NICE National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Contents:

0. **Pre-Meeting Briefing**

1. **Final Scope** **and** **Final Matrix** **of Consultees and Commentators**

2. **Company submission** from Alexion Pharma UK

3. **Clarification letters**

- **NICE request to the manufacturer for clarification on their submission and Company response** to NICE's request for clarification

4. **Consultee Submissions** from:

- **British Inherited Metabolic Disease Group and Birmingham Children's Hospital** (Joint Statement)
- **Children's Liver Disease Foundation**
- **NHS England**
- **Salford Royal Hospital**

5. **Expert personal perspectives** from:

- **Sophie Thomas**, nominated by the MPS Society
- **Amjad Akhtar**, nominated by the MPS Society
- **Stuart Lancaster**, nominated by the MPS Society
- **Charlotte Doyle**, nominated by the Willink Unit
- **Dr Simon Jones** (**Part 1** and **Part 2**) Clinical Expert, nominated by the Willink Unit
- **Dr Elaine Murphy**, Clinical Expert, nominated by British Inherited Metabolic Disease Group
- **Dr Patrick Deegan**, Clinical Expert, nominated by Royal College of Pathologists and Alexion - **see above joint statement with Dr Elaine Murphy**

6. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

7. **Evidence Review Group report – factual accuracy check**

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

Premeeting briefing

Sebelipase alfa for treating lysosomal acid lipase deficiency

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees, and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Evaluation Committee meeting and should be read with the full supporting documents for this evaluation.

Key issues for consideration

Nature of condition

- LAL deficiency is a heterogeneous condition in terms of symptom severity which is partly dependent on age of onset.
  - What defines the need for treatment?
  - What outcomes are most relevant to people with LAL deficiency?
  - What is the relationship between biochemical markers and long-term clinical outcomes in LAL deficiency?
  - What is the life expectancy for people with LAL deficiency?
  - How do treatment needs vary across the population (for example, by age of onset and severity)? Are there any groups of people with LAL deficiency who are clinically distinct with respect to treatment needs?

Impact of the new technology

- LAL-CL03 investigated the effect of sebelipase alfa on survival in children aged 2 years and under with rapidly progressive LAL deficiency. The study did not have a control arm and results were compared with a historical cohort in LAL-1-NH01.
  - Was the historical cohort appropriately defined?
  - Are the populations in the 2 trials comparable?
- In LAL-CL02, biochemical markers of liver disease were decreased and lipid levels were stabilised with sebelipase alfa compared with placebo. However, there were no long-term outcomes measured in the trial.
  - Would treatment with sebelipase alfa be expected to fully prevent longer-term complications of the disease such as loss of liver function and atherosclerosis?
  - Is it reasonable to expect that the treatment effect observed in the trial would be maintained over the long term?
- The company stated that there is currently no evidence to inform treatment continuation rules. How would people treated with sebelipase be monitored? In what instances would treatment with sebelipase alfa be stopped?
- Is treatment with sebelipase alfa expected to be lifelong? Would treatment with a haematopoietic stem cell transplant be considered in people whose condition is stabilised by sebelipase alfa?
- The clinical trial data do not allow a comparison of sebelipase alfa with best supportive care including a liver transplant as needed or with haematopoietic stem cell transplant. How would the long term clinical outcomes compare between people treated with sebelipase alfa and people who have a liver transplant or stem cell transplant?

Value for money

- The economic modelling focuses on progressive liver disease and does not account for the potential benefits of sebelipase alfa in reducing risk of

damage in the cardiovascular system or other organs in the body besides the liver or its effect on growth or malabsorption.

  - Does the model adequately capture the manifestations of LAL deficiency?
  - Is the model likely to underestimate the value of sebelipase alfa in treating of LAL deficiency?

- The modelled probability of liver disease progression with best supportive care is based on estimates for non-alcoholic fatty liver disease (NAFLD).
  - Is the rate of progression of liver disease comparable in LAL deficiency and NAFLD?
- What is the view of the Committee on the:
  - company's assumed price reduction of 30% after 10 years (because of patent expiry)?
  - most relevant discount rates to use for costs and health effects (1.5% or 3.5%)?
  - incremental costs and incremental QALYs for sebelipase alfa compared with best supportive care?

Impact of the technology beyond direct health benefits

- The model does not include:
  - Schooling, productivity benefits or other indirect costs
  - Impact of LAL deficiency on carers

  How would these factors impact on the costs and QALYs associated with sebelipase alfa?

Cost to the NHS and personal social services

- The company estimated a 5 year net budget impact with sebelipase alfa of £54 million.
  - Are the company's prevalence and incidence estimates reasonable?
  - In the company's budget impact model, uptake of sebelipase alfa is determined by diagnosis and treatment rate, treatment continuation and

compliance rates based on the company's experience of ultra-rare diseases and its advice from clinical experts. The ERG estimated higher uptake because it considered diagnosis and treatment rates would be higher than those estimated by the company and all people would continue to take sebelipase alfa as it is indicated. What is the Committee's view on each of these estimates?

The impact of the technology on the delivery of the specialised service

- The company noted that sebelipase alfa may be administered in an outpatient setting or at home, but modelled costs based only on sebelipase alfa being administered in an outpatient setting.
  - What proportion of people would be expected to receive sebelipase alfa at home?
  - What are the cost and other implications to the NHS of providing homecare arrangements for sebelipase alfa infusions?

1 Nature of the condition

1.1 Lysosomal acid lipase (LAL) deficiency is an inherited autosomal recessive lysosomal storage disorder. It is caused by a deficiency of the LAL enzyme because of mutations in the lysosomal acid lipase (LIPA) gene. This results in abnormal accumulation of lipids, primarily in the gastrointestinal, hepatic and cardiovascular systems.

1.2 The prevalence of LAL deficiency in England is unknown based on currently available information. The estimated incidence of LAL deficiency is 1:500,000–1:1,000,000 in children presenting in infancy and 1:40,000–300,000 in those presenting in childhood or adulthood.

1.3 Although LAL deficiency is a single disease, its rate of progression and mortality markedly differs in people presenting with symptoms in infancy compared with later in life. Infants who present with LAL deficiency aged less than 6 months generally experience a rapidly progressive condition, although some have a milder course. The rate of progression in children and adults is slower and more variable than in infants. Most people present with symptoms during childhood: 83% of patients present by 12 years of age, with a median age of onset of 5 years.

1.4 Rapidly progressing LAL deficiency in infants is usually diagnosed within the first weeks of life. It causes gastrointestinal and liver problems including malabsorption, growth failure, profound weight loss, steatorrhoea (excretion of fat in stools) and hepatomegaly (enlarged liver). Survival is less than 12 months and the median life expectancy of an infant with rapidly progressing LAL is 3.7 months.

1.5 Children and adults with LAL deficiency frequently experience abdominal pain, fatigue, diarrhoea, nausea, loss of appetite, itchy skin and a swollen abdomen. Lipid accumulation can lead to liver cirrhosis, liver failure, atherosclerosis and other systemic complications such as an enlarged spleen, anaemia and blood platelet deficiency. Around 87% of patients have manifestations of LAL deficiency in more than 1 organ. It is estimated that approximately 50% of children and adults with LAL deficiency progress to have liver complications such as fibrosis, cirrhosis and need a liver transplant within 3 years from onset of clinical symptoms. The life expectancy of people with LAL deficiency that presents after infancy is not clear cut because of the variability of severity of symptoms and rate of progression.

1.6 The patient groups explained the impact of LAL deficiency that presents in infancy on the lives of people who have the condition, and their families and carers:

- Because of the rarity of the condition, delays in diagnosis are common. Parents of symptomatic infants are usually adjusting to having a new baby and recovering from childbirth when the diagnosis is made. Delays in diagnosis are unbearable for them because they can see their child refusing feeds, crying in pain and vomiting continuously.
- After diagnosis, parents have to come to terms with the prognosis of their child having weeks or months to live. They need to take large amounts of time off work and be away from home in order to be with their critically ill child in hospital, which may be far from the family home.
- The patient group stated that the main advantage for infants treated with sebelipase alfa is the chance to live beyond 6 months. Parents of infants treated with sebelipase alfa have reported that for the most part their children are able to live as near life as normal, development is delayed only slightly in some children but attribute this to the children being critically ill for a long period of time before their condition was stabilised.

1.7 A patient group reported that people with symptoms that presented later in life find their wellbeing is impaired by constant pain and nausea. Symptoms affect their ability to carry out everyday tasks and participate in sports. For example, they may be anxious about being in crowded places because of the chance of being accidentally knocked, which increases their pain. People receiving sebelipase alfa commented that their pain had been reduced to a manageable level and that their wellbeing had improved (for example, they are now able to get out more and have more energy). The patient group stated that there may be some patients

who have needle phobia or poor venous access but that these problems can be overcome. It stated that patients have reported that sickness and pain can develop during the infusion but this is managed by taking medications before the infusion and by reducing the infusion and feeding rates.

