time horizons tested. The company altered the cost of acquiring sebelipase alfa by exploring scenarios where there is a patient-level cap (scenario 21) and where there is a change in intellectual property and thus more price competition (scenario 30). Both scenarios lower the costs of sebelipase alfa and therefore reduce the ICER to £208,134 and £145,355, respectively, relative to the base-case analysis (Table 6.3).

The CS also considered the impact of changes in the discount rate as a mechanism for changing the costs of sebelipase alfa (scenarios 17-19). Increasing the discount rate (scenarios 18-19) from the 1.5% used in the base-case analysis did indeed reduce the life-time costs of sebelipase alfa but also reduced QALYs. The net impact is that as the discount rate increases the ICER increases (Table 6.3 and see also Table 6.1). The ICER was considerably lower than the base-case in scenario 17, where the discount rate is 0.0%. The company use of a discount rate of 1.5% was justified in the CS because treatment with sebelipase alfa was assumed, based upon the modelling assumptions adopted, to restore people who would otherwise die to full or near total health, and this is sustained over a long period. The discount rate recommended by the NICE reference case was 3.5%.[4]

6.2.2.4 Alternative scenarios insensitive to ICER

The CS reported that the ICER was relatively insensitive to alternative approaches to estimating utilities (scenarios 6, 28, 29, 31, 32), sebelipase alfa treatment compliance (scenario 7), drug administration cost (scenarios 14-16, 22), costs of specialist nutrition (scenario 33) and changes to any cause mortality (scenarios 27, 29).

Figure 6.3: Tornado diagram of key alternative inputs (with PAS)

Source: Figure 30 from the CS[2]
Abbreviations: ADA, anti-drug antibody; CS, company submission; HR, hazard ratio; HRQoL, health related quality of life; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost effectiveness ratio; kg, kilogram; mg, milligram; PAS, patient access scheme; QALY, quality adjusted life year; SA, sebelipase alfa; VAS, visual analogue scale.

Table 6.3: Results of scenario analyses

Analysis	Sensitivity analysis		Costs			QALYs			ICER
		Original value	SA	BSC	Incremental	SA	BSC	Incremental	
1	Base-case	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
2	Predicted survival - exponential	K-M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£266,462
3	Predicted survival - Weibull	K-M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£268,215
4	Predicted survival - Gompertz	K-M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£269,300
5	Predicted survival - log-normal	K-M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£335,369
6	HRQoL = EQ-5D VAS	EQ-5D TTO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£238,595
7	100% SA compliance	0.96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£248,469
8	No death after loss of venous access without HSCT	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£237,287
9	Only 50% of patients have early HSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£394,538 £63,794
10	All patients have early HSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
11	No patients have early HSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£656,664
12	Only 50% discontinue SA after HSCT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£563,225
13	Venous access never fails	Age 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£408,641

14	Cost HSCT 20% higher	139123.1992	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£240,531
15	2-week round-up vial consumption	1-week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£224,458
16	No homecare service	Included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242,560
17	Cost & QALY discount rate = 0.0%	0.015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180,397
18	Cost & QALY discount rate = 3.5%	0.015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,078
19	Cost & QALY discount rate = 5.0%	0.015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£346,459
20	Horizon = 6-years	Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£415,975
21	SA patient cost cap at [redacted] pa	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£208,134
22	Patients who don't receive HSCT (No ADAs) increase to 5mg/kg	0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£296,679
23	Venous access loss at 40-years of age	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£284,115
24	Venous access loss at 20-years of age	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£187,641
25	20% have dose reduction at age 18	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£271,516
26	Only 50% have dose reduction after early HSCT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£686,352

27	20% hazard ratio applied to other cause mortality	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£241,826
28	10% reduction in HRQoL all ages	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£251,323
29	10% decrease HRQoL & 20% HR on other cause mortality	No hazard ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£253,651
30	Lifecycle price - one-third lower SA price after 10-years	Static price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£145,355
31	Family bereavement disutility included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£230,490
32	HSCT procedure and recovery disutility	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£255,359
33	Specialist nutrition excluded	Included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£221,273
34	Economic productivity included	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£149,072

Source: Source: Table B60 of CS (amended to correct typo in scenario analysis 23, age changed from 30-years to 40-years)[2]
Abbreviations: ADA, anti-drug antibody; BSC, best supportive care; CS, company submission; HRQoL. health-related quality of life; HR, hazard ratio; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost effectiveness ratio; kg, kilogram; K-M, Kaplan-Meier; mg, milligram; QALYs, quality-adjusted life years; SA, sebelipase alfa; TTO, time trade-off; VAS, visual analogue score.

EAG comment: The CS clearly illustrated that the assumptions surrounding how long sebelipase alfa would be used for were important determinants of the ICER. Changing assumptions that led to more sebelipase alfa being used substantially increased the ICER. This is important as the evidence base available around for example when HSCT is started is sparse. A further critical assumption was around the choice of discount rate. Adopting a higher discount rate reduced both total costs and total QALYs but the effect was proportionally greater on QALYs and hence the ICERs increased (see also section **Error! Reference source not found.** below).

6.3 Benefits outside of the NICE methods reference case

The company provided three scenario analyses by assessing the impact of economic productivity and bereavement separately and together, which led to a reduction in ICERs as compared with the base-case analysis (Table 6.4).

Table 6.4: Decision modifiers

Scenario	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Base-case	[redacted]	[redacted]	£239,608
Inclusion of family health spill-over (bereavement) (A) (scenario 31, Table 6.3)	[redacted]	[redacted]	£230,490
Inclusion of productivity gains (B) (scenario 34, Table 6.3)	[redacted]	[redacted]	£149,072
(A) and (B)	[redacted]	[redacted]	£143,400

Source: reproduced from Table 61 in the CS[2]
Note: Costs and QALYs are discounted at 1.5% per annum.
Abbreviations: CS, company submission; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years.

EAG Comment: According to the NICE methods guide (PMG36), the Committee will consider the wider benefits of the new technology outside of the reference case with the company presenting economic productivity gain and family bereavement effects as decision modifiers.

6.4 Model validation and face validity check

6.4.1 Face validity assessment

The company reported that health economists validated the economic model against the CHEERS 2022 checklists and internal quality checks.[88] The company used UK clinical experts to validate the model's key assumptions to ensure the plausibility of inputs and assumptions, making sure that the model is relevant to clinical practice.

The company assumed that patients treated with sebelipase alfa were equal to the general population after age 16; there was little evidence available to justify this, which brings into question the strength of this justification. The EAG checked the company's assumptions with another clinical expert, and some discrepancies reduced the face validity of the CEM. Our clinician suggested that despite it being difficult to predict, sufficient loss of venous access to prompt HSCT would occur earlier than age 30-years, which was assumed in the base-case. Our clinical expert disagreed with the company's cost of administration of sebelipase alfa used in the base-case, which was assumed equal to the cost of a visit to the paediatric metabolic disease specialist. According to our clinical expert, the administration cost

would be "*much more intensive than seeing a metabolic specialist in clinic*" and should include a day case with a doctor/ senior nurse present for the infusion. Therefore, our clinical expert suggested that administration cost should be higher than in the CEM's base-case.

There were also discrepancies regarding healthcare resources associated with the condition. Our clinical expert recommended that more physician monitoring would be required in the first year.

As discussed in previous sections disabilities due to AE were not included in the CEM which the EAG believes diminishes the validity of the model.

6.4.2 Technical verification

The EAG can confirm that the model works appropriately in the way it was designed to work, so there are no significant issues with the model itself. The main issue was that the model structure described in the CEM differed from the model structure described in the CS, as discussed in the EAG report.[2] The CEM contains all the relevant equations necessary for the economic model to run.

6.4.3 Comparisons with other technology appraisals

A HTA on the treatment of sebelipase alfa in lysosomal acid lipase deficiency was published in 2015 and had an economic model that was a cost-consequence analysis of a broader LAL-D population, which included adults as well as children with less severe LAL-D.[36] The CS states that this HTA has low generalizability in the current decision problem and uses a model structure based on non-alcoholic steatohepatitis (NASH).[2] The company therefore built a new model for the current submission for a younger and more ill population with rapidly progressive LAL-D.

6.4.4 Comparison with external data used to develop the economic model

The external data used in the CEM was clearly referenced in the model. Outcomes reported in the referenced literature match the data used within the model. The parenteral utility values that were obtained from Ballinger *et al.,* 2018 were from an adult population with a mean age of 38.04 years which is older than the population in the base-case.[73]

6.4.5 Comparison with external data not used to develop the economic model

The EAG located a study on the healthcare resource use and costs of managing children and adults with LAL-D at a tertiary referral centre that the company did not use in the economic model (Guest *et al.,* 2018).[69] The EAG has concerns about why this study was omitted from this analysis.

7 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the EAG

This section describes the EAG base-case and scenario analyses conducted on both the EAG and the company base-case analyses. The EAG base-case and scenario analyses use the company's economic model but adopts alternative assumptions.

7.1.1 EAG base-case

Table 7.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm *et al*., 2020[89]:

1. Transparency (e.g., lack of clarity in presentation, description, or justification)
2. Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
3. Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
4. Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
5. Unavailability (e.g., lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 7.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler *et al.,* 2016)[90]:

1. Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
2. Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
3. Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 7.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

7.1.1.1 Fixing errors

Coding Error 1: The equation in Cells P6-P91 in the "HU Norms" spreadsheet of the CEM were incorrectly formulated.

Correction: The company provided a corrected equation during the PfC which was used to replace the incorrect version in Cells P6-P91. The changes are provided in Appendix 7.1.

Coding error 2: The CEM incorrectly referred to Age-adjusted TTO and VAS in spreadsheet "HU Norms" Cells D5-D91 and E5-E91.

Correction: The EAG revised the equations for this error. In Table 1A (appendix) the EAG provide the initial CEM equations and the revised EAG equations for Cells D5-D91 and E5-E91. The changes are provided in Appendix 7.1.

Coding error 3: The CEM spreadsheet "Medical cost" Cell H18 used an incorrect value for the cost per visit to a paediatric metabolic disease physician (reported as being £565.60). The changes are provided in Appendix 7.1.

Correction: On checking the source, the EAG identified a discrepancy in the unit cost. The unit cost should read £625.24 and this value was revised in the CEM and the EAG analysis.

7.1.1.2 Fixing violations

An overview of the violations relating to cost-effectiveness is presented in Table 7.1.

Violation 1: Discount rate for both costs and QALYs (sections 5.16 and 5.1.10; Table 5.2; Key Issue 6)

In the CS a discount rate of 1.5% was used. This was justified in the CS because treatment with sebelipase alfa was assumed, based upon the modelling assumptions adopted, to restore people who would otherwise die to full or near total health, and this is sustained over a long period. The discount rate recommended by the NICE reference case was 3.5%.[4] In the EAG analysis this was changed to 3.5% in line with the NICE reference case.

7.1.1.3 Matters of judgement

An overview of the key issues related to the cost effectiveness after fixing errors and violations is presented in Table 7.1.

7.1.1.3.1 Wolman related survival (Key Issue 7)

As shown in

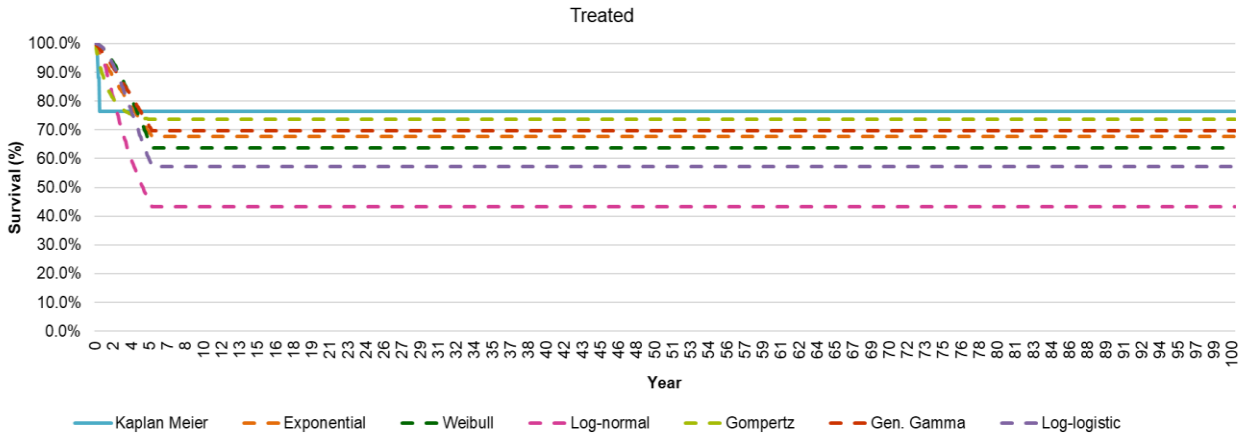


Figure 7.1, the CEM model applied parametric distributions only for patients` trial follow-up (below age 5-years) and assigned a fixed value of survival (from month 60) for the remaining of the patients` lifetime. The EAG adjusted the model to assign parametric distributions for the Wolman disease related survival for patients' lifetime (Figure 7.2). The EAG also adjusted the CEM to include further options

to apply distributions for patients before 5-years (i.e., trial follow-up) and above 5-years (i.e., extrapolation over the patients` lifetime).

The EAG first included the parametric calculations in sheet "Survival summary" cells K123-K1223 (for exponential distribution), L123-L1235 (for Weibull distribution), M123-M1235 (for log-normal distribution), N123-N1235 (for Gompertz distribution), O123-O1235 (for Gen-Gamma distribution) and P123-P1235 (for log-logistic distribution). The EAG also adjusted the "Markov traces" sheet in the CEM by revising the equations for Wolman related survival in the treated group (for sebelipase alfa, cells: AI23-AI1235 and for HSCT: AJ23-AJ1235) to provide an option to choose different distributions for patients` trial follow-up time (below 5-years) and after trial follow-up over a patient's lifetime. Appendix 7.2 provides the initial equations used in the CEM along with the EAG revised equations and justifications. All associated Wolman related survival curves considered by the EAG are displayed in Appendix 7.3. The EAG also assigned a 75% survival for patients who are receiving the sebelipase alfa + HSCT. This is based upon the EAG's view that the survival would be lower for children receiving HSCT. In the CS the corresponding assumption was 80%.

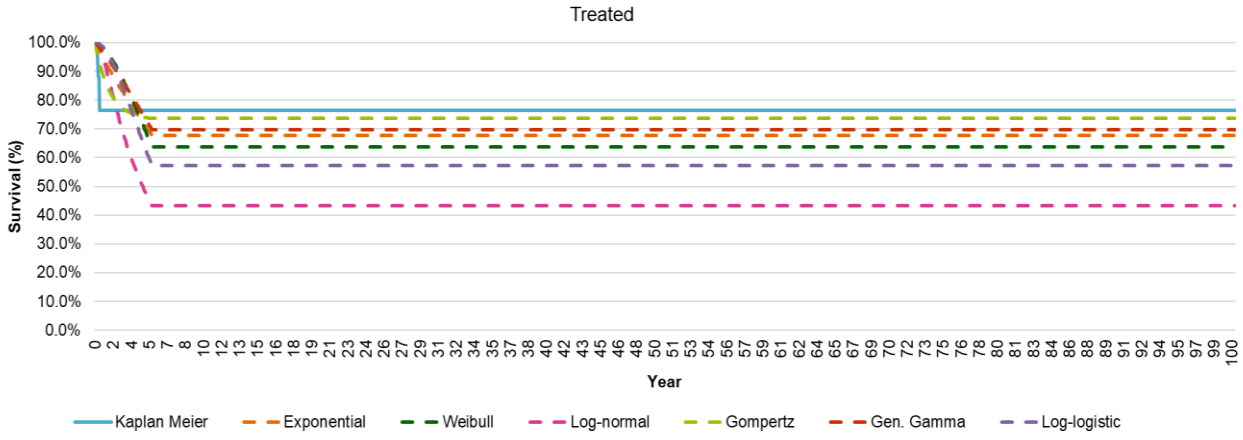
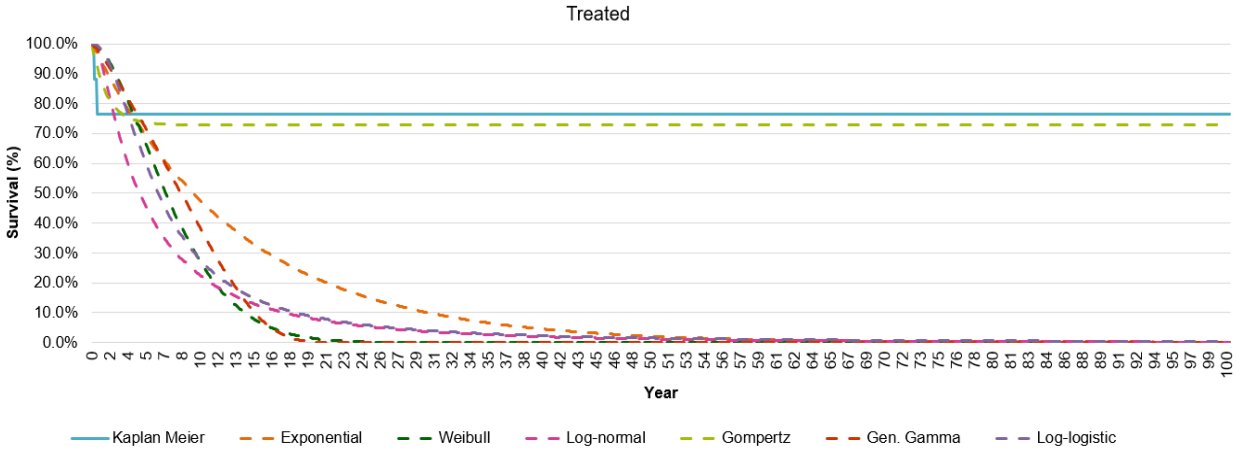


Figure 7.1: Parametric curves and Kaplan–Meier data: treated (CEM model)

Source: EAG base-case model
Abbreviations: CEM, company economic model; Gen Gamma, generalised gamma

Figure 7.2: Parametric curves and Kaplan–Meier data: treated (EAG model)



Source: EAG base-case model
Abbreviations: EAG, Evidence Assessment Group; Gen Gamma, generalised gamma

7.1.1.3.2 Utility decrement for HS2 (rescue care) (section 5.1.13 and Key Issue 8)

The EAG adjusted the CEM to include a utility decrement for patients who receive rescue care. For this the EAG adjusted the equations in "Benefits" sheet E23-E1235 and applied the same utility as patients who received parenteral nutrition utility (cell F11: as most patients moved from HS1). The EAG also defined an option in "Inputs&Outputs" sheet cell: E48 to apply the utility decrement in scenario analysis.

7.1.1.3.3 Utility decrement for informal care provided to patients (section 5.1.13 and Key Issue 8)

The CEM included the utility decrement for caregiver bereavement as an option in the model (for sensitivity analysis), but the EAG also adjusted the CEM model to include a utility decrement for providing care for patients. For this the EAG provided related equations in "Benefits" sheet cells: L23-L1235 and then linked all other cells that calculate the undiscounted/discounted QALYs in the same sheet. The EAG also provided an option (in cell: K19) to limit the utility decrement in the model by the age of the patient.

7.1.1.3.4 Utility decrement for nasogastric feeding (section 5.1.13 and Key Issue 8)

The EAG noted that the CEM included the cost of nasogastric feeding in the model but did not include a corresponding utility decrement. The EAG included the utility decrement in equations defined for HS3 (F23-F1235) and HS4 (G23-G1235). The EAG also included an option in the sheet "Benefits" cells K9 & K10 to apply the utility decrement in the scenario analysis.

7.1.1.3.5 Adjusting utility value for children at age 1–11-year-old (section 5.1.13 and Key Issue 8)

The CEM included an option for adjusting the utility value at all ages, but the EAG also included an option to adjust the utility value for children (ages 1–11-year-old) as QALYs for children could be lower in comparison with adult patients.[82] For this the EAG provided an option in "HU norms" sheet cell: H6 to include the different weighting in the EAG base-case utility values (equations in cells F5-F15 were adjusted for this).