1.8 A patient organisation explained the experiences of patients and their families facing the possibility of needing a liver transplant in the future. For parents, there is constant anxiety of knowing their child will need a liver transplant one day but not knowing when that is likely to be. When a patient is told they need a transplant, there is uncertainty about when a suitable liver will be available which is overwhelming stressful because they may die before a liver donor is found. Patients (and their families) need to be immediately available when a suitable liver is found, which can impact daily activities and travel. People who have had a transplant require intensive care to recover and may be away from their family, school (or work) and friends for a long period of time. After transplant, people need to have treatment for the rest of their lives. Fear of liver transplant failure can be an ongoing source of anxiety for some people.

1.9 There are no NICE, NHS England or other national guidelines on treating LAL deficiency. However, standard operating procedures have been developed by a multidisciplinary group working in specialist centres in the UK (see Committee papers). Current treatment for LAL deficiency is based on supportive therapies that aim to reduce lipid levels and treat complications. These include lipid-lowering therapies such as statins and vitamin E. Haematopoietic stem cell transplantation (HSCT) has been used to treat LAL deficiency presenting in infancy as a medical emergency

with rapid disease progression. People who experience liver failure need a liver transplant.

2 The technology

2.1 Sebelipase alfa (Kanuma, Alexion Pharma UK) is a recombinant human lysosomal acid lipase. It has a marketing authorisation in the UK that is for long-term enzyme replacement therapy in patients of all ages with lysosomal acid lipase (LAL) deficiency. For infants under 6 months of age with rapidly progressing LAL deficiency, 1 mg/kg sebelipase alfa is administered by intravenous infusion once weekly. The dose may be escalated to 3 mg/kg once weekly based on clinical response. For children and adults who did not present with rapidly progressive LAL deficiency before 6 months of age), 1 mg/mg sebelipase alfa is administered by intravenous infusion once every other week.

2.2 The summary of product characteristics lists the most serious adverse reactions for sebelipase alfa (seen in around 3 in 100 patients) as being signs and symptoms of severe allergic reactions. The summary of product characteristics also states that development of antibodies against the medicine has been reported especially in infants. If antibodies develop sebelipase alfa may not work effectively. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Sebelipase alfa is available in vials containing 20 mg of sebelipase alfa, at a list price of £6286 per vial (excluding VAT; company's evidence submission). The annual cost of treatment is estimated as £491,992 per patient (excluding VAT). This estimate is based on the average yearly cost over 10 years for a patient starting treatment at 11 years of age. The weight of the patient is based on Royal College of Paediatrics and Child Health indices (2015).

3 Remit and decision problem

3.1 The remit from the Department of Health for this evaluation was: to evaluate the benefits and costs of sebelipase alfa within its marketing authorisation for treating lysosomal acid lipase deficiency for national commissioning by NHS England.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with lysosomal acid lipase deficiency	
Intervention	Sebelipase alfa	
Comparators	Established clinical practice without sebelipase alfa	
Outcomes	Outcome measures to be considered include: • mortality • cholesterol level (total, LDL and HDL) • triglycerides level • transaminase level • liver synthetic function • liver disease progression • liver transplant • liver fat content • cardiovascular events • adverse effects of treatment • health-related quality of life (for patients and carers).	As scope except for: • liver synthetic function, • liver disease progression, • liver transplant, and • cardiovascular events. The company explained that it had included minimal information on these measures because it did not have new or additional data at the time of submission.

3.2 The ERG commented that the company submission did not include subgroup analyses for infants with very rapidly progressing LAL deficiency or people who have had a liver transplant. These groups were suggested as potential subgroups in the final scope issued by NICE.

4 Impact of the new technology

4.1 The company submission described 6 clinical trials (LAL-CL01, LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08), a

retrospective cohort study (LAL-1-NH01) (see page 34 of the company submission for a summary). The submission focused on results from LAL-1-NH01, LAL-CL03 and LAL-CL02. The company explained that follow-up of people treated with sebelipase alfa in LAL-CL02 and LAL-CL03 is ongoing and that there are 2 further ongoing phase II clinical trials of sebelipase alfa for LAL deficiency (LAL-CL06 and LAL-CL08) which are expected to complete in 2017.

Overview of the key studies

4.2 LAL-1-NH01 was a natural history study that retrospectively evaluated data from 35 infants with confirmed LAL deficiency (presenting before the age of 2 years, mean age of onset, 1.5 months) at 21 study sites. Diagnosis was from 1985 onwards. The company used a subgroup of 21 patients who had growth failure but who did not have a haematopoietic stem cell transplant or liver transplant as a historical control for LAL-CL03.

4.3 LAL-CL03 is a single-arm, open-label multicentre study in 9 infants aged 2 years or under with rapidly progressive LAL deficiency (defined primarily on growth failure within the first 6 months of life; see table C9.5 on page 82 of the company submission for details). Median age was less than 1 month at onset of symptoms and 3 months at the start of the study. Patients are receiving sebelipase alfa 1 mg/kg every other week. Follow up of participants in this study is ongoing.

4.4 LAL-CL02 is a randomised, double-blind, placebo-controlled study in 66 people aged 4 years or older. Median age at symptom onset was 4 years; the median age at randomisation was 13 years. Thirty-six people had 1 mg/kg sebelipase alfa and 30 had placebo every other week. It had a 20-week double blind treatment period.

The duration of each patient's treatment was expected to be at least 78 weeks. An open-label follow up period of up to 130 weeks is ongoing. The primary outcome was measured in the 'Full Analysis Set' defined as randomised patients who received any amount of sebelipase alfa or placebo.

Clinical trial results

Clinical effectiveness

4.5 The primary outcome in LAL-CL03 was the proportion of infants who survived to 12 months of age. It was assessed in the 'Primary Efficacy Analysis Set', which was defined as all patients who received any amount of sebelipase alfa and were 8 months or younger at their first infusion. Six out of 9 infants survived beyond 12 months (67% survival, [redacted]. The median age at death for the 3 infants who died prior to 12 months of age was 2.92 months (range 2.8 to 4.3 months). None of the historical control group from LAL-1 NH01 survived past 12 months [redacted]

4.6 A secondary outcome in LAL-CL03 was growth. Of the infants with data on median weight for age at the start of LAL-CL03 [redacted], the median was [redacted]. For the infants who survived beyond week 4 [redacted] the mean weight for age percentile was [redacted] For the infants who survived to week 48 [redacted] the mean weight for age percentile was [redacted]. In the natural history cohort there were decreases in weight for age percentiles in the majority of patients

4.7 The primary outcome in LAL-CL02 was normalisation of alanine aminotransferase (ALT) levels at week 20 (defined as ALT below the age-and gender-specific Upper Limit of Normal provided by the

central laboratory performing the assay). The company assessed ALT levels as a measure of liver injury owing to lipid accumulation resulting from LAL deficiency. At 20 weeks, 31% of participants in the sebelipase alfa arm and 7% of patients in the placebo arm had ALT levels within the normal range (p=0.0271). The company stated that normalisation was maintained over the open-label phase of the study (it provided data up to 36 weeks).

4.8 Secondary outcomes in LAL-CL02 included relative reduction in LDL- and non-HDL-c, normalisation of AST, relative reduction in triglyceride, relative increase in HDL-c, relative reduction in liver fat content, improvement in liver histopathology and relative reduction in liver volume. There were statistically significant improvements favouring sebelipase alfa for all of the secondary endpoints apart from improvement in liver histopathology and reduction in liver volume.

Adverse events

4.9 The company carried out a pooled analysis of adverse events using data from LAL-CL02, LAL-CL03, and LAL-CL01/2 (n=84). Treatment emergent adverse events were determined using LAL-CL02. In addition to the 4 studies, data specific to deaths, serious adverse events, and moderate or severe infusion-associated from 2 further ongoing studies (LAL-CL06 and LAL-CL08) were included. The most commonly reported types of adverse events were gastrointestinal disturbances, headache, body temperature increases and upper respiratory signs and symptoms. Most treatment reported adverse events were non-serious, mild or moderate in severity and reported as unrelated to treatment with sebelipase alfa. Sixteen (19%) of the 84 people in LAL-CL01/02/03/04 had a mild or moderate possible hypersensitivity reaction. [redacted]

[redacted]. Three people died in LAL-CL03, and died after receiving 4 or fewer doses of sebelipase alfa. Since the cut-off for safety analysis [redacted]

Quality of life

4.10 CDLQ (Chronic Liver Disease Questionnaire, the FACIT fatigue (Functional Assessment of Chronic Illness Therapy-fatigue) and Peds QL were used to collect quality of life data in LAL-CL02. CDLQ and FACIT-fatigue were completed by 13 people in the sebelipase alfa arm and 7 people in the placebo arm. Of the patients aged 5 to 18 at enrolment, 25 in the sebelipase alfa arm and 23 in the placebo arm completed Peds QL. [redacted] (the study excluded people who had severe liver impairment, or had a stem cell or liver transplant) [redacted]

4.11 The company also provided quality of life data from the European LAL Deficiency Patient/Carer Survey (EU LAL-D Survey). This was an online questionnaire developed by the company to ask about the symptoms experienced and their severity and burden. It also collected EQ-5D data. There was a child-carer and an adult version of the survey.

4.12 Eleven patients participated in the survey (mean age 17 years, median 11 years; range 3 to 49). The mean age at diagnosis was 5.6 years. Most participants were children (n=8, 73%) and were receiving sebelipase alfa (n=7, 64%). The mean age at symptom onset was 3.3 years for the children and 16 years for the adults who responded. One of the children and the 3 adults were from the UK. Abdominal pain was the most commonly reported symptom (91% of respondents). More than half of the respondents reported fatigue, diarrhoea, nausea, loss of appetite, itchy skin and having a swollen abdomen. Swollen abdomen, weight problems and itchy skin were experienced mainly by children. Having a swollen abdomen and anaemia were mainly reported as very burdensome symptoms by children, while adults mainly indicated nausea as a very burdensome symptom. EQ-5D was collected in all patients, and patients who were taking sebelipase were asked to recall their quality of life before taking sebelipase alfa in addition to their current quality of life. The company noted that this meant that these scores were subject to recall bias. In children receiving sebelipase alfa, the mean EQ-5D score was 0.76 before treatment and 0.84 afterwards. In adults, the mean EQ-5D scores before and after treatment were 0.34 and 0.76 respectively.

4.13 Seven carers of children and 1 carer of an adult with LAL deficiency took part in the carer survey. All but 2 of the carers were from the UK. Carers reported that caring for a child with LAL deficiency was stressful and caused them to be anxious and exhausted. Caring for someone with LAL deficiency affected daily activity and leisure activities. A moderate impact was reported by children's carers (3–4 on a scale of 0–10 where 0 is 'no effect' and 10 is 'completely prevented activities'). The carer of the adult patient reported this to be a heavier burden (a score of 7–8). Most of the carers reported that they took fewer holidays due to their child's condition and that

they reduced their time spent with other family members to care for their child. Most carers (88%) worked part time or were unemployed.

ERG comments

4.14 The ERG commented that 2 of the sebelipase alfa clinical trials were non-comparative and may be subject to bias. It noted that the comparability between LAL-CL03 and the historical comparator cohort from LAL-1-NH01 was uncertain because of differences in eligibility criteria and the natural history study recruited people earlier (from 1985 compared with from 2010). It stated the majority of people in LAL-1-NH01 [redacted] and it was likely that best supportive care options have since improved. The ERG noted that the average monthly weight gain for [redacted]. However, the ERG also noted that monthly weight gain varied widely and there were very few other data to compare the prognosis for patients in each study.

4.15 The ERG noted that there were several outcomes listed in the final scope issued by NICE which were not assessed in the clinical trials (liver synthetic function, liver disease progression, liver transplant and cardiovascular events). The ERG agreed that sebelipase alfa had reduced lipid levels, liver fat content and liver enzymes but was unclear how these surrogate outcomes related to key clinical outcomes. In particular, it was uncertain if sebelipase alfa delayed or stopped progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events or death. The ERG commented that, across the sebelipase alfa clinical trials, 9 older infant patients had received treatment for up to 208 weeks and 8 older patients received treatment for up to 156 weeks, but this was

only a fraction of the expected lifelong treatment people in clinical practice would receive. The ERG therefore considered the long-term safety and efficacy profile of sebelipase alfa to be uncertain.

5 Cost to the NHS and personal social services and value for money

5.1 No published economic studies of LAL deficiency were found. The company adapted a cost-utility Markov model of non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis (NAFLD/NASH) (Mahady et al 2012) to determine the costs and consequences of treatment with sebelipase alfa or best supportive care for people with LAL deficiency. The company stated that NAFLD and its progressive form NASH have a similar pattern of liver disease progression to LAL deficiency (from fibrosis to cirrhosis to hepatocellular carcinoma or liver transplant). However, the company noted that LAL deficiency may progress more rapidly than NAFLD. Although the company acknowledged that patients with LAL deficiency have cardiovascular, gastrointestinal and other manifestations, it considered it appropriate to focus on modelling liver disease progression because this is often the most prominent. The model had a cycle length of 1 year with a half-cycle correction, a lifetime horizon and had an NHS perspective. The company used a discount rate of 1.5% for costs and health outcomes because it considered that sebelipase alfa restored people who would otherwise die or had a very severely impaired life to full or near health, which would be sustained over a long period.

5.2 The company's model had 6 health states:

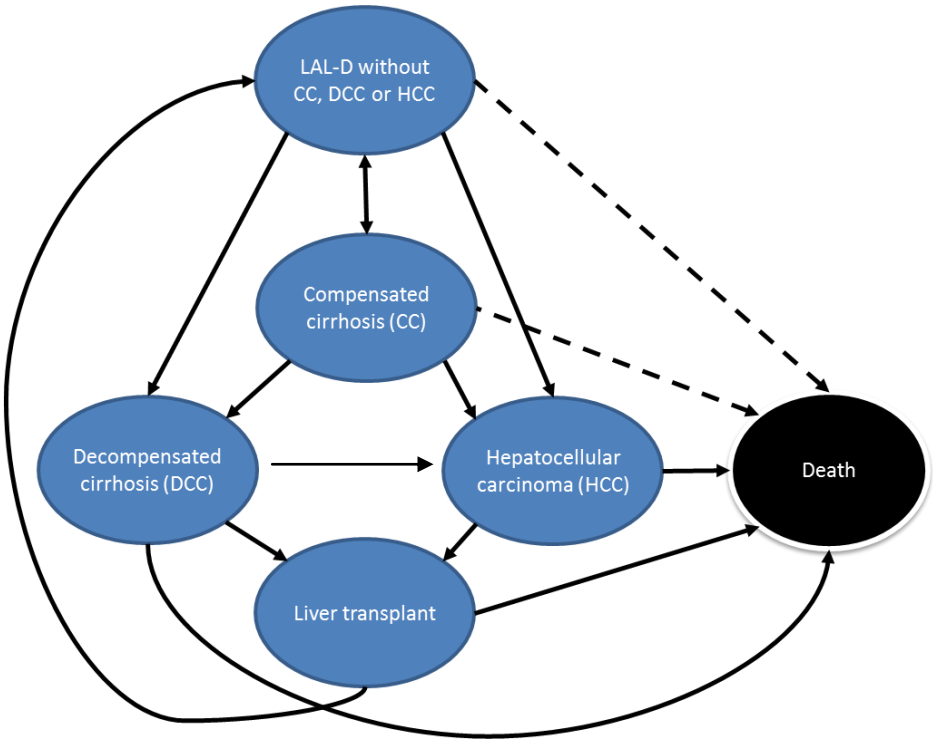
- LAL deficiency without compensated cirrhosis (CC), decompensated cirrhosis (DCC) or hepatocellular carcinoma

(HCC): This health state included people with LAL deficiency who did not have advanced liver complications. People in this state could have fibrosis of the liver.

- Compensated cirrhosis: This health state included people with cirrhosis (severe liver scarring) but with enough healthy liver for the liver to perform all of its functions.
- Decompensated cirrhosis: This health state included people with cirrhosis with impaired liver function.
- Hepatocellular carcinoma: This is the most common type of liver cancer and may be secondary to liver cirrhosis.
- Liver transplant: It was assumed that patients who had a successful liver transplant would transition back to the 'LAL deficiency without CC, DCC or HCC' state, but post-transplant costs and impact on quality of life were not tracked in the model
- Death.

A diagram of the model is shown in Figure 1.

Figure 1: Model structure, adapted from figure D12.1 page 165 company submission (n.b. the diagram in the company submission did not show the transition from DCC to HCC)



Dashed lines describe transitions that were only modelled for people aged less than 1 year.

5.3 The model compared sebelipase alfa with best supportive care for treating LAL deficiency in people of all ages. The modelled cohort reflected the combined populations of LAL-CL02, LAL-CL03 and LAL-1-NH01, the natural history comparator cohort for LAL-CL03. The modelled age when starting treatment was 11 years and mean starting weight was 42.2 kg. In a scenario analysis the company modelled infants (reflecting the combined populations of LAL-CL03 and the natural history comparator cohort) and children and adults (reflecting the population in LAL-CL02) separately. People were modelled to have lifelong treatment with sebelipase alfa without any stopping rules or adjustment for treatment adherence.