7.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

7.1.2.1 Exploratory scenario analyses

This section describes the scenario and sensitivity analyses conducted by the EAG. The EAG conducted 34 scenario analyses included in the CS. In addition, the EAG conducted 12 scenario analyses not conducted by the company. These 12 additional scenarios are described below.

7.1.2.1.1 Utility decrement for informal care for those receiving ERT (section 5.1.13 and Key Issue 8)

The CEM included the utility decrement for caregiver bereavement, but the EAG was also interested in exploring the utility decrement for informal care provided by family to patients. The utility decrement identified for caregiver for caring a child on ERT was 0.155 and the EAG defined this based on the Simon *et al.,* 2019 study which estimated a disutility of parental spillover due to childhood conditions in a scenario on ERT treatment (Mean 0.155, 95% CI: 0.110–0.200).[82]

7.1.2.1.2 Weighting for utility values of all age (section 5.1.13 and Key Issue 8)

The CEM provided an option to adjust the utility value for all ages and the CS report also included weighting for the utility value (0.9) in their scenario analysis. The EAG also considered a different lower weighting for the utility value (0.8) in the EAG scenario analysis.

7.1.2.1.3 Weighting for utility values of children 0–11-year-old (section 5.1.13 and Key Issue 8)

The EAG also explored the impact of adjusting the model for the weighted utility value for children aged 1–11 years old. The EAG explored different utility values in the model for children by applying a weighting of 0.9 to the NICE-DSU utility.[72]

7.1.2.1.4 Utility decrement for nasogastric feeding (section 5.1.13 and Key Issue 8)

Given that the CS included the cost of nasogastric feeding the EAG also explored the impact of including a utility decrement for this (of 0.2) with the EAG model. This was based upon McFarland *et al.,* (2017), which investigated the cost-utility of a clinical algorithm for nasogastric tube placement confirmation in adults.[84]

7.1.2.1.5 Utility Decrement for HS2 (for 12 month) (section 5.1.13 and Key Issue 8)

The EAG explored the impact of assuming that patients in HS2 (the rescue care state) have the same level of health utility of those in HS1. For this the EAG included the same health utility decrement of HS1 (0.0085) for patients in the rescue care state (HS2).

7.1.2.1.6 Vial sharing: Yes (1-week count) (section 5.1.14 and Key Issue 10)

The CEM has the option to include vial sharing with one-week count. The EAG included this scenario within the EAG analysis.

7.1.2.1.7 Vial sharing: Yes (2-week count) (section 5.1.14 and Key Issue 10)

The CEM has the option to include vial sharing with two-weeks count. The EAG included this scenario within the EAG analysis.

7.1.2.1.8 Predictive Wolman related survival: K-M below 5-year & exponential (above 5 years) (sections 5.1.11, 6.2.2 and Key Issue 7)

The EAG included further options in the model with regards to Wolman-related survival both below and above 5-years of age. In this scenario the EAG fits K-M below the age of 5-years and exponential distribution above the age of 5-years.

7.1.2.1.9 Predictive Wolman related survival: K-M below 5-year & Weibull (above 5 years) (sections 5.1.11, 6.2.2 and Key Issue 7)

The EAG included further options in the model with regards to Wolman-related survival both below and above 5-years of age. In this scenario the EAG fits K-M below the age of 5-years and Weibull distribution above the age of 5-years.

7.1.2.1.10 Predictive Wolman related survival: K-M below 5-year & Gompertz (above 5 years) (sections 5.1.11, 6.2.2 and Key Issue 7)

The EAG included further options in the model with regards to Wolman-related survival both below and above 5-years of age. In this scenario the EAG fits K-M below the age of 5-years and Gompertz distribution above the age of 5-years.

7.1.2.1.11 Predictive Wolman related survival: K-M below 5-year & log-normal (above 5 years) (sections 5.1.11, 6.2.2 and Key Issue 7)

The EAG included further options in the model with regards to Wolman-related survival both below and above 5-years of age. In this scenario the EAG fits K-M below the age of 5-years and log-normal distribution above the age of 5-years.

7.1.2.1.12 Doctor used to administer sebelipase alfa (section 5.1.10 and 5.1.14)

As discussed with our clinical expert, the EAG increased the cost of administering sebelipase alfa by including the cost of a medical doctor in the model within the EAG scenario analysis. Our clinical expert suggested that administration costs should include the additional cost of a nurse or doctor during infusion within the first few months of starting and establishing infusion rates and drug reactions.

7.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 7.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in section 7.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
1. Use of 1.5% discount rate for both costs and QALY	5.1.11	Methods	Use 3.5% discount rate as recommended by the NICE reference case.[4]	+	Resolved in EAG base-case analysis	No
2. Utility decrement for informal care provided to patients on ERT	5.1.13	Bias	Include utility decrement for informal care	+	Explored in EAG scenario analysis 1	Further evidence on HRQoL using measures suitable for use in an economic evaluation for this patient population
3. Using age and sex adjusted utility values	5.1.13	Bias	Exploring the impact of lower weighing for health state utilities	+	Explored in EAG scenario analysis 1	Further evidence on HRQoL using measures suitable for use in an economic evaluation for this patient population
3. Adjusting utility values for children at age 1-11-years-old	5.1.13.1, 5.1.13.2	Imprecision	Include an option to adjust utility value for children (age 1-11-year-old)	+	Explored in EAG scenario analysis 3	Further evidence on HRQoL using measures suitable for use in an economic evaluation for this patient population

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
4. Utility decrement for nasogastric feeding	5.1.13.3.2	Bias	Include utility decrement for nasogastric feeding	+	Explored in EAG scenario analysis 4	Further evidence on HRQoL using measures suitable for use in an economic evaluation for this patient population
5. Utility decrement for HS2 two (rescue care)	5.1.13	Bias	Include utility decrement for patients at Health State rescue care	+	Explored in EAG base-case and EAG scenario analysis 5	Further evidence on HRQoL using measures suitable for use in an economic evaluation for this patient population
6. Impact of sharing of vials of SA	5.1.14	Bias	Include the option of vial sharing	-	Explored in EAG base-case and EAG scenario analysis 6-7	Evidence on clinical utility of vial sharing for this condition
7. Uncertainty over methods to estimate Wolman related survival	5.1.12	Methods, Imprecision	Alternative distributions were included to explore the impact of these alternative distributions based upon the same underlying data.	+	Explored in the EAG base-case and EAG scenario analysis 8-11	Further evidence on the Wolman related survival in the long-term to improve the evidence underpinning assumptions about Wolman-related survival

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
8. Uncertainty over who may administer SA	5.1.10, 5.1.14	Bias	Administration by a medical doctor to administer SA was explored	+	Explored in EAG scenario analysis 12	Real world data on NHS practice.

Source: Produced by the EAG.
a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; b Explored
Abbreviations: EAG, Evidence Assessment Group; FE, fixing errors; FV, fixing violations; HRQoL, health related quality of life; HS, health state; MJ, matters of judgement; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year, SA, sebelipase alfa.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

7.2.1 The EAG base-case, scenario and sensitivity analyses

In section 7.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 7.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. A list of the EAG additional exploratory scenario analyses is presented in Table 7.3. The EAG also replicated the scenarios reported in the CS and reported in Table 6.3. These analyses were replicated conditional on the corrected CEM (Table 7.4) and conditional on the EAG base-case analysis (

Table 7.5).

Table 7.6 and Table 7.7 report the EAG additional exploratory scenario analyses described in Table 7.3. The analyses in

Table 7.6 are all conditional on the CEM corrected model. The analyses reported in Table 7.7 are conditional on the EAG base-case analysis model. The analysis numbers in Table 7.2, Table 7.3,

Table 7.6, and Table 7.7 correspond to the numbers reported in section 7.1.2.1. The submitted EAG model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment). These are also described in Appendix 7.1 and 7.2.

Table 7.2: Deterministic EAG base-case results (unless otherwise stated) sebelipase alfa versus BSC

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Deterministic					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
CS base-case – Probabilistic					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,518
Fixing error 1: equation in Cells P6-P91 in the "HU Norms" spreadsheet					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
Fixing error 2: refer to Age-adjusted TTO and VAS in spreadsheet "HU Norms" Cells D5-D91 and E5-E91.					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
Fixing error 3: "Medical cost" Cell H18					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,871
Violation 1 – Discount rate (Key Issue 6)					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£308,078
Matter of judgement 1: Justifications for Wolman-related survival distributions (Key Issue 7)					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£240,032
Matter of judgement 2: Utility decrement for Heath states two (rescue care) (Key Issue 8)					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
Matter of judgement 3: Utility decrement for care provided to patients (Key Issue 8)					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
Matter of judgement 4: Utility decrement for nasogastric feeding (Key Issue 8)					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
Matter of judgement 5: Adjusting utility value for children at age 1–11-year-old (Key Issue 8)					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,608
CS all errors fixed					
BSC	[redacted]	[redacted]			
SA	[redacted]	[redacted]	[redacted]	[redacted]	£239,871
EAG base-case – Deterministic					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£308,960
EAG base-case – Probabilistic					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
SA	[redacted]	[redacted]	[redacted]	[redacted]	£308,130

Source: Produced by the EAG.

Abbreviations: BSC, best supportive care; CS, company submission; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year, SA, sebelipase alfa.

Table 7.2 provides the model results for both the CS model and CEM corrected model. As is shown the CEM corrected model has slightly higher ICER than the CS initial model. The ICER for the base-case analysis for the CS model was £239,608 and the ICER for base-case CEM corrected model is £239,871. Also shown in Table 7.2 is the ICER from the EAG base-case analysis. For the EAG base-case analysis the ICER increases to £308,960; an increase from £239,871 in the CEM corrected model. The primary driver of this change is the adoption of a 3.5% discount rate in the EAG base-case analysis.

Table 7.3: List of EAG additional exploratory scenario analyses

Scenario	Scenario description	Base-case value
1	Utility decrement for informal care: 0.155	0
2	Weighting for utility values of all ages: 0.8	1
3	Weighting for utility values of children 0–11-year-old: 0.9	1
4	Utility decrement for nasogastric feeding: 0.02	0
5	Utility Decrement for HS2 (for 12 month): 0.0085	0
6	Vial sharing: Yes (1-week count)	No (1-week count)
7	Vial sharing: Yes (2-week count)	No (1-week count)
8	Predictive Wolman related survival: K-M below 5-year & exponential (above 5 years)	K-M below 5-year, K-M (above 5-year)
9	Predictive Wolman related survival: K-M below 5-year & Weibull (above 5 years)	K-M below 5-year, K-M (above 5-year)
10	Predictive Wolman related survival: K-M below 5-year & Gompertz (above 5 years)	K-M below 5-year, K-M (above 5-year)
11	Predictive Wolman related survival: K-M below 5-year & log-normal (above 5 years)	K-M below 5-year, K-M (above 5-year)
12	Doctor used to administer sebelipase alfa	0

Source: Produced by the EAG.
Abbreviations: EAG, Evidence Assessment Group; HS, health state; HSCT, haematopoietic stem cell transplant; K-M, Kaplan-Meier.

Table 7.4: Deterministic scenario analysis for scenarios explored in the CS for the corrected CEM

#	Sensitivity analysis	Base-case value	ICER (CS report)	CEM corrected model						
				Cost of SA	Cost BSC	Incremental cost	QALY SA	QALY BSC	Incremental QALY	ICER
1	Base-case	-	£239,608	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,871
2	Predicted survival – exponential	K-M	£266,462	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£434,768
3	Predicted survival – Weibull	K-M	£268,215	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£450,235
4	Predicted survival – Gompertz	K-M	£269,300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£407,322
5	Predicted survival - log-normal	K-M	£335,369	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£260,827
6	HRQoL = EQ-5D VAS	EQ-5D TTO	£238,595	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£238,868
7	100% SA compliance	0.96	£248,469	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£248,731
8	No death after loss of venous access without HSCT	Yes	£237,287	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£237,550
9	Only 50% of patients have early HSCT	0.75	£394,538	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£394,801
10	All patients have early HSCT	0.75	£63,794	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,057
11	No patients have early HSCT	0.75	£656,664	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£656,927
12	Only 50% discontinue SA after HSCT	1	£563,225	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£494,274

13	Venous access never fails	Age 30 years	£408,641	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£408,903
14	Cost HSCT 20% higher	139123.1992	£240,531	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£240,793
15	2-week round-up vial consumption	1-week	£224,458	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£224,721
16	No homecare service	Included	£242,560	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242,823
17	Cost & QALY discount rate = 0.0%	0.015	£180,397	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180,653
18	Cost & QALY discount rate = 3.5%	0.015	£308,078	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,356
19	Cost & QALY discount rate = 5.0%	0.015	£346,459	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£346,752
20	Horizon = 6 years	Lifetime	£415,975	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£416,432
21	SA patient cost cap at [redacted] pa	No	£208,134	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£208,396
22	Patients who don't receive HSCT (No ADAs) increase to 5mg/kg	0.5	£296,679	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£296,941
23	Venous access loss at 40-years of age	30-years	£284,115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£284,378
24	Venous access loss at 20-years of age	30-years	£187,641	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£187,904
25	20% have dose reduction at 18-years of age	0	£271,516	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£271,779

26	Only 50% have dose reduction after early HSCT	1	£686,352	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£601,170
27	20% hazard ratio applied to other cause mortality	No hazard ratio	£241,826	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242,089
28	10% reduction in HRQoL all ages	No hazard ratio	£251,323	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£266,515
29	10% decrease HRQoL & 20% HR on other cause mortality	No hazard ratio	£253,651	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£268,979
30	Lifecycle price - one-third lower SA price after 10-years	Static price	£145,355	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£145,617
31	Family bereavement disutility included	Excluded	£230,490	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£230,743
32	HSCT procedure and recovery disutility	Excluded	£255,359	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£255,639
33	Specialist nutrition excluded	Included	£221,273	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£221,536
34	Economic productivity included	Excluded	£149,072	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£149,335

Source: Based on Table 60 in the CS[2]
Abbreviations: #, scenario; ADA, anti-drug antibody; BSC, best supportive care; CS = company submission; CEM, company economic model; EAG, Evidence Assessment Group; HR, hazard ratio; HRQoL, health related quality of life; HSCT, Haematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio; K, thousand; K-M, Kaplan-Meier; QALY, quality adjusted life-year; SA, sebelipase alfa; TTO, time trade-off; VAS, visual analogue scale

Table 7.5: Deterministic scenario analysis for scenarios explored in the CS conditional on the EAG base-case analysis model

#	Scenario analysis	Base-case value	ICER (CS report)	EAG base-case model						
				Cost of SA	Cost BSC	Incremental cost	QALY SA	QALY BSC	Incremental QALY	ICER
1	Base-case	-	£239,608	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,960
2	Predicted survival – exponential **(Key Issue 7)**	K-M	£266,462	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£472,104
3	Predicted survival – Weibull **(Key Issue 7)**	K-M	£268,215	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£483,062
4	Predicted survival – Gompertz **(Key Issue 7)**	K-M	£269,300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£488,590
5	Predicted survival - log-normal **(Key Issue 7)**	K-M	£335,369	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£446,868
6	HRQoL = EQ-5D VAS	EQ-5D TTO	£238,595	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£305,084
7	100% SA compliance	0.96	£248,469	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£320,636
8	No death after loss of venous access without HSCT **(Key Issue 2)**	Yes	£237,287	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£306,767
9	Only 50% of patients have early HSCT **(Key Issue 2)**	0.75	£394,538	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£499,604

10	All patients have early HSCT **(Key Issue 2)**	0.75	£63,794	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£92,093
11	No patients have early HSCT **(Key Issue 2)**	0.75	£656,664	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£823,700
12	Only 50% discontinue SA after HSCT **(Key Issue 2)**	1	£563,225	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£606,398
13	Venous access never fails **(Key Issue 2)**	Age 30-years	£408,641	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£414,649
14	Cost HSCT 20% higher **(Key Issue 2)**	139123.1992	£240,531	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£310,157
15	2-week round-up vial consumption **(Key Issue 10)**	1-week	£224,458	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£287,021
16	No homecare service	Included	£242,560	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£312,836
17	Cost & QALY discount rate = 0.0% **(Key Issue 6)**	0.015	£180,397	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180,938
18	Cost & QALY discount rate = 3.5% **(Key Issue 6)**	0.015	£308,078	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,960
19	Cost & QALY discount rate = 5.0% **(Key Issue 6)**	0.015	£346,459	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£347,478
20	Horizon = 6- years	Lifetime	£415,975	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£424,205

21	SA patient cost cap at [redacted] pa **(Key Issue 9)**	No	£208,134	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£266,611
22	Patients who don't receive HSCT (No ADAs) increase to 5mg/kg **(Key Issue 2 and 5)**	0.5	£296,679	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£379,112
23	Venous access loss at 40-years of age **(Key Issue 2)**	30-years	£284,115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£346,924
24	Venous access loss at 20-years of age **(Key Issue 2)**	30-years	£187,641	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£255,085
25	20% have dose reduction at age 18 **(Key Issue 5)**	0	£271,516	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£343,072
26	Only 50% have dose reduction after early HSCT **(Key Issue 2 and 5)**	1	£686,352	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£742,174
27	20% hazard ratio applied to other cause mortality **(Key Issue 7)**	No hazard ratio	£241,826	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£310,148
28	10% reduction in HRQoL all ages **(Key Issue 8)**	No hazard ratio	£251,323	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£343,270
29	10% decrease HRQoL & 20% HR on other cause	No hazard ratio	£253,651	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£344,590

	mortality **(Key Issue 8)**									
30	Lifecycle price - one-third lower SA price after 10 years **(Key Issue 9)**	Static price	£145,355	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,048
31	Family bereavement disutility included	Excluded	£230,490	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£296,606
32	HSCT procedure and recovery disutility **(Key Issue 2)**	Excluded	£255,359	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£340,253
33	Specialist nutrition excluded	Included	£221,273	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£290,762
34	Economic productivity included	Excluded	£149,072	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£248,639

Source: Based on Table 60 in the CS[2]
Abbreviations: #, scenario; ADA, anti-drug antibody; BSC, best supportive care; CS = company submission; CEM, company economic model; EAG, Evidence Assessment Group; HR, hazard ratio; HRQoL, health related quality of life; HSCT, haematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio; K, thousand; K-M, Kaplan-Meier; QALY, quality adjusted life-year; SA, sebelipase alfa; TTO, time trade-off; VAS, visual analogue scale

Table 7.6: Deterministic scenario analysis for EAG exploratory scenarios conditional on the corrected CEM

#	Model parameter	Base-case value	Cost of SA	Cost BSC	Incremental cost	QALY SA	QALY BSC	Incremental QALY	ICER
	Base-case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,871
1	Utility decrement for ERT care: 0.155	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£254,830
2	HR for utility of all ages: 0.8	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£299,818
3	HR for utility of children 0–11-year-old: 0.9	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£245,773
4	Utility decrement for nasogastric feeding: 0.02	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£246,907
5	Utility Decrement for HS2 (for 12 month): 0.0085	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,473
6	Vial sharing: Yes (1-week count)	No (1-week count)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£198,427
7*	Vial sharing: Yes (2-week count)*	No (1-week count)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£224,721
8	Predictive survival: K-M below 5-year & exponential (above 5 years)	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£434,768
9	Predictive survival: K-M below 5-year & Weibull (above 5 years)	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£450,235
10	Predictive survival: K-M below 5-year & Gompertz (above 5 years)	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£260,827
11	Predictive survival: K-M below 5-year & log-normal (above 5 years)	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£407,322

12	Doctor used to administer SA	Paediatric metabolic disease specialist used to administer SA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242,912

Source: Produced by the EAG.
Abbreviations: #, scenario; BSC, best supportive care; CEM, company economic model; EAG, Evidence Assessment Group; ERT, enzyme replacement therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; K-M, Kaplan-Meier; QALY, quality adjusted life-year; SA, sebelipase alfa.
*For scenario 7 the EAG base-case analysis model produced a result which is counter intuitive. The EAG have not resolved this at time of submission.