5.4 People started treatment either in the 'LAL deficiency without CC, DCC or HCC' health state or the 'compensated cirrhosis' health state. Because liver biopsies had not been routinely performed in the clinical trials, the company estimated the proportion of people with cirrhosis when starting treatment using a published method which mapped AST and ALT levels and platelet count to a fibrosis/cirrhosis score called FIB-4 (Sterling, 2006). In its base case, the company assumed a FIB-4 score of over 1.45 meant that people had compensated cirrhosis, and a score lower than this meant that people did not have cirrhosis. In the base case, based on the AST/ALT scores in the combined population from the clinical trials (LAL-CL)2, LAL-CL03 and LAL-1-NH01), it was assumed that 84% of people would start treatment in the 'LAL deficiency without CC, DCC or HCC' health state and 16% of people would start treatment in the 'compensated cirrhosis' state. The company assumed no one would start treatment with more advanced liver disease because these people had been excluded from its clinical trials.

5.5 The company used different approaches to determine transition probabilities between the health states for people having sebelipase alfa or best supportive care. For sebelipase alfa, the company modelled the probability of transitioning from the 'LAL deficiency without CC, DCC or CC' to the 'compensated cirrhosis' health state based on data collected at baseline and week 20 in LAL-CL02. It noted that no people without cirrhosis at baseline in the sebelipase arm developed cirrhosis by week 20, however 4 people (25%) who had cirrhosis at baseline had an improved FIB-4 score (constant with not having cirrhosis) at week 20. For best supportive care, this transition was calculated using data from the pre-trial period of LAL-CL02 in patients with a known baseline Ishak score (n=32). The company performed a survival analysis of time

from LAL deficiency onset to earliest mention of confirmed compensated cirrhosis. The company noted that the FIB-4 results in the placebo-controlled phase of LAL-CL02 showed that no one in the best supportive care arm of LAL-CL02 developed cirrhosis over the period of the trial using the 1.45 threshold but argued that other FIB-4 thresholds and liver outcomes measured in the trial showed liver disease progression in the best supportive care arm. The company did a scenario analysis using placebo data from LAL-CL02 (see tables D1216 and D12.23 on pages 195 and 203 of the company's submission).

5.6 The company assumed that nobody would progress to more advanced liver disease in the sebelipase alfa arm because it considered that the clinical trials had shown that sebelipase alfa stopped disease progression. This meant that people receiving sebelipase stayed in the 'LAL deficiency without CC, DCC or HCC' health state or the 'compensated cirrhosis' health state or moved from the 'compensated cirrhosis' to the 'LAL deficiency without CC, DCC or HCC' health state or died. People in the best supportive care arm progressed through the more advanced liver disease health states and could go on to have a liver transplant. The probabilities of transitioning between liver disease health states with best supportive care were from Mahady et al 2012.

5.7 Rates of all-cause mortality were based on UK reference tables. Mortality rates associated with decompensated cirrhosis and liver transplant were from Mahady et al 2012. Mortality associated with hepatocellular carcinoma was from Hartwell et al 2011. The company's model did not include the risk of death associated with other non-liver related complications of LAL deficiency. The company took into account the higher risk of death for people presenting with LAL deficiency in infancy by allowing extra

transitions. It assumed that patients under 1 year of age could die whilst in the 'LAL deficiency without CC, DCC or HCC' state. All patients under 1 year of age who received best supportive care died within the first year cycle of the model, the first-year mortality rate for patients receiving sebelipase alfa was 0.33 (based on data from LAL-CL03).

5.8 The company obtained utility values from Mahady et al 2012 for liver outcomes. It also used a value from Mahady to represent LAL deficiency without compensated cirrhosis, decompensated cirrhosis or HCC. This was the same value as people defined as being 'well with F3/F4 fibrosis' (F3 is severe fibrosis; cirrhosis is defined as stage F4, when scar tissue exists throughout the liver). The company did not apply a disutility for caregivers in its modelling because it said there were no data that corresponded to the health states in its model. The company did not identify health state utility values for infants. It therefore assumed that quality of life was 0.25 for infants who die in the first year of life and 0.50 for infants who survive the first year of life. The company did not include disutilities for adverse events because treatment with sebelipase alfa (or placebo) had not negatively affected quality of life in LAL-CL02.

Table 1: Health state utility values used in the company's model

State	Utility value	95% confidence interval	Reference	Justification
LAL deficiency without CC, DCC or HCC	0.92	0.65–0.95	Mahady et al (2012)	'Well with F3/F4 fibrosis' state from Mahady et al (2012) is comparable to 'LAL deficiency without CC, DCC or HCC' state
CC	0.82	0.65–0.89		Best available source
DCC	0.60	0.46–0.81		
HCC	0.73	0.50–0.80		
Liver transplant	0.69	0.62–0.86		
Infant surviving first year	0.50	Standard error 0.19		
Infants dying (annualised rate)	0.07	0–0.14	Assumption	No published data on quality of life of infants with severe growth failure due to LAL deficiency

5.9 The list price for sebelipase alfa is £314.30 per mg or £6286 per 20 mg vial. The company noted that it is in the process of making sebelipase alfa available in 5 mg vials, which it intends to cost at an equivalent price per mg to the 20 mg vials currently available. It said that these 5 mg vials will be available from January 2017. The company used the costs for 20 mg vials in the first year of its model and 5 mg thereafter. The company also reduced the price of sebelipase alfa by 30% after 10 years to account for the potential reduction of pricing when sebelipase alfa's patent expires and generic versions may be available. The dosing regimen for sebelipase alfa in the model was the same as stipulated in the marketing authorisation for sebelipase alfa. As patients age, they were assumed to gain weight over time using UK growth charts. The company noted that sebelipase alfa may be administered in an outpatient setting or at home. It was assumed in the base case that sebelipase alfa would be administered in an outpatient setting for

all people. The NHS reference costs for administration were £68.66 per infusion. Best supportive care drug costs and costs for treating adverse events were not included in the model. Please see table D12.12 on page 188 of the company submission for a summary of sebelipase costs per patient per year.

5.10 The company did not identify published resource costs for LAL deficiency. The company used cost data from a UK cost study and economic evaluation for patients with hepatitis C virus (Backx, 2014; Shepherd 2007) which were inflated to 2014 values using the Office for National Statistics Consumer Prince Indices for Health (Table 2). The company considered its health-state costs to be conservative because children with LAL deficiency may need additional specialist care and because the costs of treating symptoms in organs other than the liver were not included. The company assumed that infants who had treatment with sebelipase alfa and survived would have a 3-month hospital stay; infants who had treatment with best supportive care would stay in hospital for the duration of their lives (3.45 months, based on mean life expectancy in LAL-1-NH01).

Table 2: Health state costs (table D12.13 page 190 company submission).

Health state	Mean cost (£)	Variation	Source
LAL deficiency without CC, DCC or HCC	620	439–877	Backx, 2014; ONS, 2015b
Compensated cirrhosis	962	590 – 1,570	Backx, 2014; ONS, 2015b
Decompensated cirrhosis	12,523	Not reported	Shepherd, 2007; ONS, 2015b
HCC	11,159	Not reported	Shepherd, 2007; ONS, 2015b
Liver transplant	50,515	Not reported	Shepherd, 2007; ONS, 2015b
1st year cost of hospital stay for dying infants	103,604	Not available	Jones, 2015a; NHS, 2015
1st year cost of hospital stay for surviving infants	90,090	Not available	NHS, 2015 and assumption

5.11 The company presented the modelled survival curves for people treated with sebelipase alfa compared with best supportive care in the whole modelled cohort and the infant only cohort (see figures D12.8 and D12.9 on page 199 of the company submission). In the full modelled cohort, people receiving best supportive care were modelled to live for 22.08 years on average (19.14 quality adjusted life years [QALYs]). People receiving sebelipase alfa were modelled to live for 43.24 years (39.73 QALYs) .In the company base case, the total costs associated with sebelipase alfa were [redacted]; the total costs with best supportive care were £46,748. The incremental costs were [redacted], the incremental QALYs were 20.48.

5.12 The company carried out one-way deterministic sensitivity analysis (see table 12.14 on page 193 of the company submission). The variables that had the greatest impact on the incremental QALYs were the discount rate, transition probabilities for people on best supportive care) and utility values for people in the ‘LAL deficiency

without CC, DCC or HCC' health state'. The variable that had the greatest effect on incremental costs was the discounting rate used. None of the other variables had any notable impact. For the tornado diagrams of these sensitivity analyses, see figures D12.10 and D12.12 on pages 202–203 of the company submission.

5.13 The company carried out several scenario analyses exploring the definitions of fibrosis and cirrhosis. These included using different FIB-4 score thresholds to define compensated cirrhosis, and alternative scoring systems for fibrosis (Forns and APRI scores) to determine whether a person was in the 'LAL deficiency without CC, DCC or HCC' health state. These scenarios had a minimal effect on the incremental costs. However, the incremental QALYs gained with sebelipase treatment halved when using FIB-4 scores greater than 0.6 versus the sebelipase base-case values for the probability of transitioning from 'LAL deficiency without CC, DCC or HCC' to CC with best supportive care (see table D12.23 on page 203–4 of the company submission).

5.14 The company conducted scenario analyses that modelled cohorts according to age. For a cohort of only patients presenting with LAL deficiency in infancy, 100% of infants started treatment in the 'LAL deficiency without CC, DCC or HCC' state at baseline). The incremental costs for sebelipase alfa compared with best supportive care were [redacted], the incremental (undiscounted) life years gained were 54.1 and the incremental QALYs were 28.6. For a cohort of children and adults with LAL deficiency (no infants) based on the LAL-CL02 population, 69% of people were in the 'LAL deficiency without CC, DCC or HCC' state at baseline and the remainder in the CC state. The incremental costs for sebelipase alfa compared with best supportive care were [redacted] the

incremental (undiscounted) life years gained were 38.2 and the incremental QALYs were 20.4.

ERG comments

5.15 The ERG commented that the model structure differed for sebelipase alfa and best supportive care because of the company's approach of using different transition probabilities (see figures 5.2 and 5.3 on page 60 of the ERG report). The ERG considered that using a different approach to model transition from 'LAL deficiency without CC, DCC or HCC' to CC health states for sebelipase alfa (FIB-4 scores over placebo controlled period of the LAL CL02) and for best supportive care (time to confirmed compensated cirrhosis using pre-trial data from LAL-CL02) had not been justified. The ERG further considered that the assumption that no people receiving sebelipase alfa would go on to develop decompensated cirrhosis or hepatocellular carcinoma because 'these outcomes were not observed in the trial' was not justified, because this was also the case for people in the best supportive care arm of LAL-CL02. It also considered it was not appropriate to assume that all people receiving sebelipase alfa would not develop decompensated cirrhosis or hepatocellular carcinoma on the basis of 20-week trial data. The ERG further commented that the company had not provided the primary sources for the transition probabilities from the Mahady model and it was also unclear how the survival analyses used to determine time to cirrhosis had been applied in the model.

5.16 The ERG considered using FIB-4 scores to estimate the presence of cirrhosis was reasonable, but noted that the sensitivity (proportion of test positive people who are disease positive) and specificity (proportion of test negative people who are disease negative) of the FIB-4 score was 66.7% and 71.2% respectively

when using the 1.45 threshold and liver histology as a reference standard. As such, uncertainty surrounded the estimates of fibrosis and cirrhosis in the model. The ERG commented that the transition probabilities based on FIB-4 scores came from 20-week data and the company had not adjusted these for the year-long cycle length.

5.17 The ERG considered that the way the company had identified utility values in its model had not been transparently described. The ERG presented utility data from Crossan et al 2015 (see Table 3), which was a systematic review and cost-effectiveness evaluation of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease. The ERG also commented that the utility values used in the company's model were higher than the utility values estimated for the general UK population. For example, 90% of people expected to be alive at age 65 had a utility value of 0.92, whereas the estimated utility value for a person aged 65 in the UK is 0.784. In its exploratory analyses, the ERG capped the utility values in the model so that they wouldn't exceed the general population values. Given there were no data for quality of life in infants, the ERG preferred taking a more conservative approach of assuming that quality of life would be 0.5 for all health states in the first year of life.

Table 3: ERG's preferred utility values (table 5.7 page 73 of the ERG report)

Health state	Estimate	Standard error	Source	Distribution[c]
LALD without CC, DCC or HCC	0.66	0.02	Crossan	Beta
CC	0.55	0.03	Crossan	Beta
DCC	0.49	0.06	Crossan	Beta
HCC	0.49	0.06	Crossan	Beta
Liver transplant	0.51	0.05	Crossan	Beta
Infant scenario				
Alive	0.50	0.19	Assumption	Beta
Dying	0.14	0.07	Assumption	Beta

5.18 The ERG discussed the following additional issues with the company's cost consequence model:

- **Using the Mahady model as a proxy for LAL deficiency.** The ERG commented that the clinical similarities and differences between LAL deficiency and NAFLD had not been fully explained by the company and the justification for using the Mahady model rather than making a new model was not complete.
- **Lack of any treatment-related adverse events.** The ERG noted that treatment-related adverse events, such as allergic reactions (including anaphylaxis), were identified as important risks of sebelipase alfa by the European Medicines Agency, but were not included in the cost-consequence analysis. It understood that 3% of people in the clinical trials had anaphylaxis but no one discontinued sebelipase alfa permanently because of this.
- **Excluding the effect of LAL deficiency on other organ systems.** The ERG noted that the company stated that

excluding severe disease manifestations other than liver disease meant that it was likely that the model underestimated the value of sebelipase alfa. The ERG considered this statement couldn't be supported and suggested that excluding damage to other organ systems could overestimate the value of sebelipase alfa by underestimating health state costs and overestimating utility values.

- **Post liver transplant state excluded.** The ERG considered that not taking into account the effect of a liver transplant on subsequent quality of life and the post-transplant drug costs meant the costs and utility values associated with best supportive care may have been underestimated.
- **Exclusion of surgical and drug treatment options for hepatocellular carcinoma.** The ERG considered it was not fully justified why these treatment options were excluded by the company.
- **Appropriateness of discount factor.** The ERG considered using a 1.5% discount factor for costs and health benefits was appropriate because the NICE technology appraisal methods guide specifies that this rate may be used if it is highly likely that the long term benefits will be achieved and the cost consequence model had shown that the incremental QALYs were 20.48.

5.19 The ERG made the following comments about how the company had modelled costs:

- The company's assumption that people would not gain weight after 18 years was implausible, and this meant that the costs were uncertain because drug costs were dependent on a person's weight.

- Assuming that the price of sebelipase alfa would reduce by 30% after 10 years because of the presumed availability of generic versions was not appropriate because it is highly uncertain if and when, and at what price, a generic version of sebelipase alfa would enter the market
- The costing of sebelipase alfa should not be based on using 5 mg vials because they are not yet available
- The methodology used by the company to identify the studies providing health state costs was not transparent and it was unclear whether these were the most appropriate sources for the current economic evaluation
- A half-cycle correction should not be made for the costs incurred by infants because costs would be underestimated.
- Potential costs which may fall under personal social services were not reported (the ERG did not specify what these costs may be).
- The costs of treating adverse events and the costs of concomitant medications were not included in the model.
- The incremental costs in the company's model were driven by the sebelipase alfa drug cost. Costs of background resource use had very little impact.

ERG exploratory analyses

5.20 The ERG was able to reproduce the company's results when it ran the model. It carried out a number of scenario analyses that are summarised in table 4. The ERG combined its preferred scenarios to produce an exploratory base case that showed that sebelipase alfa produced 0 additional QALYs compared with best supportive care and was associated with additional costs of [redacted].

Table 4: ERG scenario analyses and exploratory base case Scenario 1: health state utility values could not exceed UK population utility values for the general population			
	BSC	**Sebelipase alfa**	**Incremental**
Total costs (95% CI)	£45,118 (£29,930–£73,645)	[redacted]	[redacted]
QALYs (95% CI)	20.24 (11.28–29.64)	37.15 (30.44–41.76)	16.91 (8.00–26.56)
Scenario 2: health state utilities from Crossan et al 2015 rather than Mahady 2012 used			
	BSC	**Sebelipase alfa**	**Incremental**
Total costs (95% CI)	£44,666 (£29,744–£75,279)	[redacted]	[redacted]
QALYs (95% CI)	15.1 (8.49–22.35)	28.49 (25.23–30.89)	13.39 (5.89–20.62)
Scenario 3: Transition probabilities Liver disease progression not halted with sebelipase alfa: 1. Equal probability of transiting from 'LAL-D without CC, DCC or HCC' to 'CC' for both treatments, using the annual probability of 3.2% obtained through the survival analysis. 2. Probability of transiting from 'CC' to 'LAL-D without CC, DCC or HCC' based on FIB-4 scores for both treatments. 3. All other transition probabilities based on Mahady et al (equal for both treatments). People in with compensated cirrhosis can show improvement and move to LAL deficiency without CC, DCC state when treated with sebelipase alfa or BSC (transition probability of 0.528 for both based on FIB-4 scores mapped from LAL-CL02 data)			
	BSC	**Sebelipase alfa**	**incremental**
Total costs (95% CI)	£42,116 (£25,659–£74,778)	[redacted]	[redacted]
QALYs (95% CI)	27.52 (13.68–38.12)	27.52 (13.68–38.12)	0.00 (0.00 – 0.00)
Scenario 4: price reduction of sebelipase alfa by 30% after 10 years (to account for potential lower cost generic versions being available) is removed			
	BSC	**Sebelipase alfa**	**incremental**
Total costs (95% CI)	£44,875 (£29,437–£74,198)	[redacted]	[redacted]
QALYs (95% CI)	20.87 (11.23–31.47)	39.75 (30.89–44.77)	18.87 (8.73–29.74)
Scenario 5: costs were estimated using 20 mg vials rather than 5 mg vials of sebelipase alfa			
	BSC	**Sebelipase alfa**	**incremental**
Total costs (95% CI)	£44,925 (£29,996–£73,343)	[redacted]	[redacted]
QALYs (95% CI)	20.88 (11.52–31.44)	39.72 (30.71–44.64)	18.84 (8.33–29.44)