Table 7.7: Deterministic scenario analysis for EAG exploratory scenarios conditional on the EAG base-case analysis model

#	Model parameters	Base-case value	EAG base-case model						
			Cost of SA	Cost BSC	Incremental cost	QALY SA	QALY BSC	Incremental QALY	ICER
	Base-case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£308,960
1	Utility decrement for ERT-related care: 0.155 **(Key Issue 8)**	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£338,709
2	HR for utility of all ages: 0.8 **(Key Issue 8)**	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£386,152
3	HR for utility of children 0–11-yearold: 0.9 **(Key Issue 8)**	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£320,666
4	Utility decrement for nasogastric feeding: 0.02 **(Key Issue 8)**	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£323,995
5	Utility decrement for HS2 (for 12 month): 0.0085 **(Key Issue 8)**	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£307,884
6	Vial sharing: Yes (1-week count) **(Key Issue 10)**	No (1-week count)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£254,079
7*	Vial sharing: Yes (2-week count)* **(Key Issue 10)**	No (1-week count)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£287,021

8	Predictive Wolman related survival: K-M below 5-year & exponential (above 5 years) **(Key Issue 7)**	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£445,595
9	Predictive Wolman related survival: K-M below 5-year & Weibull (above 5 years) **(Key Issue 7)**	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£455,540
10	Predictive Wolman related survival: K-M below 5-year & Gompertz (above 5 years) **(Key Issue 7)**	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£343,803
11	Predictive Wolman related survival: K-M below 5-year & log-normal (above 5 years) **(Key Issue 7)**	K-M below 5-year, K-M (above 5-year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£431,634
12	Doctor used to administer sebelipase alfa	Paediatric metabolic disease specialist used to administer sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£312,205

Source: Produced by the EAG.
Abbreviations: #, scenario; BSC, best supportive care; CEM, company economic model; EAG, Evidence Assessment Group; ERT, enzyme replacement therapy; HR, hazard ratio; HS, health state; ICER, incremental cost-effectiveness ratio; K-M, Kaplan-Meier; QALY, quality adjusted life-year; SA, sebelipase alfa.

*For scenario 7 the EAG base-case analysis model produced a result which is counter intuitive. The EAG have not resolved this at time of submission.

7.3 EAG's preferred assumptions

The EAG ran the EAG base-case model to produce base-case point estimates with accompanying 95% credible intervals in a probabilistic analysis. The probabilistic analysis included a broad range of parameters which were varied simultaneously by sampling 1,000 times from individual probability density functions presented (Table 7.8). As can be seen from Table 7.8 the ICER reported for the PSA is very similar to the ICER presented for the EAG base-case analysis deterministic model (Table 7.2). Comparing the deterministic results (Table 7.2) and the probabilistic results (Table 7.8), the costs for both sebelipase alfa and BSC are slightly lower but QALYs are very similar.

Table 7.8: Probabilistic sensitivity analysis results for the EAG base-case analysis

		Mean	Lower 95% CI bound	Upper 95% CI bound
Costs	Sebelipase alfa	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
	Incremental	[redacted]	[redacted]	[redacted]
QALYs	Sebelipase alfa	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
	Incremental	[redacted]	[redacted]	[redacted]
ICER		£308,130	£301,821	£315,440

Source: Produced by the EAG.
Abbreviations: BSC, best supportive care; CI, credible interval; EAG, Evidence Assessment Group; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; SA, sebelipase alfa

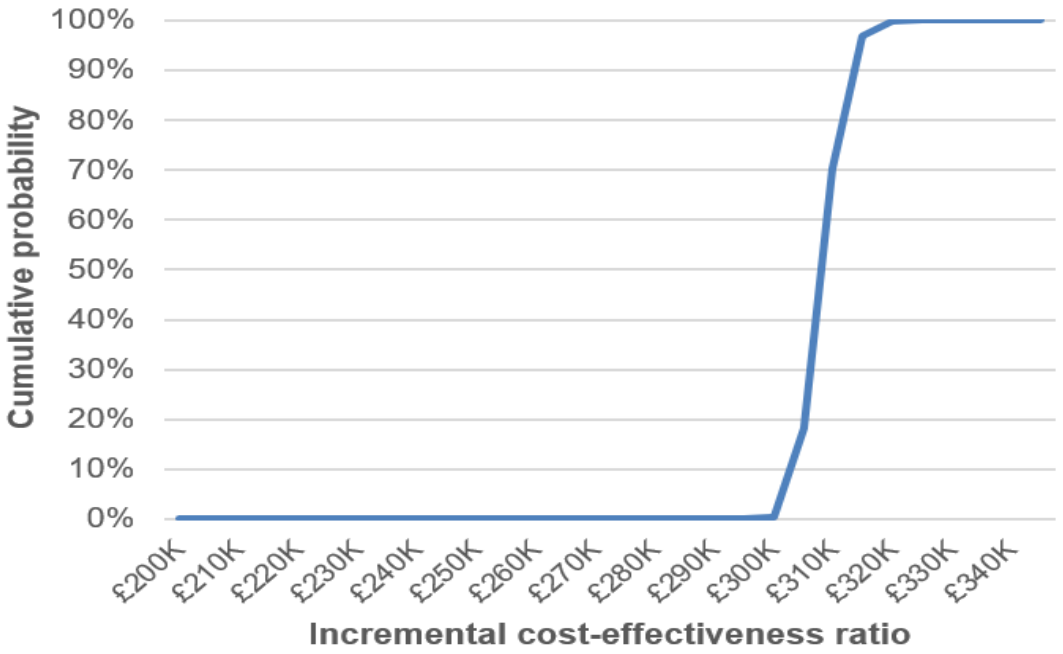
The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in section 7.1, was £308,130 per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of 0% at WTP thresholds of £100,000 and £300,000 per QALY gained. The chance of being cost-effective at the WTP threshold of £320,000 is 100%. These results are shown in the form cost-effectiveness plane and cost-effectiveness acceptability curve (CEACs) in Figure 7.3 and Figure 7.4.

Figure 7.3: Cost-effectiveness plane for the EAG base-case analysis

[redacted]

Source: Produced by EAG.
Abbreviations: CEAC = cost-effectiveness acceptability curve; EAG, Evidence Assessment Group.

Figure 7.4: Cost effectiveness acceptability curve for the EAG base-case analysis



Source: Produced by EAG.
Abbreviations: CEAC = cost-effectiveness acceptability curve; EAG, Evidence Assessment Group; K, Thousand.

As shown in Table 7.4 and

Table 7.5 which report the scenario analyses that replicate those conduced in the CS and correct-CEM but conditional on the EAG base-case analysis. Based on the EAG base-case model (presented in

Table 7.5), only one scenario had an ICER that is below £100,000 (Scenario 10 where all patients receive early HSCT) and 24 (72%) scenarios have ICER values higher than the £300,000 WTP threshold value. Nine scenarios have an ICER lower than £300,000.

The five scenarios that resulted in the largest increase in the ICER were as follows:

1. Assuming no patients have early HSCT/ £823,700
2. Assuming only 50% have sebelipase alfa dose reduction after early HSCT/ £742,174
3. Assuming only 50% discontinue sebelipase alfa after HSCT/ £606,398
4. Assuming only 50% of patients have early HSCT/ £499,604
5. Assuming predicted survival – Gompertz/ £488,590

As can be seen, the highest ICERs were associated with the proportion of patients receiving early HSCT, sebelipase alfa dose reduction or discontinuation. Another important scenario related to the method adopted for extrapolation of Wolman disease-related mortality over patients` lifetime (however, it should be noted that all methods of extrapolation are based on very few data).

For the 12 EAG additional exploratory analyses (Table 7.6 and Table 7.7) there were 10 scenarios in Table 7.7 (which was based upon the EAG base-case analysis model), where the ICER values were higher than a £300,000 WTP threshold value (all 12 analyses were over the £100,000 threshold). The two remaining scenarios considered vial sharing assumptions for the 1-week count and 2-week count. They resulted in ICERs of lower than £300,000 but as was noted in the footnotes to Tables 7.6 and 7.7, there is a fault within the CEM that the EAG has not resolved.

Of the EAG additional exploratory analyses the five most influential scenarios (i.e., the ones that resulted with the greatest increase in the ICER) were:

1. Assuming predictive survival: K-M below 5-year & Weibull (above 5-years)/ £455,540
2. Assuming predictive survival: K-M below 5-year & exponential (above 5-years)/ £445,595
3. Assuming predictive survival: K-M below 5-year & log-normal (above 5-years)/ £431,634
4. Assuming HR for utility of all ages: 0.8/ £386,152
5. Assuming predictive survival: K-M below 5-year & Gompertz (above 5-years)/ £343,803

As it can be seen, these scenarios are associated with two key assumptions, relating to the methods adopted for extrapolating Wolman disease-related survival and assumptions around the HRQoL for those with Wolman disease.

7.4 EAG Budget Impact Analysis

The EAG also calculated budget impact analysis (expected 5-year budget impact for the NHS and PSS in England) based on CS assumptions. Table 7.9 reports the budget impact results for the EAG base-case analysis.

Table 7.9: Annual budget impact over 5 years, with PAS

Net budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
SA acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: PAS, patient access scheme.					

The population expected to receive sebelipase alfa, taking account of expected disease mortality, in the EAG base-case is presented in Table 7.10.

Table 7.10: Population to receive sebelipase alfa

Incident and prevalent cases	Current year	Year 1	Year 2	Year 3	Year 4	Year 5
Adjusted for mortality	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: NA, not applicable						

7.5 Conclusions of the cost effectiveness section

The company conducted a targeted literature review for cost effectiveness analyses and an SLR for HRQoL. These searches were conducted to inform the CEM. No search was undertaken for costs and resource use but the EAG felt that relevant references might have been missed. The search for the cost effectiveness analyses identified no relevant studies. The search for HRQoL identified one small study which did not directly provide any health utilities data. The EAG are of the view that although the company has sought to identify all relevant economics evaluations, it cannot be definitively said that there are no further data.

The EAG considers that the company mostly complied with the elements presented in the reference case. The company adopted a partial NHS perspective in that costs falling on primary care were not considered. The company were hampered by the lack of data on Wolman-related survival. Specifically, data with which to extrapolate survival over the patient's life time were very sparse and short-term. Similarly, there were no useable HRQoL data that could be directly incorporated into the CEM. This is unsurprising as patients were modelled from birth and the EAG are unaware of any valid tools for estimating health state utilities directly from very young patients. This necessitated the company making a set of assumptions on how the patient population both with and without treatment would differ from the UK population values. The EAG are sympathetic to this approach but were concerned that the assumptions made either excluded some disutilities associated with the condition or care received or otherwise assumed maximal effects e.g., utility values were the same as age and sex adjusted general population values.

The EAG had no substantial concerns over the model structure (except for the exclusion of some adverse events as noted above). The model adopted a life-time time horizon which was appropriate for the decision problem. However, the company argues that both future costs and health effect be discounted at 1.5% rather than the recommended 3.5%. The company argued that this was justified because the way in which treatment with sebelipase alfa was modelled by the company resulted in very long survival at near full health. The company also argued that the appropriate cost per QALY WTP threshold was £300,000 and not £100,000 as is more typical for HSTs. Again, this was argued because of the very long survival (in life years) that was estimated by the CEM.

The population modelled was defined by the company as patients with rapidly progressive LAL-D. This was justified because rapidly progressive LAL-D had historically been defined as Wolman disease. The data available for this population were sparse. As described in section 4 there was some variation in patient characteristics in the studies available. Data from identified studies were treated as if it came from a single study sample and pooled to provide the data to estimate Wolman-related survival.

The cost effectiveness of sebelipase alfa was compared with established clinical practice without sebelipase alfa, which is described as BSC. Both the intervention and comparator are in line with the decision problem and NICE final scope. Sebelipase alfa is administered intravenously. The company mentioned that the recommended dose for patients aged < 6-months presenting with rapidly progressive LAL-D is either 1mg/kg or 3mg/kg QW, depending on clinical status. Once patients are stable, they are monitored until loss of response to sebelipase alfa or loss of venous access. If this occurs patients receive HSCT. Loss of response results in an early move to HSCT (assumed to occur in [redacted] of patients) with the remaining surviving patients transitioning to HSCT by an assumed 30-years of age.

The company fitted several parametric models and finally decided to choose a non-parametric K-M approach for the base-case analysis as the parametric models were not fitted via visual inspection. The EAG agree that the K-M is the best fitted model for the trial follow-up, however using more flexible parametric modelling could be more relevant to estimate survival over a patient's lifetime. Scenario analyses were conducted by both the company and the EAG exploring the impact of these alternative survival models. The EAG specifically explored the impact of different models to predict both early (covered by the observed data) and long-term (i.e., extrapolated) survival (Key Issue 7).

The company provided a summary of the adverse events in the trial data and they stated that AEs temporarily impact HRQoL and in most cases were managed by infusion adjustments and treatment. It was mentioned that the majority of TEAEs were non-serious, mild or moderate and unrelated to treatment with sebelipase alfa. Thus, disutilities due to AEs were not included in the model developed by the company. The exception to this is HSCT but disutilities for this were only applied in a scenario analysis by the company. Other adverse events that may result in utility decrements in the long-term were not considered.

Costs include the cost of sebelipase alfa itself. This cost is based upon the confidential PAS cost. All analyses used this cost. The costs for each of the health states in the model related to the initial care of patients with Wolman disease from birth; rescue care (including end-of-life care for a month prior to Wolman-related death); physician and dietician monitoring for this population group for the first 5-years; long-term follow-up until loss of venous access; and delivery of HSCT and follow-up after that. The EAG had some concerns that resource use seems to be largely restricted to the tertiary setting. The company noted in response to PfC that sebelipase alfa treatment in people with rapidly progressive LAL-D comes from a specialised NHS service. The EAG accept this but also note that in the long-term and following HSCT this may not be the case. The EAG also note that access to extra support may also be needed and it would be reasonable to assume that patients affected by Wolman disease may also need to access primary and social care services.

Apart from the features noted above, the CEM complied with the NICE reference case. These were 3 coding errors. Two of these related to estimation of utilities and one related to the use of an incorrect cost value. Correcting the first two did not alter the ICER and correcting the cost increased the ICER by £263. There was one violation, the use of a 1.5% discount rate (Key Issue 6). Revising this to 3.5% increased the ICER by £68,470. The main matters of judgement considered by the EAG and reflected in the EAG base-case analysis related to adoption of utility decrements associated with aspects of care, use of age and sex adjusted utility values, the utility values for children up to 11-years-old, the role of vial sharing, uncertainty over extrapolation methods for estimating Wolman-related survival and uncertainty over who may administer sebelipase alfa (Key Issue 8). These matters of judgement mainly introduced functionality into the model and did not change the ICER. Only one changed the ICER, changing the way Wolman related survival was calculated in the model. This resulted in an increase in the ICER of £424.

The company's base-case deterministic results were that sebelipase alfa had an ICER of £239,608 compared with BSC. The EAG base-case results, were that sebelipase alfa had an ICER of £308,960 compared with BSC. This was driven by the change in discount rate. The EAG replicated the scenario analyses conducted by the company but using the EAG base-case model. Across all the scenarios considered only one had an ICER below £100,000 (where all patients receive early HSCT). Results were sensitive to assumptions around the use of sebelipase alfa and its cost, the proportion of patients that received early HSCT (the higher the proportion then the lower the ICER) and method used to extrapolate Wolman survival (Key Issues 2 and 7). For the additional 12 EAG exploratory analyses, 10 resulted in ICERs above £300,000 (all 12 analyses were over the £100,000 threshold). The two remaining scenarios considered vial sharing assumptions for the 1-week count and 2-week count (Key Issue 10). They resulted in ICERs of below £300,000 but as was noted earlier a fault resides in the CEM that the EAG has not resolved.

The results of the EAG deterministic analysis were very similar to the EAG probabilistic analysis. For the probabilistic analysis there was a near 0% chance that sebelipase alfa would not be cost-effective at a £300,000 WTP threshold and a near 100% chance it would be cost-effective at a £320,000 WTP threshold.

No sub-groups were provided by the company or conducted by the EAG.

In summary, the EAG's base-case analysis resulted in an ICER beyond £300,000. The probability that sebelipase alfa being considered for all thresholds up to £300,000 per QALY was approximately 0% compared with BSC. Circumstances that could reduce the ICER included situations where the use or unit cost of sebelipase alfa was reduced. These include situations where it was assumed all patients get early HSCT (and hence reduce the need for sebelipase alfa). Other circumstances included reducing the discount rate to 0%. Some uncertainty (e.g., Wolman-related survival) and health-related quality of life may be resolved by more data but given the rarity of the condition this would be slow to accrue even where studies were multinational.

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Appendices

10.1 Appendix 7.1: Details of changes made to CEM for the factual accuracy check

Reason	Cell name	CEM	EAG revised
Revising the equation for EQ-5D weighted average (suggested by company at clarification step)	HU norms P6 to P91	=(O6*P_Prop_Male)+(N6*(1-P_Prop_Male))*DSA_HU_norms to =((O6*P_Prop_Male)+(N6*(1-P_Prop_Male)))*DSA_HU_norms	=(O6*P_Prop_Male)+(N6*(1-P_Prop_Male))*DSA_HU_norms to =((O6*P_Prop_Male)+(N6*(1-P_Prop_Male)))*DSA_HU_norms
Correcting health utility score referring cells for age-adjusted TTO and VAS	HU norms D5 to D91	=INDEX(AR$5:AR$12,MATCH($B5,$AP$5:$AP$12,1),1)	=INDEX(AY$5:AY$12,MATCH($B5,$AP$5:$AP$12,1),1)
	HU norms E5 to E91	=INDEX(AY$5:AY$12,MATCH($B5,$AP$5:$AP$12,1),1)	=INDEX(AR$5:AR$12,MATCH($B5,$AP$5:$AP$12,1),1)

Source: Produced by the EAG.

Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; TTO Time trade off,: VAS Visual analogue.