ERG base case (combination of scenarios 1-5)			
	BSC	**Sebelipase alfa**	**incremental**
Total costs (95% CI)	£41,685 (£25,857–£76,648)	[redacted]	[redacted]
QALYs (95% CI)	19.79 (10.19–26.92)	19.79 (10.19–26.92)	0.00 (0.00–0.00)
ERG base case (combination of scenario 1-5) plus using a 3.5% discount rate			
	BSC	**Sebelipase alfa**	**Incremental**
Total costs (95% CI)	£27,629 (£16,166–£52,297)	[redacted]	[redacted]
QALYs (95% CI)	12.92 (7.80–16.23)	12.92 (7.80–16.23)	0.00 (0.00–0.00)

5.21 The ERG explored the following scenarios in the infant-only subgroup (Table 1Table 5).

Table 5: ERG exploratory analyses in modelled infant population Scenario 6 (infants): half-cycle correction removed for infants dying during the first year			
	BSC	Sebelipase alfa	Incremental
Total costs (95% CI)	£52,212 (£43,111–£62,193)	[redacted]	[redacted]
QALYs (95% CI)	0.07 (0.02–0.15)	14.36 (5.6–23.42)	14.29 (5.5–23.34)
Scenario 6 (infants): half-cycle correction removed for infants dying during the first year plus using a 3.5% discount rate			
	BSC	Sebelipase alfa	Incremental
Total costs (95% CI)	£52,595 (£42,711–£64,149)	[redacted]	[redacted]
QALYs (95% CI)	0.07 (0.02–0.15)	9.17 (4.17–14.14)	9.1 (4.09–14.07)
Scenario 7 (infants): alternative utilities were assumed for infants (0.25 for infants dying in 1st year of life; 0.50 for infants dying after 1 year of age)			
	BSC	Sebelipase alfa	Incremental
Total costs (95% CI)	£52,466 (£42,391–£62,459)	[redacted]	[redacted]
QALYs (95% CI)	0.07 (0.02–0.16)	14.34 (5.29–24.14)	14.27 (5.22–24.03)
Scenario 7 (infants): alternative utilities were assumed for infants plus using a 3.5% discount rate (see description of scenario 7; Section 6.1)			
	BSC	Sebelipase alfa	Incremental
Total costs (95% CI)	£51,876 (£42,390–£63,478)	[redacted]	[redacted]
QALYs	0.07 (0.02–0.16)	9.13 (4.14–14.14)	9.06 (4.11–14.07)

5.22 The ERG carried out the following additional scenarios that were conditional on its exploratory base case (Table 6).

Table 6: ERG further exploratory analyses Explorative scenario 1: reduced the transition probabilities for transitioning from LAL deficiency without CC, DCC or HCC to CC (relative to best supportive care) for sebelipase alfa by 50%			
	BSC	**SA**	**Incremental**
Total Costs	£44,744	[redacted]	[redacted]
QALYs	19.38	20.91	1.53
Explorative scenario 2: using health state costs from Crossan et al			
	BSC	**SA**	**Incremental**
Total Costs	£101,399	[redacted]	[redacted]
QALYs	19.38	19.38	0.00
Explorative scenario 3 (infants): assumed a 4 year time horizon (consistent with follow up in LAL-CL03). Assumed that after 1 year 1 out 6 surviving patients die at 15 months and the remaining 5 patients survive for the rest of the modelled 4 years			
	BSC	**SA**	**Incremental**
Total Costs	£103,604	[redacted]	[redacted]
QALYs	0.14	1.59	1.44
Explorative scenario 4 (infants): Assumed a 4 year time horizon. Survival with sebelipase alfa was the same as explorative scenario 3. It was assumed that 21 out of 25 would survive on average 3.45 months, of the remaining patients 3 would survive for 1 year and the remaining patients would survive for the remainder of the time horizon (this was based on the data the subgroup from LAL-1-NH01)			
	BSC	**SA**	**Incremental**
Total Costs	£103,135	[redacted]	[redacted]
QALYs	0.28	1.59	1.31

Company's budget impact model

5.23 The company estimated that the prevalence of LAL deficiency in people presenting with symptoms aged over 1 year in England was 4.38 per million (or 1 per 228,311). For patients presenting aged younger than 1 year, the company estimated the incidence to be 1.52 per million or (1 per 657,895). The company stated that the incidence and prevalence would be expected to be the same for the population presenting with LAL deficiency before the age of 1 year because the life expectancy is less than 1 year in this group

The company assumed that there would be 237 prevalent patients in the Age 1+ presentation group in 2016 and between 5 and 8 incident patients. It assumed that there would be 1 incident patient aged 0-1.

5.24 The budget impact model had the following assumptions:

- **Weight by age/sex (for sebelipase alfa treatment cost).** The company estimated size by age and sex in the same way as it had done for its cost consequence model based on the expected age weight percentile (see table D13.2 on page 216 of the company submission for details). The age distribution was based on Bernstein et al 2013 (please see table D13.3 company submission page 217). In a sensitivity analysis, the company assumed that the age distribution of people presenting with LAL deficiency over 1 year was the same as in LAL CL02 (see table D13.4 page 218 of the company submission).
- **Death rates in the model.** Mortality in infants was based on LAL CL03 (33% per 1st year if treated with sebelipase alfa; 100% if treated with best supportive care). For people presenting with symptoms aged over 1 year, the company assumed that there was no additional mortality risk associated with LAL deficiency (noting that this was a conservative assumption).
- **Diagnosis rate.** Based on its experience with other ultra-rare diseases (including eculizumab for treatment of paroxysmal nocturnal hemoglobinuria and atypical uremic syndrome), the company expected the diagnosis rate to be affected by whether sebelipase alfa had market access or not.

Table 7: diagnosis rate of LAL deficiency (table D13.10 page 222 company submission)

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario: **sebelipase alfa with market access in England**					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: **sebelipase alfa without market access in England**					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- **Treatment rate with sebelipase alfa.** The company assumed that [redacted] people diagnosed with LAL deficiency aged less than 1 year and between [redacted] of people diagnosed with LAL deficiency aged 1 year and above would receive treatment if sebelipase alfa had market access.
- **Treatment continuation.** The company noted that dose modifications due to adverse events were uncommon in the sebelipase alfa clinical trials but the company's experience from other ultra-rare diseases was that some patients may not continue treatment over the long term. It assumed [redacted] of people with LAL deficiency presenting in infancy would discontinue by 5 years, [redacted] of people with LAL deficiency presenting after 1 year of age would discontinue by 5 years (see table D13.13 on page 223 of the company submission).
- **Compliance rates.** The company assumed that all people with LAL deficiency presenting in infancy and 85% of people with LAL deficiency presenting at 1 year or above would comply with treatment.
- **Drug dose.** The average dose of sebelipase alfa for LAL deficiency presenting in infancy was 2.3 mg/kg. The dose for

LAL deficiency presenting at 1 year or over was 1 mg/kg. As in the cost consequence model the company assumed that a 5 mg vial (rather than a 20 mg vial) would be available in year 2. Therefore less drug wastage was assumed from year 2.

- **Non drug direct medical costs.** Costs of treating liver complications, hospital stay and administration costs were the same as the cost consequence model (see table D13.16 on page 227 of the company submission).

The results of the budget impact model are presented in

5.25 Table 8.

Table 8: Budget impact results (tables D13.17 to D13.19 company submission page 230)

Costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
Sebelipase alfa has market access						
Sebelipase alfa costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-drug costs:						
SA-treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC-treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	£4,418,612	£7,038,926	£10,140,215	£13,828,533	£18,608,038	£54,034,324
Sebelipase alfa does not have market access						
Sebelipase alfa costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-drug costs:						
SA-treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC-treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	£126,476	£86,751	£89,136	£90,841	£92,547	£485,752
Net budget impact						
SA with market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA without market access (all people have BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	£4,292,136	£6,952,175	£10,051,079	£13,737,692	£18,515,491	£53,548,573

5.26 The company presented 3 sensitivity analyses around its budget impact model:

- Assuming the age distribution of people presenting with LAL deficiency at 1 year or older was the same as in LAL CL02 rather than in Bernstein et al 2013 (people were on average younger in Bernstein et al. 2013). This increased the total net budget impact to £82,194,168.
- Assuming only the 20 mg vial was available for the 5 years of the budget impact model rather than a 5 mg vial. This increased the total net budget impact to £63,866,314.
- Assuming the maximum annual cost per person treated with sebelipase alfa was [redacted]. This decreased the total net budget impact to [redacted].