8.1 10.2 Appendix 7.2: Details of changes made in the CEM to produce the EAG base-case model (including base-case analysis and scenarios analysis)

Reason	Cell name	CEM	EAG revised
Defining an adjusting ratio of 0.9 as HR for utility childhood (0–11-year-old)	HU norms F5 to F16	=IFERROR(INDEX('HU norms'!$P$6:$P$91,MATCH($B6,'HU norms'!$I$6:$I$91,1),1),'HU norms'!$P$6)	=IFERROR(INDEX('HU norms'!$P$6:$P$91,MATCH($B6,'HU norms'!$I$6:$I$91,1),1),'HU norms'!$P$6)*$H$6
Changing HS2 utility (to same as HS1)	Inputs & Outputs E48	=INDEX('HU norms'!$G$5:$G$106,MATCH(Benefits!$C23,'HU norms'!$B$5:$B$106,1),1)/12	=IF($B23<'Inputs & Outputs'!$E$48, $F$11,INDEX('HU norms'!$G$5:$G$106,MATCH(Benefits!$C23,'HU norms'!$B$5:$B$106,1),1)/12)
Including utility decrement for nasogastric feeding (HS3, HS4)	Benefits K9	=INDEX('HU norms'!$G$5:$G$106,MATCH(Benefits!$C23,'HU norms'!$B$5:$B$106,1),1)/12	=INDEX('HU norms'!$G$5:$G$106,MATCH(Benefits!$C23,'HU norms'!$B$5:$B$106,1),1)/12-NG_utility_Dec
Including utility decrement for care	Inputs & Outputs F73	NA	=IF(C23<=$K$19,$K$18, 0)
Distributions for Wolman related mortality: The CEM only defined different distributions (K-M, Weibull, etc.) for Wolman related mortality for patients during the	Markov trace AH23 to AH1235	=IF($AE23>60,AH22,INDEX('Survival summary'!$C$62:$I$122, MATCH('Markov Traces'!$AE23,'Survival summary'!$B$62:$B$122,0), MATCH('Markov Traces'!AH$17,'Survival summary'!$C$61:$I$61,0)))	=IF($AE23<60,INDEX('Survival summary'!$C$5:$I$1205, MATCH('Markov Traces'!$AE23,'Survival summary'!$B$5:$B$1205,0), MATCH('Markov Traces'!AH$18,'Survival summary'!$C$4:$I$4,0)),INDEX('Survival summary'!$C$5:$I$1205,

trial period (i.e., below 5-years) and simply copied the last values across for the time period above the 5-years for the patients` lifetime. The EAG revised the equations in the model and have provided options of including different distributions for Wolman related mortality for both the first 5-years and for the patients' lifetime above 5-years-old.			MATCH('Markov Traces'!$AE23,'Survival summary'!$B$5:$B$1205,0), MATCH('Markov Traces'!AH$17,'Survival summary'!$C$4:$I$4,0)))
	Markov trace AI23 to AI1235	=IF($AE23>60,AI22,INDEX('Survival summary'!$J$62:$P$122,MATCH('Markov Traces'!$AE23,'Survival summary'!$B$62:$B$122,0), MATCH('Markov Traces'!AI$17,'Survival summary'!$J$61:$P$61,0)))	=IF($AE23<60,INDEX('Survival summary'!$J$5:$P$1205,MATCH('Markov Traces'!$AE23,'Survival summary'!$B$5:$B$1205,0), MATCH('Markov Traces'!AI$18,'Survival summary'!$J$4:$P$4,0)),INDEX('Survival summary'!$J$5:$P$1205,MATCH('Markov Traces'!$AE23,'Survival summary'!$B$5:$B$1205,0), MATCH('Markov Traces'!AI$17,'Survival summary'!$J$4:$P$4,0)))
	Markov trace AJ23 to AJ1235	=IF($AE23<60,INDEX('Survival summary'!$Q$62:$W$122,MATCH('Markov Traces'!$AE23,'Survival summary'!$B$62:$B$122,0),MATCH('Markov Traces'!AJ$17,'Survival summary'!$Q$61:$W$61,0)),IF($AE23<$AN$14+1,AJ22,MIN($AM$11,AJ22)))	=IF($AE23<60,INDEX('Survival summary'!$Q$5:$W$1205,MATCH('Markov Traces'!$AE23,'Survival summary'!$B$5:$B$12055,0),MATCH('Markov Traces'!AJ$18,'Survival summary'!$Q$4:$W$4,0)),INDEX('Survival summary'!$Q$5:$W$1205,MATCH('Markov Traces'!$AE23,'Survival summary'!$B$5:$B$1205,0),MATCH('Markov Traces'!AJ$17,'Survival summary'!$Q$4:$W$4,0)))

Source: Produced by the EAG.

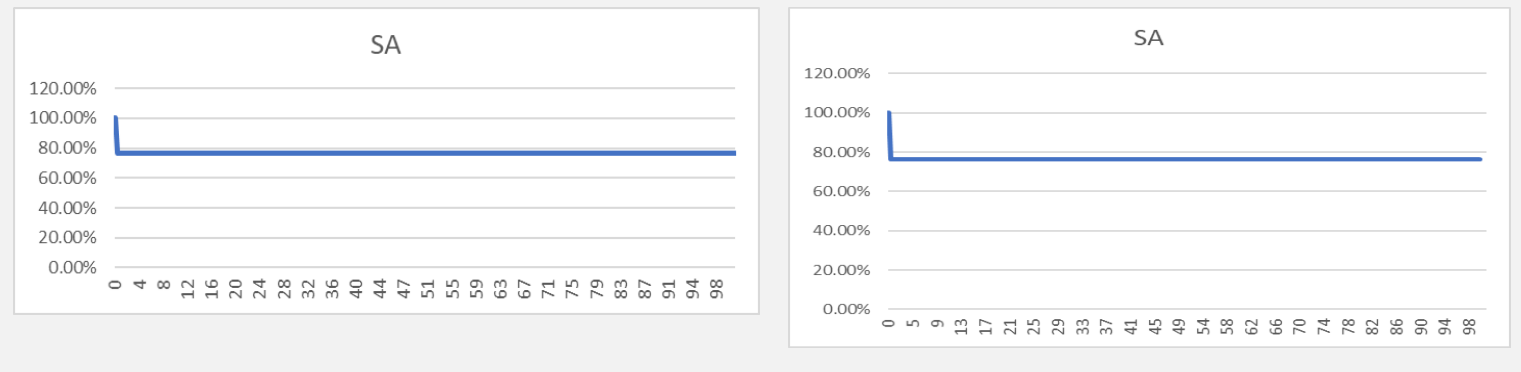
Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; HR, hazard ratio; HS, health state; K-M, Kaplan-Meier

8.2 10.3 Appendix 7.3: Alternative Wolman related disease survival in treated group

The horizontal (x-)axis for all survival curves presented below display the time in years from 0-100-years. The vertical (y-)axis for all survival curves presented below show the probability of surviving (or the proportion of people surviving) on a scale of 0% to 100% starting at 100% at birth (age 0-years).

Figure A1: Exponential fitted model for Wolman related disease survival in treated group

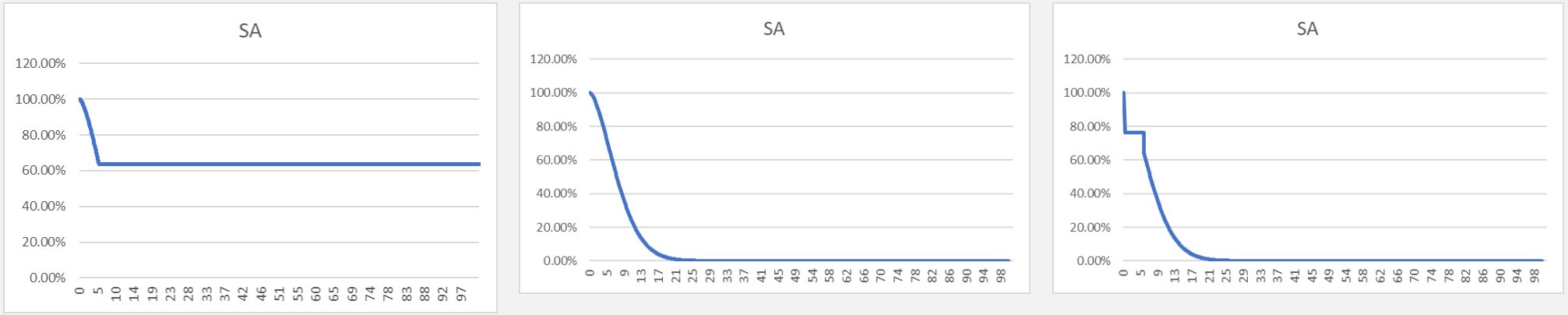
a) CEM model **b) EAG base-case model**



Source: Produced by the EAG.
Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; SA, sebelipase alfa.

Figure A2: Weibull fitted model for Wolman related disease survival in treated group

a) CEM model **b) EAG base-case model** **c) EAG base-case model (K-M for below 5 year)**

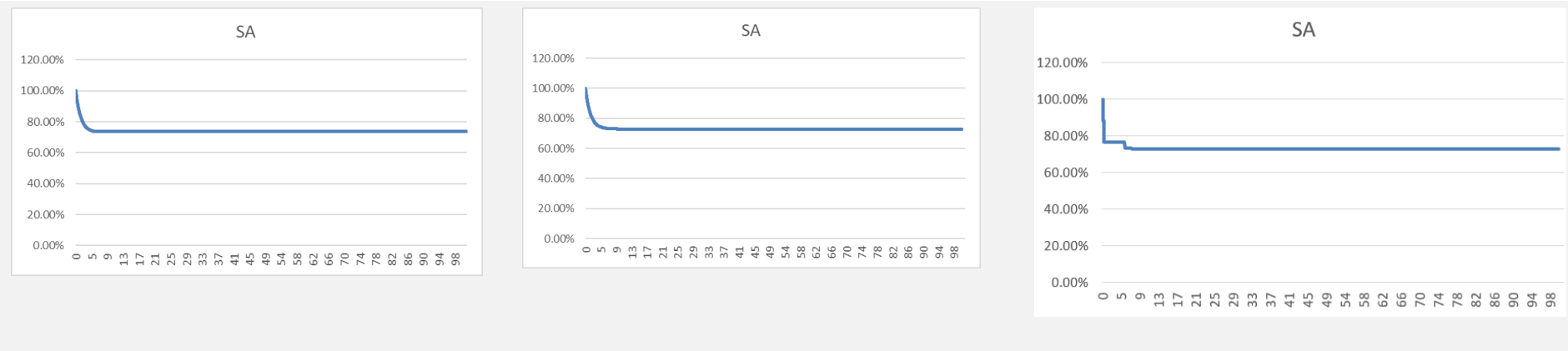


Source: Produced by the EAG.

Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; K-M, Kaplan-Meier; SA, sebelipase alfa.

Figure A3: Gompertz fitted model for Wolman related disease survival in treated group

a) CEM model **b) EAG base-case model** **c) EAG base-case model (K-M for below 5 year)**

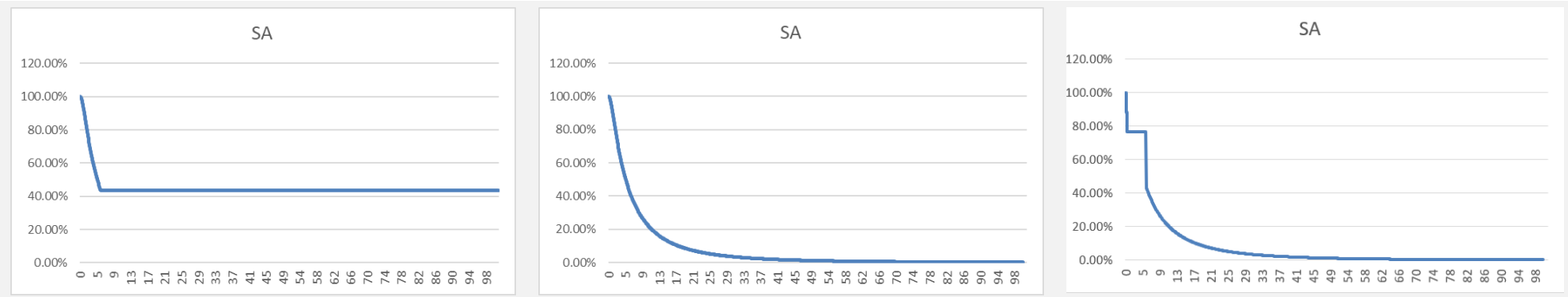


Source: Produced by the EAG.

Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; K-M, Kaplan-Meier; SA, sebelipase alfa.

Figure A4: Log-normal fitted model for Wolman related disease survival in treated group

a) CEM model **b) EAG base-case model** **c) EAG base-case model (K-M for below 5 year)**

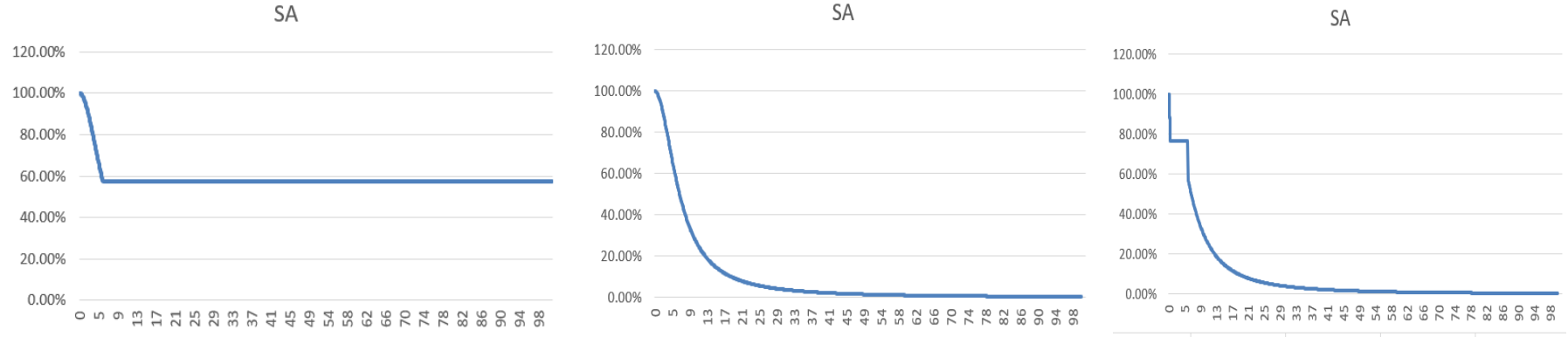


Source: Produced by the EAG.

Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; K-M, Kaplan-Meier; SA, sebelipase alfa.

Figure A5: Log-logistic fitted model for Wolman related disease survival in treated group

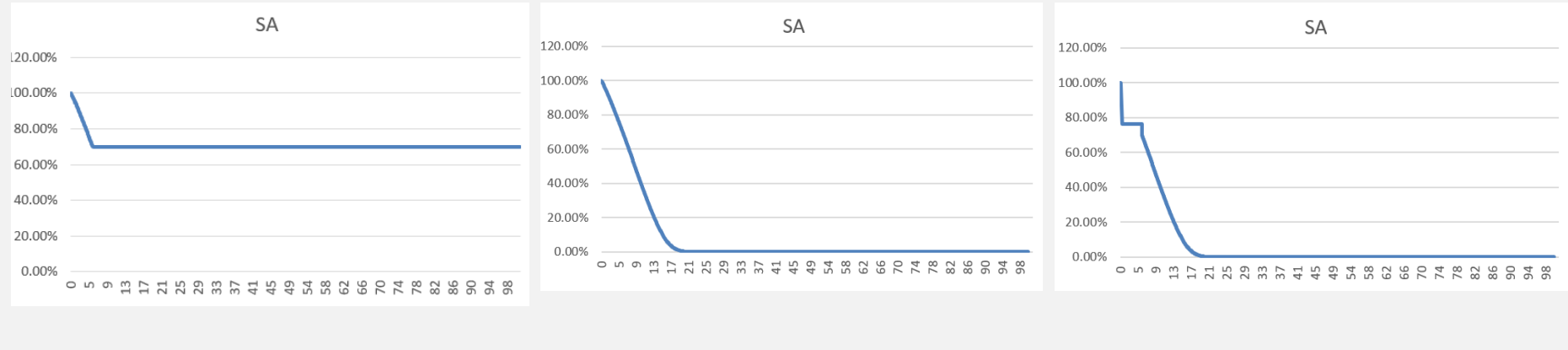
a) CEM model **b) EAG base-case model** **c) EAG base-case model (K-M for below 5 year)**



Source: Produced by the EAG.
Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; K-M, Kaplan-Meier; SA, sebelipase alfa.

Figure A6: Generalised Gamma fitted model for Wolman related disease survival in treated group

a) CEM model **b) EAG base-case model** **c) EAG base-case model (K-M for below 5 year)**



Source: Produced by the EAG.
Abbreviations: CEM, company economic model; EAG, Evidence Assessment Group; K-M, Kaplan-Meier; SA, sebelipase alfa.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Sebelipase alfa for treating Wolman disease [ID3995]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 02 February 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Evaluation 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 Key Issue 6 Discount rate for costs and QALYs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report pages 19, 139, 164. The company acknowledges the EAG's balanced appraisal of its submission for sebelipase alpha but believe the EAGs description of the company's use of 1.5% as a violation [of the reference case] to be inaccurate (p142). Use of the 1.5% discount rate in the base case is premised on well-defined criteria set out in the NICE manual.	Rather than describe the base case position as a violation, we would suggest reframing the discussion on the use of the 1.5% discount rate in quantitative terms with reference to the content in subsections 4.5.3, 4.5.4 and 4.5.5 of the NICE health technology evaluation manual 2022.	The manual states the follow: *The committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met:* *The technology is for people who would otherwise die or have a very severely impaired life. It is likely to restore them to full or near-full health. The benefits are likely to be sustained over a very long period.* The company believes that compelling evidence is provided within their submission to demonstrate that all three criteria are met.	As set out in section 4.2 and table 4.1 of the NICE manual, the reference case discount rate is 3.5% which the EAG have applied to their base-case analyses. It is for the NICE committee (as stated in the NICE manual) to judge whether it is material in this circumstance. No change to the report has been made.

Issue 2 Key Issue 10 Uncertainty over feasibility of vial sharing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report pages 22 and 23, 162, 165 In respect to the EAGs findings of inconsistent results indicating an issue with the CEM, the company would like to clarify that '1-week round-up' ("Weight and Dosing" cell J9) is the base case selection and does not involve vial sharing but single use of vials (the administration cycle is 1 week); i.e., the base case calculates that 2 vials are costed when the content requirement equates to 1.2 vials. The '2-week round-up' selection provides the single scenario analysis for the calculation of vial consumption. In the CS CEM this selection reduces the lifetime consumption from 148 in the base case to 133 vials in the scenario. This is reflected in the reduced cost	If the company have correctly interpreted this highlighted issue as misunderstanding of the term '1-week round-up', then perhaps the EAG would remove this concern within key issue 10 of their report. Notwithstanding any broader commentary within the key issue.	Given the problem described and checking of the CEM, the company do not believe the scenario outcome to produce an inconsistent result. The real-world practice of modulating vial consumption within an individual's treatment schedule leads to a lower consumption of sebelipase alpha vials and lower lifetime ERT cost. As the scenario shows.	Within the CEM, there was an option to explore the impact of a scenario for 1-week vial sharing as well as a scenario for 2-week vial sharing (which formed a scenario in the CS and the EAG report). The inclusion of the 1-week option suggested that this was an option that could be explored. As suggested by the company and interpreted by the EAG, the opinion is that 1-week vial sharing in the CEM may not be relevant due to the weekly nature for the administration of the drug. The EAG notes that this option is not part of the scenario analyses submitted by the company. Further work conducted by the EAG has identified that the 2-week round-up as explored within the model should equal the 1-week round-up vial sharing scenario.

and reduced ICER of sebelipase alpha in the scenario result (ICER reduces from £239,608 to £224,458).			The EAG do note in the report that vial sharing could reduce costs and reduce the ICER. However, the ambiguity within the model does remain and hence no change to the report has been made.

Issue 3 Decision modifier weighting (Not identified by the EAG as a key issue)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 126. The company acknowledge the balanced appraisal of its submission for sebelipase alpha but contest as inaccurate the EAGs description of the company's use of the 3.0 decision modifier as a matter of judgement.	Please reframe the commentary with reference to subsections 6.2.25 of the NICE health technology evaluation manual 2022. Please state the number of undiscounted QALYs gained by sebelipase alpha in the company and EAG base cases.	The manual states in Table 6.2 that 'greater than or equal to 30 [QALYs gained]' is the defining qualification for a decision modifier of 3. In turn the appropriate HST Willingness to Pay threshold is £300,000 per QALY gained. The company believe that compelling evidence is provided within their submission to demonstrate that at least 30 QALYs are gained and would suggest that framing the discussion with quantitative commentary	The EAG have not commented on this except as a matter of judgement. The EAG has concentrated on showing the ICER for various scenarios and has shown the likelihood that sebelipase alfa is cost-effective at various thresholds from £0 to greater than £300,000. Ultimately it is the NICE committee who make the decision and not the EAG. No change to the report has been made.

		against the criteria would be insightful.	

Issue 4 Key Issue 7 Uncertainty in extrapolation models used to estimate Wolman related survival

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 139 and 140; Figure 7.1 and Figure 7.2 The Kaplan-Meier plots in each of these figures appears to show survival that does not represent the pooled data from patients participating on CL-03 and CL-08. Mortality with sebelipase alpha appears to be overestimated (all deaths occurring within the first month).	Please could the EAG check the KM curves and provide the underlying evidence and or assumptions around long-term survival used to describe the parametric curves in Figure 7.2.	Visual inspection of the KM plots in Figures 7.1 and 7.2 suggest a possible error in the illustrative implementation of the trial outcomes.	Figure 7.1 and Figure 7.2 are based on CEM inputs (data from patients participating in CL-03 and CL-08). The time scale in both Figure 7.1 and Figure 7.2 is in years (Figure 1 has been relabeled). The EAG revised the equations in the CEM to provide a parametric distribution for the patients' lifetime. As mentioned in the EAG report, the CEM used a fixed value of survival after 60 months (5-year) for all parametric distributions and the EAG has explored the impact of changing this assumption. No change to the report has been made.

Issue 5 Incorrect data points

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Key issue 1, Page 14 'The company states however that rarely patients can present with the rapidly progressive and advanced form of LAL-D between 6 and 24-months; noting only on [redacted] might present with rapidly progressive disease between 6 to 24-months.[1]'	The company propose the following changes: 'The company states however that rarely patients can present with the rapidly progressive and advanced form of LAL-D between 6 and 24-months; [redacted] where the patient presented with an advanced form of LAL-D between 6 and 24-months.'	The number of patients diagnosed with rapidly progressive LAL-D between the age of 6 to 24 months is currently reported as one patient every other year, which is incorrect. The reference to an [redacted] relates to the observed incidence in the UK of patients with rapidly progressive LAL-D presenting in patients <6 months of age. Data held on file by the company identify [redacted] in the UK of rapidly progressed and advanced LAL-D in patients aged between 6 and 24-months over the last	Many thanks for highlighting this. The EAG has made the following change: 'The company states however that rarely patients can present with the rapidly progressive and advanced form of LAL-D between 6 and 24-months; there have been [redacted] where the patient presented with an advanced form of LAL-D between 6 and 24 months.'

		7-years.	
EAG report, Section 2.1.7, Page 25 'Among the subgroup in LAL-1-NH01 who were both untreated and had experienced early growth failure (number of people; N=21), the median age of death was [redacted].	The company propose the following wording: 'The median age of death in the untreated population (n = 21) of the LAL-1-NH01 study was 3.0 months.'	Data point to be corrected from '[redacted]' to '3.0 months' to align with published evidence. Please note this data point is published in Jones et al. 2016[2] and therefore does not need to be marked as AIC.	Many thanks for highlighting this. The EAG has amended the text to align with the published data and removed the AIC marking. The EAG has made the following change: 'Among the subgroup in LAL-1-NH01 who were both untreated and had experienced early growth failure (number of people; N=21), the median age of death was 3.0 months.'
EAG report, Page 85 'This can be compared to the natural history cohort where median age of death was 3.5 months and none of the 21 untreated patients who had early growth failure survived beyond 12-months of age.'	Please consider specifying the population of focus for the reported median age of death in the LAL-1-NH01 study.	The median age of death for the three populations in the LAL-1-NH01 study are as follows: • Overall cohort: 3.7 months • Patients with early growth failure: 3.5 months • Patients who were untreated with early growth failure:	The EAG have amended to clarify and made the following change: 'median age of death in patients with early growth failure (N=26) was 3.5 months'.

		3.0 months	

Issue 6 Minor text amendments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 1, Table 1.12, Page 23	Sixth row, first column requires the following text: 'BSC'	For completeness	This has now been added.
EAG report, Section 4.1.6.2.1, Table 4.4, Page 52	Information is missing from the population row of the table for the LAL-1-NH01 trial. Please consider including the following: 'Patients with a confirmed diagnosis of LAL Deficiency prior to 2 years of age'	For completeness	The following text has now been added: 'Patients with a confirmed diagnosis of LAL-D prior to 2 years of age'.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, Section 2.1.8, Page 26 '[redacted]	As the Hassall et al. 2022[3] paper is published and therefore the data is in the public domain, the text does not require marking as AIC.	'A qualitative study has been carried out however with parents and caregivers of children living with rapidly progressive LAL-D exploring their own quality of life which found that the themes impacting parents were around living with uncertainty, feeling powerless and ultimately	Many thanks for noting this. AIC highlighting has now been removed from this sentence.

<table>
<tr><td>[redacted]3’</td><td></td><td>accepting a life with LAL-D.[3]’</td><td></td></tr>
<tr><td>EAG report, Section 4.1.7, Page 57

‘Of the [redacted] patients who were enrolled and allocated to receive treatment for LAL-CL03 [redacted] completed, [redacted] people died before 12-months of age, due to [redacted] ([redacted]), [redacted] ([redacted]) and peritoneal haemorrhage ([redacted]) and [redacted] person died due to [redacted] at age 15-months. ‘</td><td>The latter part of the sentence does not require AIC marking as this data is published in Vijay et al. 2021.[4]</td><td>‘Of the [redacted] patients who were enrolled and allocated to receive treatment for LAL-CL03 [redacted] completed, three people died before 12-months of age, due to liver failure (N=1), cardiac arrest (N=1) and peritoneal haemorrhage (N=1) and one person died due to sudden cardiac death at age 15-months.</td><td>Many thanks for identifying this. The AIC highlighting has been removed as recommended. The Vijay et al. 2021 reference has been included alongside a reference to the Consort diagram that is detailed in the appendices of the company submission.</td></tr>
<tr><td>EAG report, Section 4.1.10.3, Table 4.8, Page 68-69</td><td>Several data points in the LAL-1-NH01 columns of Table 4.8 are unpublished and therefore require marking as AIC.</td><td><table>
<tr><th></th><th colspan="2">LAL-1-NH01</th></tr>
<tr><th></th><th>Baseline (diagnosis) (N=35), median (range)</th><th>Death or at last measurement median (range)</th></tr>
<tr><td>ALT</td><td></td><td></td></tr>
<tr><td>U/L</td><td>56.5[i]</td><td>110.5 (13-851)[k]</td></tr>
<tr><td>µkat/L</td><td>0.94[i]</td><td>1.85 (0.22-14.21)[k]</td></tr>
<tr><td>AST</td><td></td><td></td></tr>
</table></td><td>Many thanks for identifying this. The AIC highlighting has been applied as recommended. However, it is unclear why total cholesterol (2.99 mmol/L) is not highlighted, could you confirm this is correct?</td></tr>
</table>

		U/L	151[j]	283 (35-4,250)[l]
		µkat/L	2.52[j]	4.73 (0.58-70.97)[l]
		Ferritin		
		µg/L (ng/mL)	[redacted]	[redacted]
		Albumin, g/L	[redacted]	[redacted]
		Haemoglobin, g/L	[redacted]	[redacted]
		Total cholesterol		
		mg/dL	[redacted]	[redacted]
		mmol/L	2.99 (N=18)	[redacted]
		LDL-C		
		mg/dL	[redacted]	[redacted]
		mmol/L	[redacted]	[redacted]
		HDL-C		
		mg/dL	[redacted]	[redacted]

		<table><tr><td>mmol/L</td><td></td><td></td></tr><tr><td>Triglycerides</td><td></td><td></td></tr><tr><td>mg/dL</td><td></td><td></td></tr><tr><td>mmol/L</td><td></td><td></td></tr><tr><td>Liver volume, MN</td><td></td><td></td></tr><tr><td>Spleen volume, MN</td><td></td><td></td></tr></table>	
EAG report, Section 4.1.10.10, Page 83 'Data provided for LAL-CL03 report ten cardiovascular events...'	Data point unpublished and therefore requires AIC marking as	'Data provided for LAL-CL03 report [redacted] cardiovascular events…'	Many thanks for highlighting this, the AIC marking has now been applied.
EAG report, Page 85 'The proportion of patients surviving to 12-months in LAL-CL08 is 90% (95% CI: 55.5% to 99.7%)'	Confidence intervals are unpublished and therefore require AIC marking.	'The proportion of patients surviving to 12-months in LAL-CL08 is 90% (95% CI: [redacted]% to [redacted]%)'	Many thanks for highlighting this, the AIC marking has now been applied (and a reference added for the preceeding sentence).
EAG report, Table 1.10 pages 21 & 22; Table 6.3 Scenario 21 page 134; Table 7.4 Scenario 21 page 151; Table 7.5 Scenario 21 page 155	Any information or suggestions relating to a cost cap is commercially sensitive and we therefore kindly request that any	Any reference to cost cap value to be marked as CIC: Table 1.10, column 2, row 2 (paragraph 2) and row 4: [redacted]	In Document B of the CS table 60 p159 the sensitivity analysis (number 21) referring to the cost cap of £[redacted] pa was not highlighted as CIC. As requested

Reference to EAG scenario analysis exploring use of cost cap of [redacted]	reference to the explored cost cap value is marked as CIC.	Table 6.3, Scenario 21, column 2: [redacted] Table 7.4, Scenario 21, column 2: [redacted] Table 7.5, Scenario 21, column 2: [redacted]	we have now applied the marking as CIC to this value.

References

1. Alexion Pharmaceuticals Inc. Sebelipase alfa for treating Wolman disease (rapidly progressive LAL-D) [ID3995] Document B. Company evidence submission. Highly specialised technologies evaluation (HST). Boston, Massachusetts: Alexion Pharmaceuticals Inc, 2022.
2. Jones SA, Valayannopoulos V, Schneider E, et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. *Genet Med*. 2016; 18(5):452-8.
3. Hassall S, Smith DM, Rust S, et al. “Why them, why me, why us?” The experiences of parents of children with lysosomal acid lipase deficiency: an interpretative phenomenological analysis study. *Orphanet J Rare Dis*. 2022; 17(1):193.
4. Vijay S, Brassier A, Ghosh A, et al. Long-term survival with sebelipase alfa enzyme replacement therapy in infants with rapidly progressive lysosomal acid lipase deficiency: final results from 2 open-label studies. *Orphanet J Rare Dis*. 2021; 16(1):13.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Sebelipase alfa for treating Wolman disease [ID3995]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13th March 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Alexion Pharma UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR (as summarised in EAG report section 1.3 and 1.4 (pages 14-23)).

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. The age of symptom onset in Wolman disease/rapidly progressive LAL-D	Yes	While the vast majority of patients with rapidly progressive LAL-D are diagnosed within the first 3-9 months of life, in some cases, diagnosis may be delayed. At the scoping stage of this appraisal, clinicians requested that the definition of rapidly progressive LAL-D should include patients with diagnosis up to 24 months of age, to ensure patients with late diagnosis are not excluded from accessing sebelipase alfa. It should be noted that in UK clinical practice, only [redacted] patients in the past [redacted] Both patients were diagnosed between 18 and 24 months of age XXX [redacted]

		We would anticipate that the clinical experts managing these patients would be able to provide additional information, if required.
2. The role of HSCT in the pathway for patients with rapidly progressive LAL-D	No	We acknowledge the uncertainty around the current and future use of HSCT for patients with rapidly progressive LAL-D. As presented in the submission dossier, we note that the management of patients with rapidly progressive LAL-D is rapidly evolving, and UK clinical experts are at the forefront of this evolution. We have modelled what we understand to be an accurate representation of current (and future) clinical practice, based on our discussions with UK clinical experts. However, we would defer to Dr Jones to confirm this information.
3. Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa	No	This key issue mainly refers to uncertainty around long-term effectiveness associated with uncertainty around use of HSCT and potential loss of venous access. Uncertainty associated with the use of HSCT is discussed in response to key issue 2 above. We also acknowledge the uncertainty associated with the loss of venous access leading clinical experts to consider the use of HSCT. The company and EAG base case assume loss of venous access sufficient to prompt HSCT at 30 years, with additional scenarios presented exploring earlier and later loss of venous access. We note, however, that the EAG's clinical expert suggested loss of venous access would likely occur before 30 years. We would suggest therefore that both the company and EAG base case positions appear conservative and the EAG may wish to consider updating their base case to align with the feedback received from their clinical expert. We would defer to the clinical experts to provide key clinical input on the expectations for UK clinical practice.
4. Trial eligibility criteria and generalisability to the patients in England with	Yes	We note the EAG's comment that this is a currently unresolvable issue that is of limited cause for concern.

rapidly progressive LAL-D who are diagnosed between 6 and 24 months		While the EAG indicates that long-term data collection in patients with disease onset between 6 and 24 months may be helpful, we note that there have only been [redacted] such patients in the UK in the past [redacted] and collection of long-term data in such a small population would be unlikely to address this uncertainty within a reasonable timeframe. [redacted] In terms of the UK generalisability of the overall dataset presented in the company submission, we would like to flag that [redacted] patients in CL08 clinical trial and [redacted] patients in CL03 were UK patients who remain on treatment in the context of the Alexion compassionate global access to medicines programme. Further, supporting information from the sebelipase alfa global registry, which also includes all treated UK patients, were also presented in the company submission. We therefore maintain that the clinical data presented are indeed generalisable to the UK.
5. Uncertainty around ability to change dose of sebelipase alfa	No	We acknowledge the EAG's comment on uncertainty around dosing of sebelipase alfa following HSCT. We have modelled what we understand to be an accurate representation of current expectations for UK clinical practice, based on discussions with UK clinical experts, with patients able to reduce ERT doses post HSCT and ultimately discontinue ERT treatment. As discussed in response to key issue 2 above, the management of patients with rapidly progressive LAL-D is rapidly evolving, with UK clinical experts at the forefront of this evolution; therefore, we would defer to Dr Jones to provide his expertise on this issue.
6. Choice of discount rate for costs and QALYs	Yes	Both the Comany and EAG base case estimates of both quality-adjusted and unadjusted life-year gain are over 30 years. The presented scenarios are also

		supportive of this case, with the exception of the EAG 'outlier' scenarios described in Issue 7, below. Precedence for the adoption of 1.5% discount rates in HST and STA appraisals where significant life-year gains were modelled comes from Eculizumab for treating atypical haemolytic uraemic syndrome (HST1), Dinutuximab beta for treating neuroblastoma (TA538), and Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (HST7). In the appraisal of eculizumab (also manufactured by Alexion) the following commentary was offered in the FAD: *The Committee noted advice from NICE to its advisory bodies that states that, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near-full health, and when this is sustained over a very long period (**normally at least 30 years**), a discount rate of 1.5% for costs and benefits may be considered. This advice can only be implemented if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Having referred to this advice, the Committee considered that substantial restoration of health for a very long period is achieved with ongoing treatment with eculizumab. The Committee heard from the clinical experts that the underlying complement disorder is essentially reversed with eculizumab treatment and that there is emerging evidence that benefits are sustained over time. The Committee concluded that there was a case for applying a discount rate of 1.5%.* We note that the while the 2022 Combined manual supersedes HST1, we maintain that sebelipase alfa treatment satisfies the current criteria for application of the 1.5% non-reference case discounting as follows: • The technology is for people who would otherwise die or have a very severely impaired life. • It is likely to restore them to full or near-full health. • The benefits are likely to be sustained over a very long period.

7. Uncertainty in extrapolation models used to estimate Wolman related survival	No	We query the new survival scenarios presented by the EAG (EAG report, page 166, Table 7.7, scenarios 8-11). Each of these retain the KM estimates through the 5-year trial follow-up, they then use exponential, Weibull, Gompertz and lognormal parametric curves to predict survival from year 6. Our concern is the absence of any evidential basis for their parameterisation, i.e., what are the estimates based on? Three of these four curves predict a high mortality rate on-treatment, which has not been observed in trials, nor in longer term observation of patients (some of whom have been on treatment for as long as 10+ years), nor do they appear to align with any available data, and they may therefore be misinformative. We would be concerned if these scenarios were presented for committee consideration without the context of their clinical plausibility. We would therefore suggest they should be discussed with Dr Jones to confirm their plausibility prior to presentation to the Committee.
8. Uncertainty in the utility estimates applied for those treated with sebelipase alfa	Yes	We acknowledge the uncertainty around the utility estimates used in the company submission and note that the EAG base case uses the same approach as the company submission. There is, however, one scenario presented by the EAG that we do not believe to be clinically plausible, which relates to the application of a 20% reduction in utility across the treated patient population (EAG report, page 164, Table 7.6, scenario 2). The EAG use a supporting argument based on evidence for patients with Pompe disease in the Netherlands. However, this is unlikely to be an appropriate comparison, as Pompe disease is very different to rapidly progressive LAL-D, and patients with Pompe are likely to face a number of long-term issues following treatment, whereas LAL-D patients are able to thrive and live normal lives. The EAG's argument also implies that the general population PedsQL score is 100% across all domains, which we would suggest is not realistic, as the general population scores are assumed to also include individuals with chronic conditions, other existing health issues, etc. A targeted search online for supporting information identified a UK validation study of the PedsQL

		instrument, that reported a general population self-reported mean (SD) PedsQL score of 82.25 (13.09) and a proxy-reported mean (SD) PedsQL score of 81.12 (13.85).[1][Upton et al., 2005] The results were also analysed for subgroups of 'healthy' children compared to those with chronic conditions, with mean (SD) self-reported PedsQL scores of 83.89 (11.84) for healthy children, compared to 82.46 (12.76) for those with diabetes, 75.68 (15.40) for those with cancer, 75.31 (16.90) for those with asthma, and 74.18 (14.66) for those with irritable bowel disease. Given the reduction in PedsQL score for severe conditions, such as cancer, was around 10%, it does not seem plausible that patients receiving treatment and observing dietary restriction but otherwise being in good health would experience a decrement of 20%. In previous NICE appraisals, such as HST5, a utility decrement of 0.05 for patients receiving IV therapy compared to an oral therapy was considered to be acceptable. Therefore, we would argue that the use of the general population values (also EAG base case), or values up to 10% lower than the base case are appropriate (as presented in scenario 28 of the company submission). New evidence in support of this comes from a study in children with peanut allergy, which is potentially analogous with respect to dietary restriction.[2] The mean caregiver-reported utility of 13 UK children with mild peanut allergy aged 4-15 using the EQ5D tool was 0.863 (SD 0.354). This is 7% lower than the company submission base case utility in the model for ages 0-21 (based on general population utility norms). Post-HSCT, once patients have been able to taper off sebelipase alfa treatment, we maintain that general population utility values would be the most appropriate to use, as per both the company and EAG base case. This reflects the patients no longer requiring treatment and would be in line with the post-HSCT utility values accepted in the technology appraisals for CAR-T therapies. We would again defer to Dr Jones to provide his input and experience on this issue.

9. Uncertainty over life cycle price of sebelipase alfa	No	We note the uncertainty on the issue of medicine prices highlighted by the EAG and agree that prices tend to evolve over the course of a product's life cycle. While we welcome the EAG analysis, we would like to confirm that neither the company nor the EAG base case includes any such price evolution.
10. Uncertainty over feasibility of vial sharing	No [although additional clarification on existing methods is provided]	This issue was discussed with the EAG at the technical engagement meeting and some confusion over the terminology was clarified. It was confirmed that in the company base case, no vial sharing/dose modulation was used; rather, vial usage was 'rounded up' such that if a patient required the use of part of an additional vial, this was counted as a full additional vial. Therefore, wastage was fully accounted for with this approach. The EAG noted that they would reassess their scenario considering a '1-week round-up' and would update their scenarios to reflect this. While this conservative approach was included in the company base case, we note that the approach taken in UK clinical practice, as also identified by the EAG, is to take a dose modulation approach over a 2-week period, whereby doses are adjusted from one week to the next to avoid/reduce wastage. If this approach is confirmed by UK clinical experts as being part of standard practice, then we would suggest that the scenario that includes the 2-week dose modulation should be considered as the base case for consideration by the Committee.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.