For further details, see tables D13.20–22 on page 232 of the company submission.

ERG comments

5.27 The ERG made the following comments on the company's budget impact model:

- The incidence and prevalence calculations that took into account the incidence and prevalence of LIPA mutations were not transparent and because of this it could not validate them.
- An annual mortality rate of 100% for infants receiving BSC did not appear to have been included in the model.
- It considered that, in the absence of data, basing diagnosis, uptake, compliance and treatment continuation rates on experience of other ultra-rare diseases may be appropriate. The ERG stated that how the company had applied its observations

with eculizumab to sebelipase alfa were not completely transparent. It further noted that the estimated proportion of patients treated with sebelipase in the fifth year [redacted] was half the proportion of people on eculizumab with haemolytic uremic syndrome (around [redacted].

- The ERG did not consider it appropriate to assume that people would not gain weight after 18 years or the availability of 5 mg vials of sebelipase in the second year.

5.28 The ERG applied a 100% mortality rate for infants and recalculated drug medical costs in the model (£684 instead of £668 for sebelipase alfa and £1,444 instead of £1,699 for best supportive care). This increased the total net budget impact to £63,689,818. The ERG carried out further sensitivity analyses surrounding prevalence and incidence rates in the population presenting with LAL deficiency after 1 year of age. In these analyses it varied these estimates by 50%. The results of these analyses are reported in Table 9. The ERG considered that it was highly probable that all diagnosed infant patients would receive sebelipase alfa, but diagnosis and treatment rates in the adult population were more uncertain. The ERG carried out sensitivity analyses in which the diagnosis rates and treatment rates were varied by 10 and 20% around the company's base case assumptions in the population presenting with LAL deficiency after 1 year of age. The results of these analyses ranged between £23,439,245 and £126,845,895 and the number of treated patients in the fifth year of the budget impact model varied from [redacted] to [redacted] (see table 7.10 on page 102 of the ERG report for details). The ERG also carried out sensitivity analyses around treatment compliance and continuation in which both were set to 100%. It combined this with its sensitivity analyses around diagnosis and treatment rates. The number of treated patients varied between [redacted] and [redacted] and the 5-year net budget

impact varied between £36,137,359 and £206,367,686 (see table 7.11 on page 106 of the ERG report for details). Overall the ERG thought that it was most plausible to increase the company's base-case treatment rates by 10%, the company's diagnosis rates by 20% and to set the continuation and compliance rates to 100%. This resulted in a 5-year net budget impact of £178,527,667.

Table 9: results of ERGs sensitivity analyses surrounding incidence and prevalence rates (table 7.9 page 102 ERG report)

Prevalence rate\ incidence rate	Incidence rate -50% [redacted][1]	Incidence rate as in base case [redacted][1]	Incidence rate +50% [redacted][1]
Prevalence rate -50% (119)[2]	£34,250,930	£36,837,511	£39,423,151
Prevalence rate as in base case (237)[2]	£61,102,333	£63,689,818	£66,276,670
Prevalence rate +50% (356)[2]	£87,953,498	£90,541,337	£93,128,707

[1] Number of incident patients in the age 1+ presentation group in Year 1 until Year 5 of the budget impact model.
2 Number of prevalent patient in the age 1+ presentation group in the first year of the budget impact model.

6 Impact of the technology beyond direct health benefits and on the delivery of the specialised service

6.1 The company highlighted the following areas in which additional cost savings could be made if people were treated with sebelipase alfa:

- Avoided lost productivity in patients due to premature death and morbidity.
- Avoided lost productivity in carers. Carers currently report being unable to fully fulfil their employment obligations. Of 8 carers surveyed, only 1 worked full time, 5 worked part time and 2 were unemployed. On average carers worked 14.6 fewer hours per

week than they would have done had they not been carers, and spent 11.5 hours caring for their dependant.

- Avoided costs of respite care and other welfare payments.
- Avoided out of pocket costs associated with transportation and special dietary requirements, travel expenses associated with travelling to hospital and patients or carers taking time off work. If sebelipase alfa is administered at home these costs will be reduced.
- Saved carer time.

6.2 The ERG identified a published study which reported on productivity loss due to chronic liver diseases (Scalone et al 2011). It was estimated that patients and carers would lose 6.8 days of productivity each month, and 14.4 days per month for patients who had a liver transplant. The ERG applied these productivity loss estimates using the assumptions in the company's cost-consequence model and used an average UK salary of £27,607. Two methods were presented to estimate productivity loss: the 'human capital approach' and the 'friction costs method'. The results of this analysis are reported in Table 10.

Table 10: ERG exploratory scenario analysis of productivity loss in patients/ carers discounted at 1.5% (ERG report table 8.2 page 110)

Productivity approach	Time horizon 5 years	Time horizon 10 years	Time horizon lifetime
Human capital approach	£38,096	£75,366	£268,856
Friction costs method	£2,226	£2,226	£2,226

6.3 The company stated that Birmingham, Cambridge, London and Manchester are designated national centres for the diagnosis and management of lysosomal storage disorders. Some patients with LAL deficiency may also currently be under the care of

hepatologists, metabolic and/or lipid specialists. Additional infrastructure is not anticipated because the specialist centres have experience in using enzyme replacement therapies. Professional groups noted that diagnostic services including enzyme activity testing and genetic testing will be required as part of the commissioned services. Treatment would be started at specialist centres followed by transition to local hospital outpatient clinics or homecare arrangements. Professional groups estimated that infants may need to spend their first 6 months of treatment as inpatients and the staffing levels to deliver multidisciplinary care and dietetic support over this period would need to be considered. Professional and patient organisations noted that regular monitoring would be needed once the person's condition had stabilised and suggested this may be 6-monthly to annually and may include body measurement and clinical examination, laboratory tests, imaging and liver biopsies. One professional group suggested that while enzyme replacement could be provided on an indefinite period, it is possible that it could also be used to stabilise the condition prior to HSCT being offered.

6.4 The company stated that patients are currently being enrolled into the LAL Deficiency Registry. It indicated that if sebelipase alfa is recommended for national commissioning in England, it will seek to enrol additional clinical centres to allow collection and sharing of data on disease progression and longer-term outcomes such as the need for liver transplant.

7 Equality issues

7.1 No equality issues were raised by in the evidence submissions or the ERG report.

8 Innovation

8.1 Sebelipase alfa is recognised as an innovative treatment by the company, ERG and consultees because it is the first disease modifying treatment for LAL deficiency.

9 Authors

Mary Hughes
Technical Lead

Linda Landells
Technical Adviser

With input from the Lead Team (Sotiris Antoniou, Sarah Davis and Linn Phipps).

Appendix A: Supporting evidence

Related NICE guidance or NHS England policy documents

No NICE guidance or NHS England policy documents are available.

European public assessment report

The European public assessment report can be found here. A summary of the benefit–risk balance is given on pages 81–85.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of sebelipase alfa within its marketing authorisation for treating lysosomal acid lipase deficiency for national commissioning by NHS England.

Background

Lysosomal acid lipase (LAL) deficiency is an inherited autosomal recessive lysosomal storage disorder. It is caused by a deficiency of the LAL enzyme resulting in abnormal accumulation of lipids in cells primarily in the gastrointestinal, hepatic and cardiovascular systems. LAL deficiency is caused by a marked decrease or loss in LAL enzyme activity and affects people of all ages from infancy through adulthood. Infants presenting with LAL deficiency experience a rapidly progressive condition characterised by malabsorption, growth failure, and liver fibrosis and cirrhosis normally resulting in death in the first 6 months, usually due to multiple organ failure. LAL deficiency presenting later in life, mostly in childhood and adolescence, tends to have less severe presenting symptoms but leads to hepatic and cardiovascular problems including hepatomegaly, cirrhosis, liver failure, dyslipidemia and accelerated atherosclerosis.

The prevalence of LAL deficiency in England is unknown based on currently available information. It is estimated that approximately 3 to 4 infants with the most rapidly progressive disease are born each year. In addition, estimates suggest a prevalent population of children and adults with LAL deficiency of approximately 20 to 40 people in England. There were 36 admissions for LAL deficiency during 2010-11. LAL deficiency affects men and women equally.

There is currently no treatment for LAL deficiency. Although enzyme replacement therapies are used for treating people with other lysosomal storage disorders characterised by specific lysosomal enzyme deficiencies, none are currently available for treating people with LAL deficiency. Medical management is aimed at controlling symptoms and managing complications. Bone marrow transplantation, with intravenous nutritional support, used on an experimental basis for treating people with LAL deficiency presenting in infancy. A low-fat diet and cholesterol-lowering drugs such as statins are used to lower high levels of cholesterol and other fats in the blood in people with later presenting LAL deficiency. These treatments have limited efficacy and

have not been shown to improve the underlying disease. Some people who develop liver failure will require a liver transplant.