Sensitivity analyses around revised base case

NA

References

1. Upton P, Eiser C, Cheung I, et al. Measurement properties of the UK-English version of the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. *Health Qual Life Outcomes*. 2005; 3:22.
2. Acaster S, Gallop K, de Vries J, et al. Peanut allergy impact on productivity and quality of life (PAPRIQUA): Caregiver-reported psychosocial impact of peanut allergy on children. *Clin Exp Allergy*. 2020; 50(11):1249-57.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Sebelipase alfa for treating Wolman disease [ID3995]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Wolman disease or caring for a patient with Wolman disease. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (as summarised in EAG report section 1.3 and 1.4 (pages 14-23)).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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 evaluation 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.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13th March.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with Wolman disease

Table 1 About you, Wolman disease, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with Wolman disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Wolman disease? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The MPS Society
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: **Patient, clinical and previous evaluation (ID737)** ☒ I have completed part 2 of the statement **after attending** the expert

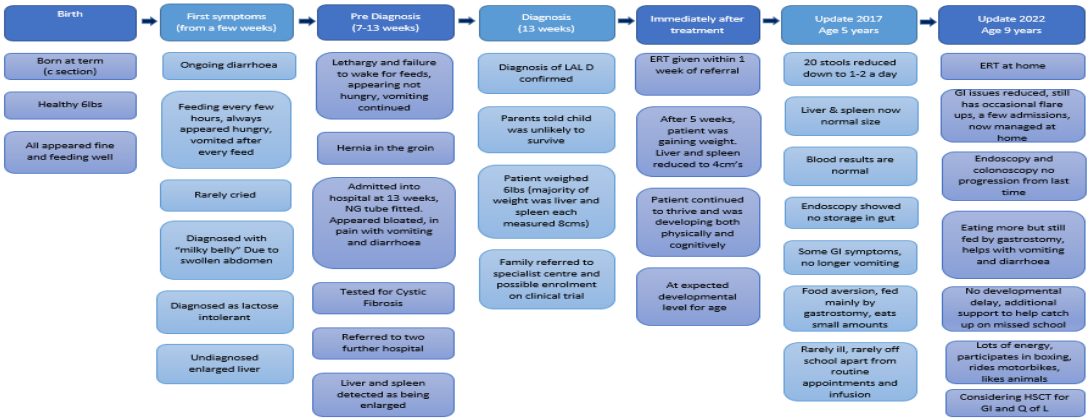
	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Wolman disease? **If you are a carer (for someone with Wolman disease) please share your experience of caring for them**	**Diagnosis / early few weeks / months** Infantile LAL D is a fatal condition. Natural History data clearly shows that without treatment of Sebelipase alfa, 100% of all infant patients died, 89% of patients died before their 1st birthday with the mean age of death being 3.7 months (Jones et al 2015). Despite exhibiting symptoms, within the first few weeks of life, diagnosis of the condition is not usually made until months later. Most babies condition is critical at diagnosis, with many only surviving days or weeks without ERT treatment and intensive clinical care. Patient expert in committee Id xxxxx 2016 shared (2) **"*Our first child with this condition was born with a large stomach. He soon started not tolerating his feeds, taking little milk and what he did he vomited up. His birth weight was low but the health visitors attributed his swollen stomach to weak muscles and gulping air during feeds".*** At 2 months after multiple tests Lal D was suspected and the family were referred to Manchester as their hospital had not heard of the condition. ***"At this time our son was 3 months old and was admitted to ICU as he was very poorly with malnutrition, vomiting and diarrhoea, high temperature and jaundice. He was transferred back to our local hospital and died shortly".*** This was in 2002**.** ***"At the time our first son was diagnosed, there was little or no information known / available about this condition. The seriousness of his condition was not recognised or known but in all fairness the outcome would not have been different because at the time no treatment was available. If we had known sooner however, we could have spent more quality time with him, rather than trying to get a diagnosis and being sent from hospital to hospital as no one knew what was wrong"*** **(2).** ***"The help and information for our son now is totally different and the benefit of having him diagnosed soon after birth and being able to start on life saving treatment is beyond our***

	expectations (2016). No one prepares you for parenthood so the thought of losing your first child was unexplainable and no one could tell you how to manage your self emotions. Waiting for the death is the worst thing. **At least with our son now, every week there this hope" (2)** One child in the study was diagnosed at 3 days old due to excess fluid on the brain in vitro and older sibling who died from LAL D at 12 weeks (1) One child was diagnosed at 6 weeks, initial concerns reported by parent at 2-3 weeks over vomiting and size of abdomen and were told this was nothing to worry about. Family history of LAL D, led to referral being made (1) One child diagnosed at 3 months, concerns reported within a few days of birth as child was constantly vomiting, had diarrhoea, not putting on weight, diagnosed as lactose intolerant, child had enlarged stomach and was struggling to put on weight, referral made (1) One child was not diagnosed until 2 years old. Symptoms of vomiting, diarrhoea, enlarged abdomen from birth. Ultrasound at 2-3 weeks old, showed enlarged liver. All symptoms attributed to child being born prematurely. Child experienced multiple gastrointestinal issues; failure to thrive, was not putting on weight and enlarged stomach was affecting their mobility and motor function (1) Families experienced shock, upset and confusion on receipt of the diagnosis (1) Local professionals had little to no information about the condition and parents were given the terminal diagnosis with little to no support. ***"It was shocking. Because it was the first time we experienced something like that. And just to give someone something like that, and not to explain anything like that. We were lost for words, we were shocked. Confused." (1)***

	"At [location] they gave us the condition on a piece of paper and left us to it. So, when we googled it, it came up they're not going to live longer than six months. And there's no cure." (1) All children diagnosed and if well enough have been fortunate to receive ERT either through enrolment in the clinical trial or compassionately. ***"And we've got that choice that we can take that. We don't have to do the trial, but we were going to lose the child, or we go on the drug trial and see how it goes. So, we accepted that. So, we got on the trial."(1)*** All survey responders had no hesitation in accepting treatment. However, one patient had to wait 5 months and faced needing a liver transplant before compassionate drug was agreed. Following initiation of ERT, parents reported a number of positive changes, especially related to gastrointestinal symptoms, energy, growth and weight ***"A big impact because we've still got him with us. If it wasn't because of that treatment, we would have lost him."(1)*** ***"So, before the treatment started, my daughter was quite… She wasn't active. She was spending most of her time sleeping, but once the treatment started, I saw a change in her. She was being more active and was sleeping less." (1)*** ***"It has made a big difference to us and him, to see his liver's clear and his spleen was clearing up. Not as much, but it was working. With the TPN they were giving him, he was gaining weight, it was helping him put on the weight. But with the enzyme, it was after a month or two we knew it was working, because when we read about it, they said he wasn't going to survive after six months, but it's been over six months now. It's definitely working, there are signs." (1)***

	"Up until the point he built antibodies, up until that point, his growth was going well. We could feel ourselves that the enzyme, up until the point, it worked. He stayed out of hospital. He was healthy. He was well, and that reflected on the growth chart. He was putting on weight, as he should be, and thriving as any six-month-old child should". (1) After treatment ERT ***"So, we don't have these explosive and smelly stools any longer. You might get one every couple of week or once a month, or something, but it's not a daily thing. She has got a lot more energy now. She's less fatigued."(1)*** ***"We do still have some issues with some trapped wind. I'd say that's the only lasting thing that we've… It can sometimes cause her a bit of pain and she knows what to do to get rid of it. Putting pressure… Maybe lying on a chair and putting pressure on it. But there's a significant difference now, compared to previously."(1)*** ERT & HSCT ***"He's completely fine now. It's done everything, to be honest, we didn't expect. The way he is in himself talking, moving about, eating, growing. He's a completely different child."(1)*** ***"And recently, since he's had so many chest infections last year and this year, he's losing a bit of his hearing. He's got some fluid in his eyes, struggling to hear. So, apart from that, he's running about, doing everything. Whatever he wants." (1)*** Activities of childhood ***"He likes to play football, cricket, hide and seek and all the normal school activities. He's got friends as well. So, he's very good in that sense.*** ***"Everything else is great, he's doing everything. Taking part in after school clubs, taking***

	part in the sports day. He's got a nativity coming up next month he's taking part in, so he's doing well. Yes, he is bossy. So, he's out and about on the playground and screaming and shouting. If he's at school, reading and football. Those are the two things that he wants. Or arts and crafts, painting, trying to recycle cans, bottles, trying to make something out of them. ***She's at Beavers. She goes to swimming lessons. To be honest, she always has loved craft activities as opposed to the more physical. Don't get me wrong, she loves being out and about and doing all sorts. But I think if you asked her what her favourite is, it would be sitting down, writing, drawing pictures, painting, all the craft things are her thing."*** <u>Progress in school</u> All children attend mainstream school and are achieving. Some require some level of support or supervision. For example; ensuring there are appropriate choice on dinner menu's to support a no fat diet, supervision during physical education and in the playground to make sure port-a-caths and gastrostomies are not damaged / dislodged. Some have additional support to help catch up on missed lessons and one needs support with some personal care needs. Many of these delays are owing to time missed from school due to Covid, hospital appointments and HSCT admission and period of isolation after. ***"His reading's outstanding. His reading is one of the best in his year. Maths is in the average. Everything else is great, he's doing everything. Taking part in after school clubs, taking part in the sports day. He's got a nativity coming up next month he's taking part in, so he's doing well."(1)*** ***"She actually quite enjoys maths, surprisingly. Certain elements of it anyway. I think she likes more English when it's story-telling. She has got quite an imagination, so she'll like to sit and write a poem or make a story up about something."(1)*** ***"at school, we've been advised by the teachers that, obviously, she's Year 4 at the moment,***

	she's at the same level as a Year 3 for English, and for maths, same as Year 2 students." Patient journey from Birth to Age 9yrs (diagnosed at 13 weeks) 
7a. What do you think of the current treatments and care available for Wolman 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?**	Patients are misdiagnosed and experience significant delays in receiving a diagnosis. Most patients are at end of life by the time they are diagnosed. ***"We know what it is like to lose a child at such a young age, where from birth it was evident that he had complex difficulties. Trying to get through the maze of healthcare professionals and tests to try and get a diagnosis and for a child to deteriorate to a life threatening stage in a matter or not just days but hours is unbearable and as parents we were helpless" (2).*** Whilst parents acknowledged the challenge for health care professionals in diagnosing such a rare condition, there are significant reported symptoms that were never investigated in depth. These included swollen abdomens and enlarged livers. One parent described how at 2-3 weeks old parents and doctors both raised concerns over the child's abdomen, an ultrasound showed an enlarged liver. This was attributed to the child's prematurity at birth,

	and no further tests were undertaken. For nearly all cases, had the presenting symptoms been linked together, a diagnosis may have been received earlier. (1) Although parents have said that the care their child received from their specialist centres has been good, the care received via their local hospital and care teams has been variable with concerns about the lack of knowledge and ability to assess and provide the right care. ***"At [location] they gave us the condition on a piece of paper and left us to it. So, when we googled it, it came up they're not going to live longer than six months. And there's no cure."(1)*** ***"It was shocking. Because it was the first time we experienced something like that. And just to give someone something like that, and not to explain anything like that. We were lost for words, we were shocked. Confused."(1)***
8. If there are disadvantages for patients of current NHS treatments for Wolman disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The alternative to receiving ERT for these patients is end of life care. HSCT is not an effective first line treatment. Findings from ten patients who underwent first line HSCT (Described by Jones et al 2015). Confirmed that out of 10 patients who underwent HSCT at a mean age of 5.4 months only two of the ten patients survived post-transplant. Survival age for these patients were 3yrs 10 months and 2yrs 2 months. D Bernstein MS, CGC; Director of the Lysosomal Storage Diseases Program at North Shore Hospital in Manhasset, New York, shared with me her experience of HSCT (2016). At their hospital they have diagnosed seven patients with LAL D. Five of these patients underwent a HSCT. Three died in infancy during the transplant process and one treated teenager died soon after HSCT. Only one patient has survived transplant (she is one of only two LAL D patients in the world who did not die secondary to HSCT). The child under D Bernstein's care is spending much of her life in the hospital for uncontrolled seizures, severe abdominal pain and recurrent infections. The other patient is under the care of Dr B Burton at the Children's Hospital, Chicago. Dr Burton confirmed that this patient was transplanted at 2 months old.

	She has short stature, restricted growth, is cognitively impaired and has recurrent liver disease. (3; 2016 ECD response) There is a risk of patients not being diagnosed, due to symptoms not being reviewed in a systematic way. Some infants could reach end of life before a diagnosis is explored. ICU care and understanding of the disease has been problematic for some centres. Some have wanted to withdraw treatment and supportive care early as they deemed patients were not recoverable. Situations include patients presenting with coagulopathy, pancytopenias, and possible HLH, which is typical for Infantile LAL D patients and is treatable with patients recovering well in most instances (3)
9a. If there are advantages of Sebelipase 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 Sebelipase 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**	Sebelipase alfa is life saving. Without access to this treatment, children will die a very cruel and unnecessary death. Clinicians view this treatment as being far superior to other ERT's currently in use. Children's height and weight has improved with a combination of ERT and nutritional support. One parent described how the changes in growth and weight were slow to start with after their child began ERT. After 6 weeks of ERT and TPN their child began to gain weight and continued to gain weight steadily reaching the 50th and 75th centile. Current weights reported for three patients showed they were all within the normal range for their sex and age. The size of the children's abdomens decreased, although this took time for some of the patients (1) Parents have shared how life saving ERT is. ***"A big impact because we've still got him with us. If it wasn't because of that treatment, we would have lost him."(1)*** One parent reported that ***"during the early treatment phase their child continued to thrive, put on weight and was meeting developmental milestones both physical and cognitive. Their liver and spleen returned to normal size, had no swollen abdomen, stomach issues***

	were much improved. Whilst they are still gastrotomy fed at night, they do suffer food aversion from spending so long not eating orally, require a low fat diet, they are however, sampling foods. GI symptoms such as vomiting are managed at home and episodes are becoming more infrequent. All clinical assessments showed child was at expected levels and school reports corroborate this"(2). ***"Yes, so the treatment did definitely help, and we felt that was a [unclear]. The vomiting and the diarrhoea reduced. It didn't stop altogether, but it was much less, and her stomach also went down." (1)*** ***"It has made a big difference to us and him, to see his liver's clear and his spleen was clearing up. Not as much, but it was working. With the TPN they were giving him, he was gaining weight, it was helping him put on the weight. But with the enzyme, it was after a month or two we knew it was working, because when we read about it, they said he wasn't going to survive after six months, but it's been over six months now. It's definitely working, there are signs."(1)*** The children were also less fatigued ***"So, before the treatment started, my daughter was quite… She wasn't active. She was spending most of her time sleeping, but once the treatment started, I saw a change in her. She was being more active and was sleeping less." (1)*** ***"She has got a lot more energy now. She's less fatigued. You can tell when there have been times… We try and not miss a dose. But there have been times when she has been poorly, she has missed it, or if we've gone away on holiday. You can tell leading up to that, she starts to get a bit fatigued. She has not got quite the same energy. So, you can notice an energy dip." (1)*** One child was doing well until he developed antibodies and reacted to immunosuppressant

	therapy, affecting his kidneys. ***"Up until the point he built antibodies, up until that point, his growth was going well. We could feel ourselves that the enzyme, up until the point, it worked. He stayed out of hospital. He was healthy. He was well, and that reflected on the growth chart. He was putting on weight, as he should be, and thriving as any six-month-old child should.*** ***But once you start needing antibodies, and he had to have anti suppressants and so on, then things started to go downhill. So, he wasn't getting the full benefit of the drug, which led to him developing the diarrhoea and vomiting, and he was prone to more infections. So, he spent most of his childhood in hospital. He'd spend, say, a day at home, and then a week in hospital or two weeks in hospital and vice versa. So, we'd bring him back home, and then the next morning, he'd have diarrhoea and vomiting again. So, he would get dehydrated, and we would have to rush him back in.Then, obviously, he started leaking protein in the kidneys. They tried to suppress the antibodies. And by doing that, the kidney started leaking protein. So then, he had kidney issues. His creatinine level increased, and so on. And he was getting other symptoms."(1)*** ***"Because of the initial six months, where the enzyme was given, the liver functions improved, the spleen got smaller. There came a point where they couldn't feel his liver. It was four or five centimetres when he went into hospital. His spleen was enlarged. There was a lot of fat in the gut. With this drug, it saved him basically. It's a life-saving drug. It kept him going."*** All parents have expressed that ERT was of great benefit and that without treatment their children would have died. ***"So, I believe that, because of the enzyme replacement therapy, my daughter is alive, and I thank God that this treatment was around when my daughter was born, because my sister's daughter, she passed away when she was three months old because this treatment wasn't around at the time. So, I am very grateful, and I think it's helped her immensely."(1)***

	"Impact? A big impact because we've still got him with us. If it wasn't because of that treatment, we would have lost him."(1) ***So, the treatment, for me, the main thing with that is that it's given somebody the chance to live and to live a normal life."(1)*** ***It has just given her a quality of life that I don't believe would've been there and that's obviously enabling then family to have a better quality of life as well. Because our life is relatively normal. It's not, but it sort of is. But if we didn't have the treatment, it would be very, very different."(1)*** Please see question 6 for more evidence on the impact related o quality of life
10. If there are disadvantages of Sebelipase alfa over current treatments on the NHS please describe these. For example, are there any risks with sebelipase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Parents felt that the lifesaving benefits of ERT far outweighed any disadvantages. Disadvantages were related to; the need for weekly infusions, the time infusions take, not being able to take long holidays. ***"The disadvantages… From our point of view, any disadvantage would be completely outweighed by what it has actually… There's not really a disadvantage" (1)*** ***"But we're fortunate enough that we get it from home. She only misses a couple of hours of school. I'm able to work around it with my work. So, from that point of view, there aren't any disadvantages."(1)***
11. Are there any groups of patients who might benefit more from Sebelipase 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,	Sebelipase alfa should be made available to all children up to 24 months who present with signs of faltering growth. 'Clinical experts felt that one of the clear, differentiating factors between, juvenile and infantile onset, is faltering growth. All patients who present under the age of 12 months have faltering growth, whether they have acute onset or subacute onset' (3).

dexterity or cognitive impairments) that affect the suitability of different treatments	The UK experience is that patients diagnosed after 6 months can follow a rapidly progressive course of the disease'.
12. Are there any potential equality issues that should be taken into account when considering Wolman disease and Sebelipase 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.	Whilst the focus of this evaluation is the infantile population, there is a subset of late onset patients (children and adults), who can present with a rapidly progressive form of LAL D. It is important that patients over 6 months but under 24 months are not excluded Committee need to consider the impact of requesting an MAA on a patient population who have been living with uncertainty since the un-concluded committee in 2017. Thankfully, for the last 6 years, the company have provided compassionate drug for both existing and new infantile patients. This period of extended treatment and clinical follow up has exceeded the standard time period of a MAA.
13. Are there any other issues that you would like the committee to consider?	(1) MPS Society & Rare Disease Research Partners. Patient and caregiver experience of Lysosomal Acid Lipase Deficiency (Wolman's disease) treated with Enzyme Replacement Therapy (ERT) Unpublished March 2023 (not for public sharing) (2) MPS Society. Patient / carer experience and case studies 2016-2022 (3) Infantile LAL D clinical meeting. Unpublished January 2023 (not for public sharing)

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement ((as summarised in EAG report section 1.3 and 1.4 (pages 14-23)).

The age of symptom onset in Wolman disease/rapidly progressive LAL-D - there is uncertainty in the efficacy results in patients with symptom onset after 6-months for which little clinical trial evidence is presented	It is important for the committee to understand that current clinical practice supersedes the historic clinical trial data *please see points raised above
The role of Haematopoietic stem cell transplant (HSCT) in the pathway for patients with rapidly progressive LAL-D - there is limited evidence to ascertain the ages of patients when they require HSCT (if at all) and limited evidence on outcomes by age at HSCT	Please see information above on the outcomes of HSCT as a first line therapy. There is no standard age of when a patient is considered for HSCT. All patients bar one underwent HSCT due to antibodies or line failure. Response rates have been variable. Currently there is insufficient data to determine if HSCT should be part of the treatment pathway in all patients.

Patient expert statement

	HSCT is not the accepted practice clinically. Whilst it may afford better corrections overall with GI symptoms being positively impacted, the long-term efficacy and limitations are unknown. There is a high risk of morbidity and mortality, associated with HSCT. Parents have already faced losing their children at diagnosis and may be unwilling to opt for HSCT if ERT is working
Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa - there are considerable uncertainties about the potential long-term use and associated benefits of treatment in patients as they transition to adolescence and beyond	We now have over 10 years of clinical experience and data of treated infants in the UK. It would in my opinion be unethical and unjust to again push this timeline to adolescence and beyond. Patients / families have had to live with the uncertainty of not knowing if treatment will continue to be provided, for 7 years, clinicians have been unable to start critical patients on treatment immediately, having to go through IFR's before compassionate use could be considered. Since 2016 an additional 7 years of data has been collected on treated UK patient (including existing and newly diagnosed). The company's commitment to providing ERT has ensured; a) no patient died without access to treatment and b) clinical data and understanding continued to be collected. Clinicians still maintain that this is one of the best ERT's with the best outcomes for infantile patients seen in a long time. NICE had the opportunity in 2017 to implement a MAA. The company, NHSE, clinical and patient experts worked tirelessly to set out how this would look for the different disease groups. However at this time, NICE were not wanting to go down the MAA route for infantile patients It is also concerning, that a recent ERT has been given a positive recommendation despite the limited evidence and lack of data for one treatment group. In this case the committee accepted that assumptions about efficacy were needed due to the rarity of the condition despite the limited data available.

Trial eligibility criteria and generalisability to rapidly progressive LAL-D population in England - trial population does not reflect the entire rapidly progressive LAL-D population in practice who are likely to receive treatment	Clinical trial eligibility and population was selected to get best results and trial outcomes. Clinical practice and understanding over the years has evolved and it's now understood, there is a small cohort of patients who, despite having rapidly progressive disease, produce a small amount of residual enzyme. This can delay onset of rapid disease. Clinical opinion is these children would still have the same disease trajectory and die in early childhood from Wolman related complications.
Uncertainty around ability to change dose of sebelipase alfa - There are uncertainties regarding dose of sebelipase alfa over time, the duration of treatment, and the proportion of patients who may be able to discontinue treatment with sebelipase alfa	It is our understanding that most patients are treated with 3-5mg per kg, weekly. Some patients who presented acutely unwell required a period of rescue therapy of twice-weekly ERT. Clinicians have tried to reduce the dose for patients who appear to be responding well. Unfortunately, patient's health deteriorated rapidly and they required a higher dose of treatment to stabilise them. Those treated with HSCT may be able to come off ERT. However, this is individual and depends on engraftment and clinical response.
Choice of discount rate for costs and QALYs - In their base-case analysis, the company assumed a 1.5% discount rate for future costs and effects. This was justified by the company on the basis that "*treatment with sebelipase alfa restores people who would otherwise die to full or near full health, and this is sustained over a very long period.".* The NICE reference case value is 3.5%. This has an impact on costs and benefit outcomes.	

Patient expert statement

Uncertainty in extrapolation models used to estimate Wolman related survival - Use of different extrapolation models may change the cost-effectiveness results	
Uncertainty in the utility estimates applied for those treated with sebelipase alfa - The assumed health related quality of life (HR-QoL) values for people with Wolman disease are uncertain. The company assume that the HR-QoL for a patient is the same as that of the UK general population. <u>We believe that patient expert input could be particularly value in response to this issue</u>.	Please see responses above and submitted by patient experts and organisations, including supplementary evidence. The treatment saves lives. Without treatment, babies and children die a very cruel, painful death due to starvation, resulting in permanent organ damage. Malnutrition is something that should not be seen in the UK today. Patients known to the MPS Society have near full health and good quality of lives. Whilst ERT has a positive impact on GI symptoms, some symptoms persist and flare ups can happen. GI symptoms are managed through low / no fat diets and supplementary feeds. Patients interviewed showed that they were at expected height and weight for age and are not cognitively affected. All patients are also showing good to normal developmental achievements. This concurs with information the Society submitted to NICE in our appeal letter, where we shared data presented by the company at the WORLD symposium (Feb 13-16 2017). This data reflected the social and developmental outcomes of five clinical trial patients all who were over the age of 3 years. Reported outcomes demonstrated that all were developing well and within normal range with four out of five children attending nursery or school. (2) 2017 ECD submission Although the cohort of infant patients is small, the life survival and demonstrated long-term benefits of treatment is undeniable compared to the alternative, which is death. This surely shows that the life survival and long term benefits for patients on Sebelipase alfa is both compelling and positive compared to the untreated patient population where the disease is fatal.

Uncertainty over life cycle price of sebelipase alfa - It is possible that both the real price paid by the NHS may change over time	
Uncertainty over feasibility of vial sharing - If the number of vials of sebelipase alfa can be reduced this would, other things being equal, reduce costs	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Children do not survive without access to ERT
- Enzyme Replacement Therapy is the first line therapy and is the only lifesaving treatment available for patients. ERT is required to be administered without delay on diagnosis
- All patients with symptoms of faltering growth that present under the age of 12 months should be treated
- Long term survivors show normal development and only have residual disease in the GI tract. Patients and carers have a good quality of life with IQ and cognitive function being unaffected
- Whilst HSCT is showing promising results, particularly related to GI, more data needs to be collected to understand outcomes. HSCT is not accepted practice currently

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.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Sebelipase alfa for treating Wolman disease [ID3995]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR **(see section 1.3 and 1.4, pages 14-23)**. 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.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13th March 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating Wolman 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 Simon Jones
2. Name of organisation	Manchester University NHS Foundation Trust
3. Job title or position	Consultant paediatric inherited metabolic disease
4. Are you (please tick all that apply)	X An employee or representative of a healthcare professional organisation that represents clinicians? X A specialist in the treatment of people with Wolman disease? ☐ A specialist in the clinical evidence base for Wolman 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)	X 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.	N/a
8. What is the main aim of treatment for Wolman disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent the rapid death associated with the disease, restore tolerance to enteral feeds and stop the progression of liver disease

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)	Survival beyond 6 months of age (now over 10 years in some individuals)
10. In your view, is there an unmet need for patients and healthcare professionals in Wolman disease?	In the absence of the NHS funding Sebelipase over 90% of infants would die
11. How is Wolman 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 infants in the UK have been offered sebelipase either as part of a trial or after licensing on a compassionate use scheme free of charge from the company. All would have died otherwise. Delays in obtaining compassionate use ERT have led to delayed treatment and death in some infants. Guidelines have been broadly agreed and presented in poster form however we delayed publication pending NICE review of the product. Unfortunately this has gone on for around 7 years. Pathway of care via established paediatric LSD centres. NHS professionals amongst the most experienced in looking after these infants and work together on complex cases already
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)	If sebelipase approved for NHS use then the main difference would be faster initiation of therapy which we know would improve the chances of survival. All infants require treatment initiation as an inpatient in a specialist centre until they are stabilised from a hyper-inflammation perspective, have no need for blood products and are growing on enteral feeds. Following this they can have home ERT infusions if they are stable and tolerating the sebelipase well. In practise there is usually around 1 year or so of infusions in hospital before home therapy practical.

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?	So if the comparator is no sebelipase then this is a group of children with 80-90% survival over 5 years. Compared with the natural history of almost all deceased in the first 6 months of life. Our oldest treated children from the clinical trials are over 10 years old now, have normal cognition and are in mainstream school.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There appears to be a group of infants all from a south asian background who have a deletion that encompasses the entire LIPA gene. While they still benefit from sebelipase they have a less clear long term outcomes as most develop antibodies against the enzyme. Most of these infants require HSCT in the longer term.
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)	Needs coordinated by an experienced MDT in a LSD centre that includes dietetic, gastroenterology, haematology, immunology and transplant team members in addition to the usual LSD multi-speciality teams
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Most of the stopping rules would relate to decisions around HSCT. These should be taken by an MDT and could involve a national MDT discussion

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?	This therapy is clearly a step change as discussed earlier.
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?	Infusion reactions can be managed as standard for ERTs; anti drug antibodies can be managed by immune modulation regimens or allo-HSCT

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?	Yes as more than 50% of infants in the trials were treated in the UK, the only changes since the trial publications are the increased use of HSCT and in a very small number twice weekly dosing in the first few weeks.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Since the commercial trials there have been case series published from the UK and France showing longer term outcomes and the need for multi-modality therapy. There is also a publication in press showing the benefit of twice weekly dosing in the sickest infants for a few months until there is stabilisation. Given the size of the infant then and that this is very temporary this would not impact the health economic case except that we would expect to improve survival from 80% to 90-95% with this approach.
22. How do data on real-world experience compare with the trial data?	There is a continued evolution of care of these infants as we understand the disease better.

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • 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 EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement (as summarised in EAG report section 1.3 and 1.4 (pages 14-23)).

The age of symptom onset in Wolman disease/rapidly progressive LAL-D	The EAG raise the issue that not all infantile onset cases present exactly as defined in the trials, this is correct and was used in the trials purely because of a desire to increase homogeneity in the population given the very small numbers able to be recruited. This is a disease that has a true spectrum however, the EAG recognise that 2 infants born in the UK in the last 10 years have presented slightly later and progressed slightly more slowly than the classical presentation. This group represents around 10-15% (UK data in our unit/lab) of infantile onset cases. This group resemble the classical infantile cases much more closely than late onset disease (true multi system presentation, rapid progression, need for infantile doses (3-5mg/kg weekly) than late onset doses (1mg/kg alternate weekly)). They would not be served by other treatment options eg liver or bone marrow transplant used in isolation. Whilst there are little data for this cohort a line must be drawn somewhere and clinically we would feel it was more reasonable to include this group in the infantile onset cohort.
The role of HSCT in the pathway for patients with rapidly progressive LAL-D	The EAG are concerned that the figures for how many infants would undergo HSCT are unreliable. The company (in their calculations) used data we supplied from our cohort in the UK, this represented 14 infants treated in Manchester and 3 in Birmingham. Over the 10 years of this cohort we feel it represented around 25% of treated infants globally, based on discussions with Alexion and many of the international clinical centres directly. Whilst the clinical pathway to optimally treat these infants continues to evolve the data and model are based on the most current and best available data. This includes published and unpublished data.

Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa	We now have over 10 years of follow up data for the oldest of the LALD infants treated in the CL03 trials. There is no reason to consider that the efficacy seen and published in the first 3 years (as published) has changed in the resulting years, either from clinical observations of as a biological hypothesis. Not all infants fully respond to ERT and some go on to require HSCT. This can now probably be predicted by the response in the first 3 years and the genotype. I am not sure how much longer there is an expectation of follow up to satisfy the EAG - 10 years which is a 20X extension of expected life is a quite remarkable follow up for any therapy, the same uncertainty could be raised after 20 for even 30 years of follow up.
Trial eligibility criteria and generalisability to rapidly progressive LAL-D population in England	As stated in response to the first question - over 85% of UK Cases were or would have been eligible for the clinical trial criteria (CL03/CL08).
Uncertainty around ability to change dose of sebelipase alfa	This is done according to clinical need and we have worked within the Alexion compassionate use programme. The vast majority of children are treated with 5mg/kg weekly, those following HSCT have gradually reduced doses with some stopping completely. Children will not be treated excessively and doses will be reduced as is clinically possible. We have shown as a LSD highly specialised service we can work within dosing boundaries and can lower doses and use these expensive therapies reasonably in the past.
Choice of discount rate for costs and QALYs	Not within my expertise

Uncertainty in extrapolation models used to estimate Wolman related survival	This is an ultra-rare previously fatal disease which we knew little about as almost all infants died within a few weeks of diagnosis. The UK has led all the infantile ERT trials and we have now extended lifespan dramatically with the longest surviving children showing stability and an excellent quality of life. While it is likely that we will continue to learn more about this population and treatment approaches will improve, the use of transplant (HSCT) in some has only prolonged life and reduced enzyme dosing. This uncertainty is unlikely to be any more or less than in any other genetic disease and in this case has already shown survival which most trials would struggle to do. Given that this is the most life changing ERT we have seen for perhaps 25 years it is hard to see what level of certainty would satisfy the ERG
Uncertainty in the utility estimates applied for those treated with sebelipase alfa	As above
Uncertainty over life cycle price of sebelipase alfa	As above
Uncertainty over feasibility of vial sharing	Vial sharing is complex in practice and is unlikely to be a significant impact on cost. We almost always use full vials by utilising alternating doses and rounding doses. The only scenario would be if there were 2 small infants attending the same hospital at exactly the same time. This is fairly inconsequential to the overall costs which are driven by dosing the patients when they are older and bigger - not by what we do in the immediate infantile period.

Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Infantile onset LALD is one of the most rapidly and universally fatal diseases in this group.
Sebelipase alfa, while not the only treatment required by patients has been the step change never before seen in this group.
While other treatments (nutritional lipid restriction, cell therapy with HSCT, future gene therapy) may help or be long term alternatives, none of them are effective enough fast enough to replace the need for Sebelipase in the initial stages.
Numbers are very small and increases over time are likely to be mitigated by those coming off ERT having HSCT.
This is the most effective ERT since the first treatment for Gaucher disease in the 1990s.
These infants will all die if we do not treat with sebelipase

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

Highly Specialised Technology

Sebelipase alfa for treating Wolman disease [ID3995]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Wolman disease or caring for a patient with Wolman disease. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (as summarised in EAG report section 1.3 and 1.4 (pages 14-23)).

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 evaluation 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.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13th March.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with Wolman disease

Table 1 About you, Wolman disease, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with Wolman disease? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with Wolman disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
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 Wolman disease? **If you are a carer (for someone with Wolman disease) please share your experience of caring for them**	Daughter diagnosed around 2 years, although symptoms from birth (distended stomach, reflux, followed by constipation / explosive stools), failure to put on weight despite eating food and drinking milk during weaning stage. Professional frequently commented on her enlarged stomach and liver but no investigations were carried out. Daughter is now 8 years old and has weekly infusions. Before ERT there were periods of her having loose & explosive stools; sometimes this stopped me from leaving the house with her. We also went through periods of bad constipation. Her tummy was badly distended and when she learned to walk she was continually tripping or falling over as she couldn't see her feet and her centre of gravity was imbalanced. Her breathing was difficult and laboured (as a result of her enlarged stomach). She was unable to sit up from a lying position unaided – she had to roll onto her tummy and get up from there. It was difficult to buy clothes as nothing would fit properly due to her tummy size. She appeared tired / lethargic. Despite seeing many specialists from birth (GP, health visitor, various hospital specialists) and undergoing multiple tests it took 18 months to get a diagnosis. Before receiving the diagnosis of LAL D my daughter was suspected of being allergic to milk and having issues with her portal vein. Following ERT her tummy size is greatly reduced and appears in line with her peers. She is no longer tired, is active and has no breathing issues. There are very few issues buying clothes and these no longer need to be modified to fit. She no longer has any constipation issues. She does still have occasional explosive stools but these are few and far between. There are some issues with gas but she is able to ensure this is passed by doing a variety of different exercises. She has no issues

	with physical activity and is bright and full of energy and to all extents and purposes is a fit and healthy 8 year old doing everything her peers are doing. ERT is given at home, so minimal interruptions to school and home life. She only needs to attend 6 monthly hospital appointments, last issue was her port which was no longer working due to her growth we believe and this needed to be replaced. GI issues are supported by a fat free diet. Daughter does not have a gastronomy. She is at expected height and weight for her age. My daughter loves arts and crafts, she attends Cubs and swimming lessons once a week. School reports show she is at expected levels for her age. She excels in reading and writing and has a good imagination. <u>Carer Views</u> When we finally received the diagnosis I was devastated. I just kept thinking she's got this condition that there's no cure for and she is never going to be able to go to school, it was difficult to even look towards her next birthday and if she would still be here with us. Now she is in Year 3 at school and thriving and living her best life. Because our daughter has a good quality of life on treatment, our life seems relatively normal, we work fulltime and are able to go on holidays and do all the things other families do. If we didn't have this treatment our lives would be very different.

7a. What do you think of the current treatments and care available for Wolman 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?**	Better information and training to support earlier diagnosis is needed. Despite my daughter exhibiting symptoms from birth and making multiple trips to healthcare professionals it still took around 18 months for a confirmed diagnosis to be made. Outside of ERT and stem cell transport, care and support is provided through a multidisciplinary team including specialist consultants and nurses, physiotherapists, speech & language therapists, dieticians, nationalists as well as local teams. ERT is crucial – without this children including our daughter would simply not survive. Liver transplants are invasive and high risk, and not appropriate for use in children and my understanding is that they are not a 'cure' and that the condition would remain and any new liver to likely be effected also. Stem cell replacement – as far as I am aware there is difficulty finding a match, it is extremely invasive to the patient and their family over a significantly long period of time, and the failure rate is high. Not aware of any other treatment available.
8. If there are disadvantages for patients of current NHS treatments for Wolman disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	My daughter has not experienced any side effects to ERT. My understanding is that any effects are usually mild and well managed when identified. Any disadvantages (such as time spent receiving the infusion, missed schooling etc) in my opinion are outweighed by the advantages treatment brings. Having treatment at home means that the time missed from school and work are minimal and can be worked around.

	As above re stem cell replacement.
9a. If there are advantages of Sebelipase 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 Sebelipase 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**	Treatment has given both my daughter and my family our lives back. She is an active normal 8 year old girl who is thriving at schools, attends a number of out of school activities and has a great circle of friends. Currently any ongoing needs are limited and managed with very little impact or support needed. Ongoing needs are: Excess wind – she has exercises to help this (daughter self manages) Diet restriction – daughter is on a no fat / fat free diet, she tolerates this very well and school ensure there are appropriate foots she can eat My daughter is able to attend to her own self care needs My daughter is not restricted in activities, she just needs to be careful her port is not knocked or dislodged. Contact sports / activities are avoided for this reason. My daughter has a good quality of life, is active and sociable and has a number of friends. My daughter attends a mainstream school. Academically she is where she needs to be for her age Our family does not have to make any adjustments I work fulltime and treatments fit around this
10. If there are disadvantages of Sebelipase alfa over current treatments on the NHS please describe these. For example, are there any risks with sebelipase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Adjustments have had to be made to employment and our daughter misses 2 hours of school each week, however she is now able to have the treatment without a drip stand and given her age we are looking at the possibility of treatment being delivered in school which would mean no adjustments for schooling or employment. In my view any adjustment with employment / home life / schooling would be welcomed if the alternative was stem cell replacement and the risks / adjustments that would be required with this.
11. Are there any groups of patients who might benefit more from Sebelipase alfa or any who may benefit less? If so, please describe them and explain why	All patients diagnosed with late infantile LAL D should have access to treatment. It is important to include patients such as my daughter who presented with symptoms from birth but was not diagnosed until around 18 months later

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 Wolman disease and Sebelipase 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.	It is important that those who present with symptoms but are not rapidly progressive are not excluded from accessing this treatment.
13. Are there any other issues that you would like the committee to consider?	By 2 years old our daughter was suffering from explosive stools, lack of weight gain, delayed physical development, mobility issues and the fact that internally her liver and spleen were significantly enlarged. She is now a happy, thriving 8 year old who is developing in line with her peers. There is no doubt in my mind that without intervention with Sebelipase alpha her story would be very different, and truthfully I did not think she would still be with us. HSTC has been mentioned but I do not believe this to be a viable treatment alternative when the success rate is so poor. I can understand this being an option should Sebelipase alpha not or no longer be suitable, but whilst there are patients out there who may benefit from Sebelipase alpha I strongly believe there is a duty allow them access to this medicine.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement ((as summarised in EAG report section 1.3 and 1.4 (pages 14-23)).

The age of symptom onset in Wolman disease/rapidly progressive LAL-D - there is uncertainty in the efficacy results in patients with symptom onset after 6-months for which little clinical trial evidence is presented	Did not attend call – believe daughter had symptoms form birth but these do not appear to have been severe when compared with information provided on others, and further symptoms presented over the coming months – further research must be carried out to remove any uncertainty as people cannot be deprived a life saving / life extending in-evasive treatment.
The role of Haematopoietic stem cell transplant (HSCT) in the pathway for patients with rapidly progressive LAL-D - there is limited evidence to ascertain the ages of patients when they require HSCT (if at all) and limited evidence on outcomes by age at HSCT	Did not attend call – there seems to be very limited information on HSCT and very limited success rate. This does not appear to be a viable alternative to sebelipase alfa.

Patient expert statement

Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa - there are considerable uncertainties about the potential long-term use and associated benefits of treatment in patients as they transition to adolescence and beyond	Did not attend call – my daughter has received treatment for around 6 years and is doing well. I am aware that some patients have received treatment for up to 10 years. Given that life expectancy for infantile LAL D is usually less than 6 months if untreated, 10 years of survival and clinical effectiveness is a good outcome. However, I agree that research must continue including that what is ongoing around the globe to remove uncertainties
Trial eligibility criteria and generalisability to rapidly progressive LAL-D population in England - trial population does not reflect the entire rapidly progressive LAL-D population in practice who are likely to receive treatment	Unable to comment
Uncertainty around ability to change dose of sebelipase alfa - There are uncertainties regarding dose of sebelipase alfa over time, the duration of treatment, and the proportion of patients who may be able to discontinue treatment with sebelipase alfa	Unable to comment
Choice of discount rate for costs and QALYs - In their base-case analysis, the company assumed a 1.5% discount rate for future costs and effects. This was justified by the company on the basis that "*treatment*	Unable to comment

Patient expert statement

with sebelipase alfa restores people who would otherwise die to full or near full health, and this is sustained over a very long period.". The NICE reference case value is 3.5%. This has an impact on costs and benefit outcomes.	
Uncertainty in extrapolation models used to estimate Wolman related survival - Use of different extrapolation models may change the cost-effectiveness results	Unable to comment
Uncertainty in the utility estimates applied for those treated with sebelipase alfa - The assumed health related quality of life (HR-QoL) values for people with Wolman disease are uncertain. The company assume that the HR-QoL for a patient is the same as that of the UK general population. We believe that patient expert input could be particularly value in response to this issue.	Unable to comment
Uncertainty over life cycle price of sebelipase alfa - It is possible that both the real price paid by the NHS may change over time	Unable to comment

Uncertainty over feasibility of vial sharing - If the number of vials of sebelipase alfa can be reduced this would, other things being equal, reduce costs	Unable to comment
Are there any important issues that have been missed in EAR?	n/a

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Our daughter would likely not be alive just now if she was not in receipt of Sebelipase Alpha, or if she was her quality of life would be severely impacted
- There are no other treatment options on the NHS – stem cell replacement cannot be considered an alternative to Sebelipase Alpha
- More research requires to be carried out to remove the uncertainties referred to within this document.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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Sebelipase alfa for treating Wolman disease (rapidly progressive LAL-D) [ID3995]

Addendum: EAG critique of company's technical engagement response

Produced by Newcastle University

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1 Introduction

This addendum provides a summary and critique of the company's technical engagement (TE) response by the External Assessment Group (EAG) and should be read alongside the company's TE response,[1] the clinical expert statement and technical engagement response,[2] the company's submission (CS)[3] and the EAG report (EAR).[4]

1.1 Overview of the company's TE response

The company's TE response consisted of a single written response document.[1] No updated or revised economic model was produced, nor did the company provide a Patient Access Scheme (PAS) discount for consideration. The company focused their response on all ten key issues raised in the EAR[4] and a brief overview is provided in Table 1 below.

Table 1: Summary of company's technical engagement response

Key issue	Description of issue	Brief overview of company's TE response
1	The age of symptom onset in Wolman disease/rapidly progressive LAL-D	The TE response from the company restates that the vast majority of patients with rapidly progressive LAL-D present and are diagnosed within the first 3-9 months of life. The company state that the clinical rationale to support diagnosis up to 24-months remains.
2	The role of HSCT in the pathway for patients with rapidly progressive LAL-D	The TE response from the company acknowledges the uncertainty regarding the current and future use of HSCT for patients with rapidly progress LAL-D.
3	Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa	The TE response from the company acknowledges the uncertainty associated with loss of venous access which would lead to clinical experts treating the patients to consider use of HSCT.
4	Trial eligibility criteria and generalisability to rapidly progressive LAL-D population in England who are diagnosed between 6 and 24 months	The TE response from the company reiterates the company position that the clinical data presented are indeed generalisable to the UK.
5	Uncertainty around ability to change dose of sebelipase alfa	The TE response from the company acknowledges that there is uncertainty around dosing of sebelipase alfa following HSCT and that current clinical practise has been followed but management is evolving.
6	Choice of discount rate for costs and QALYs	The TE response from the company restated their position that the NICE criteria for application of a discount rate of 1.5% have been met and should therefore be applied.
7	Uncertainty in extrapolation models used to estimate Wolman related survival	The TE response from the company expresses a concern regarding the additional survival scenarios presented by the EAG in the EAR which they claim are not supported by the patient follow-up currently available and observed.

Key issue	Description of issue	Brief overview of company's TE response
8	Uncertainty in the utility estimates applied for those treated with sebelipase alfa	The TE response from the company acknowledges that there is uncertainty around the utility estimates included within the CS but disagree with the scenario presented in the EAR which applies a 20% reduction in utility as not clinically plausible.
9	Uncertainty over life cycle price of sebelipase alfa	The TE response from the company notes the uncertainty over the life cycle price of sebelipase alfa.
10	Uncertainty over feasibility of vial sharing	The TE response from the company acknowledges that there was some confusion in how this was described within the CS and clarify that wastage was incorporated into the '1 week round-up' and suggest that the 2-week dose modulation is possibly closer to UK clinical practice and should be considered by the committee as the base-case.
Abbreviations: CS, company submission document; EAG, external assessment group; EAR, external assessment group report; HSCT, haematopoietic stem cell transplant; LAL-D, lysosomal acid lipase deficiency; QALYs, quality adjusted life years; TE, technical engagement		

1.2 EAG description and critique of the individual key issue responses raised in the company's TE response

1.2.1 Key issue 1: The age at symptom onset in Wolman disease/rapidly progressive LAL-D

Key issue 1 of the EAR (further detail in sections 3.1, 4.2.1, and 4.7 of the EAR)[4] states that the clinical trial evidence for LAL-CL03 centres on patients who were eligible for enrolment if they had growth failure with onset before 6-months and consequently some of the trial evidence presented in the CS from LAL-CL03 may not be indicative for the use of sebelipase alfa in this rapidly progressive population which can present between 6 and 24-months. The company notes on [redacted] might present in this age range. In their TE response[1] the company restate that in UK clinical practice, only [redacted] patients in the past [redacted]. Further information provided in the clinical TE response document states approximately [redacted] present later with a slower clinical progression fit the rapidly progressive LAL-D diagnosis, and therefore there is a clinical rationale for diagnosis to extend beyond 6-months of age.[2]

The EAG acknowledge that delayed diagnosis as indicated in the response above is likely to be an unavoidable factor in rare diseases such as this. In addition, the EAG acknowledge that clinical judgements are required to ensure all patients with rapidly progressive LAL-D can receive the most appropriate treatment.

In summary, the EAG acknowledge that patients with rapidly progressive LAL-D may be diagnosed beyond 6-months of age in their report but that all events occur very early in the life course and clinical judgement would supersede age at presentation of symptoms. However, the EAG notes no changes to the EAR or their position that longer term data collection should be undertaken to provide revised estimates of cost effectiveness in the future.

1.2.2 Key issue 2: The role of HSCT in the pathway for patients with rapidly progressive LAL-D

The company's TE response[1] acknowledges the uncertainty around the current and future use of HSCT for patients with rapidly progressive LAL-D. The company's response further states that management of patients with rapidly progressive LAL-D is evolving, but that the UK clinical experts consulted are at the forefront of that evolution. They also state that the CS and company economic model (CEM) are an accurate representation of clinical practice. The company present no additional data, evidence or analyses.

The EAG acknowledge that the company have been guided by UK clinical experts to model this rapidly changing field. The EAG are broadly supportive of the assertion that the data and derived models use the "*most current and best data available*". However, there remains uncertainty over complications arising from treatment with sebelipase alfa in the medium to long-term which may influence the timing of HSCT, for which we currently have limited data. Whilst some patients have been on treatment for sebelipase alfa for over a decade, further real-world evidence is needed to ascertain the optimal time for HSCT to be considered and the associated implications on effectiveness and cost-effectiveness of using sebelipase alfa. Furthermore, there is uncertainty in how efficacy outcomes differ between those who have HSCT in infancy or earlier life compared to patients who receive transplant early in adulthood (as is proposed and modelled in the CEM).

In summary, the EAG and company agree that there is uncertainty around the current and future use of HSCT for patients with rapidly progressive LAL-D and that the analyses presented in the EAR, in combination with key issue 3, highlight the potential impact of the role of HSCT on the incremental cost effectiveness ratio (ICER). The EAG notes that no changes to the EAR are required.

1.2.3 Key issue 3: Uncertainty surrounding long-term clinical effectiveness of sebelipase alfa

The company's TE response[1] acknowledges the uncertainty around long-term effectiveness which is linked to the potential loss of venous access and timing of HSCT. They also highlight that both the company and EAG base-case analysis include loss of venous access at 30 years and note that a scenario analysis is presented at a younger age in the EAR. The company present no additional data, evidence or analyses.

The EAG agree with the company's TE response above but of particular concern is the role of neutralising anti-drug antibody (ADAs) which attenuate therapy efficacy, and the importance of long-term venous access for the frequent administration of sebelipase alfa and blood transfusions. Complications arising from treatment with sebelipase alfa would likely require HSCT, for which there exists uncertainty in how best it fits into the treatment pathway for patients with rapidly progressive LAL-D and the subsequent impact of cost-effectiveness (see section 1.2.2 above, key issue 2).

In summary, the EAG and company agree that there is uncertainty associated with the long-term clinical effectiveness of sebelipase alfa. Exploration of when HSCT is required due to loss of venous access was explored and found to have a moderate impact on the ICER. The EAG notes that no changes to the EAR are required.

1.2.4 Key issue 4: Trial eligibility criteria and generalisability to the patients in England with rapidly progressive LAL-D who are diagnosed between 6 and 24 months

The company's TE response[1] acknowledges that long-term data collection in patients with disease onset between 6 and 24 months would be helpful although they also state that in the UK in the past [redacted]. Furthermore, they go on to state that [redacted]. Also, in terms of generalisability to the UK, the company indicate that [redacted] patients in the LAL-CL08 clinical trial and [redacted] in the LAL-CL03 clinical trial were UK patients who remain on treatment benefiting from the Alexion compassionate global access to medicines programme.

Key issue 4 of the EAR[4] relates to the trial populations/eligibility of LAL-CL03 and LAL-CL08, more specifically the eligibility of LAL-CL03 to patients who had early growth failure in the first six months of life to facilitate comparability with LAL-1-NH01. By restricting eligibility in LAL-CL03 it is not unreasonable to assume some rapidly progressive LAL-D patients who presented later than six months of age were excluded, thereby limiting generalisability. However, the clinical TE response document[2] states that approximately 85% of UK cases were or would have been eligible for inclusion in both trials.

In summary, the EAG acknowledges the limited number of patients to whom this may apply given the presentation of [redacted] but nonetheless the EAG maintains given the limited number of patients that longer-term data collection for efficacy and safety in patients with onset between 6 and 24 months should be undertaken. Furthermore, the EAG restate that this key issue is a limited cause for concern (acknowledged in the company's TE response) and as such no changes are required in the EAR.

1.2.5 Key issue 5: Uncertainty around ability to change dose of sebelipase alfa

The company's TE response acknowledges the uncertainty around dosing of sebelipase alfa following HSCT.[1] They state that the management of rapidly progressive LAL-D is evolving but that the CS and CEM represent an accurate reflection of UK clinical practice as guided by the clinical experts. The company present no additional data, evidence or analyses.

The EAG explore the same assumptions as the CS in their base-case analysis but present some additional scenarios on dosing and discontinuation post-HSCT and show in the EAR that this may have a significant impact on the ICER.

In summary, the company's TE response acknowledges the EAG's concern regarding the uncertainty of sebelipase alfa dosing following HSCT but the EAG agree with the company that this will be driven by the clinical management of the patient. The EAG notes no changes are required in the EAR.

1.2.6 Key issue 6: Choice of discount rate for costs and QALYs

The company's TE response[1] firstly acknowledges that both the company presented base-case and the EAG base-case produce estimates of life year gains in excess of 30-years. The company then reiterate their position which proposes that a 1.5% non-reference case discount rate should be adopted for this analysis as sebelipase meets the following criteria: Is a technology for people who would otherwise die or have very severely impaired lives; is likely to restore them to full or near-full health; and the benefits are likely to be sustained over a very long period of time.

The EAG considers that the base-case analysis should adopt a discount rate of 3.5% as recommended by the NICE reference case.[5] This is presented in the EAR and explored within the CEM. The EAG

notes that no changes to the EAR are required. Furthermore, the EAG believe that this is a decision for the committee.

1.2.7 Key issue 7: Uncertainty in extrapolation models to estimate Wolman-related survival

The company's TE response[1] queries the survival scenarios presented by the EAG in the EAR (page 166, Table 7.7, scenarios 8-11).[4] Whilst these extrapolated survival curves all retain the KM estimates through the 5-year trial follow-up period, they make predictions from year 6 using exponential, Weibull, Gompertz, and lognormal parametric curves. The company assert that three of the four curves predict a higher mortality than has been observed in trials or the longer-term follow-up (including 10+ years of survival) and raise a concern that they may not be informative. The company present no additional data, evidence or analyses.

Whilst the EAG agree with the company that the KM is the best fitted model for Wolman disease-related mortality during the trial follow-up period, the EAG still have uncertainty on using this to extrapolate out across a patient's lifetime or to reduce the Wolman disease mortality to zero from year 6 onwards and replace this by the population average mortality. The EAG in the EAR suggested and presented alternative approaches using a combination of the KM method followed by an extrapolation of the trial follow-up data for year 6 onwards. As suggested by the company, three of the four curves may present higher than observed mortality over the short-term but these are illustrative given the small number of patients involved and the overall impact on cost-effectiveness.

In summary, EAG base-case and the company use the same assumptions regarding Wolman and non-Wolman disease mortality in their base-case analyses. The EAG believe this is something to explore with the clinical experts in the committee. The EAG notes that no changes to the EAR are required.

1.2.8 Key issue 8: Uncertainty in the utility estimates applied for those treated with sebelipase alfa

The company's TE response[1] acknowledges the uncertainty surrounding the utility estimates used in the CS and CEM but note that the EAG base case uses the same approach as the CS. The company raise particular concern regarding the additional exploratory scenario number 2 analysis presented by the EAG (EAR Sections 5.1.13, 7.1.2.1.2, and Table 7.6).[4] The company claim that a 20% reduction in utility weights (as explored by the EAG) is not clinically plausible and that the Pompe disease study[6] highlighted by the EAG as supporting evidence is not relevant due to different post-treatment disease-related impacts on patients with Pompe disease patients facing several long-term issues versus LAL-D patients being able to thrive and live near normal lives.

The company also provide reference to a study conducted by Upton *et al*.[7] 2005 in children which suggests that a reduction in HRQoL would be in the region of 10% for serious conditions such as cancer (PedsQL mean score of 83.89, SD 12.76 for healthy children versus a mean score of 75.68, SD 15.40 for those with cancer).[7] The company then state that previous NICE appraisals have incorporated smaller utility decrements and highlight the use of a 10% reduction in the CS (scenario 28 as presented in the CS) as more appropriate and relevant. Furthermore, the company state that post-HSCT, once the patients have been able to taper off sebelipase alfa treatment, the general population utility values would be the most appropriate to use.

The EAG acknowledge that the base case used the same approach as the CS. As a series of matters of judgement, the EAG included utility decrements for health state 2 (HS2) for rescue care (EAR sections 5.1.13 and 7.1.1.3.2), informal care provided to patients (EAR sections 5.1.13 and 7.1.1.3.3), nasogastric feeding (EAR sections 5.1.13 and 7.1.1.3.4), and adjustments to utility values for children

aged 1-11 years old (EAR sections 5.1.13 and 7.1.1.3.5). Furthermore, the EAG produced additional exploratory scenario analyses including utility decrements for informal care for those receiving enzyme replacement therapy (ERT) (EAR section 5.1.13 and 7.1.2.1.1) and weighting applied to utility values of all ages (EAR section 5.1.13 and 7.1.2.1.2). The CEM provided an option to adjust the utility value for all ages and furthermore include a weighting for the utility value (0.9 or 10% reduction) in their scenario analyses. In addition to this analysis, the EAG considered a further reduction above that applied in the CS in order to explore the impact on the ICER. This approach seemed entirely reasonable given the lack of data available generally on HRQoL in rapidly progressive LAL-D patients. The CS cites one source of HRQoL data as presented in the study by Demaret *et al*. 2021.[8] This was a small study (responses available for three children and five parents) but the data do show that there is the potential for substantial reductions in HRQoL with global scores varying from 61-80 for the child responses (mean 73, median 75). Finally, the company suggest that the EAG's argument implies that the general population PedsQL score is 100% across all domains. This is not correct. This confusion may have arisen due to the EAG reporting the base-case weight as "1" in Table 7.6 in the EAR[4] which rather than applying a value of 100% would apply the base-case values as calculated by the CEM (i.e. no reduction of the base-case estimated values versus a weight of 0.8 to reduce the estimated utility values).

In summary, the EAG and company base-case use the same approach. The company acknowledge uncertainty regarding utility estimates for those treated with sebelipase alfa. The CS presents a 10% reduction in utility weights in their own scenario analyses and the EAG present a further reduction (20%) in their additional exploratory scenario analyses in order to explore this uncertainty. The EAG suggest that this uncertainty could be reduced through the collection of HRQoL data from patients treated (where possible) with sebelipase alfa and their parents in order to understand whether this remains a significant issue given that clinical and patient opinion would suggest that quality of life is near normal for successfully treated patients. Given the uncertainty in HRQoL amongst patients with rapidly progressive LAL-D and their treatment with sebelipase alfa and its exploration in both the CS and the EAR, the EAG note that no changes are made or required to the EAR.

1.2.9 Key issue 9: Uncertainty over life cycle price of sebelipase alfa

The company's TE response[1] notes the uncertainty on the issue of medicine prices over a product's life cycle. The company welcomed the exploration of this issue from the EAG in the EAR. The company present no additional data, evidence or analyses.

The EAG explored the impact on the ICER of changes in market price, and the introduction of a cost cap per patient per annum in scenario analysis. The EAG noted that introducing price reductions lead to drops in the ICER. This is noted as it is plausible that drug price and agreed maximum cost per annum (or other cost containment mechanisms) may occur over time.

In summary, the EAG recommend revisiting analyses as and when costs/price mechanisms change or are negotiated. The EAG notes no changes to the EAR are required.

1.2.10 Key issue 10: Uncertainty over feasibility of vial sharing

The company's TE response[1] acknowledges that additional clarification was required due to the complexity of vial sharing practices in the clinical setting and how this was captured within the CEM. The company clarified that under the company base-case, a conservative approach was used which used rounding-up rather than vial sharing per se. As such, if a patient required the use of part of an additional vial then this was counted as a full additional vial. The company also state that they note that in the UK, dose is modulated over a two-week period whereby doses are adjusted from one week to the next in order to reduce or avoid wastage. The company present no additional data, evidence or analyses.

The EAG note that the rounding-up would potentially explain the inconsistent results observed in the CEM. The EAG also note that the use of vial sharing only leads to moderate reductions in the ICER. In summary, the EAG therefore suggest no changes to the EAR.

1.3 Additional analyses undertaken or changes made to the EAR by the EAG

In summary, no additional analyses were undertaken by the EAG and no changes were made to the EAR.

2 REFERENCES

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