The technology

Sebelipase alfa (Kanuma, Alexion Pharma UK) is a recombinant human lysosomal acid lipase, an enzyme replacement therapy. It is given by intravenous infusion.

Sebelipase alfa has a positive CHMP opinion for 'long-term enzyme replacement therapy in patients of all ages with lysosomal acid lipase deficiency'. It has been studied in clinical trials, without a comparator, in infants with rapidly progressive LAL deficiency and, in comparison with placebo, in the prevalent population of affected children and adults with LAL deficiency.

Intervention(s)	Sebelipase alfa
Population(s)	People with lysosomal acid lipase deficiency
Comparators	Established clinical practice without sebelipase alfa
Outcomes	The outcome measures to be considered include: • mortality • cholesterol level (total, LDL and HDL) • triglycerides level • transaminase level • liver synthetic function • liver disease progression • liver transplant • liver fat content • cardiovascular events • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Impact of the new technology	• clinical effectiveness of the technology

	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Cost to the NHS and Personal Social Services (PSS), and Value for Money	• budget impact in the NHS and PSS, including patient access agreements (if applicable) • robustness of costing and budget impact information • technical efficiency (the incremental benefit of the new technology compared to current treatment) • productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• 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 • staffing and infrastructure requirements, including training and planning for expertise.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows the following subgroups will be considered • infants with very rapidly progressing lysosomal acid lipase deficiency • people who have had a liver transplant
Related NICE recommendations and NICE Pathways	None
Related National policy	NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf NHS England Standard Contract for Metabolic Disorders (Adult), 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-metab-disorders-adult.pdf

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID737]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Alexion Pharma UK (sebelipase alfa) Patient/carer groups • British Liver Trust • Children's Liver Disease Foundation • Children Living with Inherited Metabolic Diseases • HEART UK • MPS Society Professional groups • Addenbrooke's Lysosomal Disorders Unit • Birmingham Children's Hospital NHS Foundation Trust • British Inherited Metabolic Disease Group • London Guy's Hospital Genetic Centre • European Lysosomal Storage Disorder Nurses Group • Mark Holland Metabolic Unit for Adult Inherited Metabolic Disorders, SRFT • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Willink Unit, Genetic Medicine, CMFT Others • Department of Health • NHS England	General • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland Comparator manufacturers • None Relevant research groups • Cochrane Cystic Fibrosis and Genetic Disorders Group Evidence Review Group • Kleijnen Systematic Reviews Ltd • National Institute for Health Research Health Technology Assessment

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the evaluation; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and relevant NHS organisations in England.

The company that manufacture the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the recommendations.

All non-manufacturer/sponsor consultees are invited to make an evidence submission or submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the recommendations.

Commentators

Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the final evaluation documentation for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary*)*.

All non-manufacturer/sponsor commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the HST Evaluation Committee in reviewing the manufacturer/sponsor evidence submission to the Institute.

[1] Non manufacturer consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Kanuma® (sebelipase alfa) for patients with Lysosomal Acid Lipase Deficiency

October 14, 2015

Re-reviewed for AIC and CIC Data Feburary 10, 2016

(Template: INTERIM Specification for manufacturer/sponsor submission of evidence, July 2013)

Contents

List of tables and figures 3
Glossary of terms 9
Executive Summary 11
Section A – Decision problem 24
1 Statement of the decision problem 24
2 Description of technology under assessment 30
3 Regulatory information 32
4 Ongoing studies 33
5 Equality 37
Section B – Nature of the condition 39
6 Disease morbidity 39
7 Impact of the disease on quality of life 49
8 Extent and nature of current treatment options 58
Section C – Impact of the new technology 74
9 Published and unpublished clinical evidence 74
10 Measurement and valuation of health effects 145
Section D – Value for Money and cost to the NHS and personal social services 160
11 Existing economic studies 160
12 De novo cost-consequence analysis 163
13 Cost to the NHS and Personal Social Services 210
Section E – Impact of the technology beyond direct health benefits and on the delivery of the specialised service 233
14 Impact of the technology beyond direct health benefits 233
15 Impact of the technology on delivery of the specialised service 239
16 References 241
17 Appendices 251

List of tables and figures

Table ES1: Summary of sebelipase alfa for LAL Deficiency Product Characteristics 12
Table A1.1: Statement of the decision problem 25
Table A2.1: Dosing Information of technology being evaluated 30
Table A4.1: Overview of Sebelipase Alfa Clinical Development Program 34
Table A4.2: Data Cut-off Points for Ongoing Sebelipase Alfa Clinical Studies 36
Table B8.1: Description of Other Liver Diseases (NAFLD and NASH) and LAL Deficiency 64
Table C9.1: Selection criteria used for published studies 75
Table C9.2: Selection criteria used for unpublished studies 77
Table C9.3: List of relevant studies 79
Table C9.4: Summary of methodology for randomised controlled trials 80
Table C9.5: Summary of methodology for uncontrolled studies: LAL-CL03 82
Table C9.6: Summary of methodology for uncontrolled studies: LAL-1-NH01 84
Table C9.7: Summary of methodology for uncontrolled studies: LAL-CL01/04 86
Table C9.8: Sebelipase alfa clinical trial publications 89
Table C9.9: Baseline Demographic and Disease Characteristics 93
Table C9.10: Quality assessment of sebelipase alfa clinical trials 98
Table C9.11: Summary of Primary and Secondary Efficacy Endpoints, including Fixed Sequence Test Results (Study LAL-CL02, Full Analysis Set) 107
Table C9.12: Summary of Treatment-emergent Adverse Events, Regardless of Causality, Occurring in 3 or More Subjects (Study LAL-CL03, Safety Population) 126
Table C9.13: Summary of Treatment-emergent Adverse Events, Regardless of Causality, Occurring in 3 or More Sebelipase Alfa-treated Subjects, by Treatment Group (Study LAL-CL02, FAS, Double-blind Treatment Period) 127

Table C9.14: Summary of Treatment-related Adverse Events (Study LAL-CL03, Safety Population) 128
Table C9.15: Summary of Treatment-related Adverse Events (Study LAL-CL02, FAS, Double-blind Treatment Period) 130
Table C9.16: Number of UK patients enrolled in the sebelipase alfa clinical development programme 142
Table C10.1: Summary of quality-of-life values for cost-consequence analysis 156
Table D11.1: Databases searched 160
Table D11.2: Selection criteria used for health economic studies 161
Table D12.1: Assumptions made in the cost-consequence model 167
Table D12.2: Key features of model not previously reported 168
Table D12.3: Transition probabilities for NASH patients used by Mahady et al. (2012) 169
Table D12.4: Transition probabilities for best supportive care LAL Deficiency patients over the age of 1 172
Table D12.5: Analysis of FIB-4 scores and components, baseline and week 20, in LAL-CL02 174
Table D12.6: Transition probabilities between ‘LAL deficiency without CC, DCC or HCC’ and CC states, calculated using FIB-4 scores with threshold of >1.45 176
Table D12.7: Transition probabilities between ‘LAL deficiency without CC, DCC or HCC’ and CC states, calculated using FIB-4 scores with alternative thresholds and Forns Index and APRI scores 176
Table D12.8: Observable weeks on sebelipase alfa by trial and overall 177
Table D12.9: Base case transition probabilities for patients with LAL Deficiency treated with sebelipase alfa 178
Table D12.10: Baseline characteristics (age, health state distribution) in model 181
Table D12.11: Summary of variables applied in the cost-consequence model 182
Table D12.12: Costs per treatment/patient associated with the technology in the cost-consequence model 187
Table D12.13: Health state costs 189

Table D12.14: Variables used in one-way deterministic sensitivity analysis 192
Table D12.15: Variables used in multi-way scenario-based sensitivity analysis of patient scenarios 194
Table D12.16: Variables used in multi-way scenario-based sensitivity analysis of transition probabilities 194
Table D12.17: Model outputs by clinical outcomes 198
Table D12.18: Summary of QALY gain by health state 199
Table D12.19: Base-case results 199
Table D12.20: Summary of costs by category of cost per patient 200
Table D12.21: Summary of costs by health state per patient 200
Table D12.22: Results of deterministic multi-way scenario sensitivity analysis of patient scenarios 202
Table D12.23: Results of deterministic multi-way scenario sensitivity analysis of transition probabilities 202
Table D12.24: Mean and 95% CI probabilistic sensitivity analysis results ... 203
Table D13.1: Estimated Population of England, 2013-2020 211
Table D13.2: Age to weight correspondence by age of presentation group for LAL Deficiency patients receiving sebelipase alfa 215
Table D13.3: Age distribution of LAL Deficiency patients at presentation, based on Bernstein et al. (2013) 216
Table D13.4: Age distribution of LAL Deficiency patients at presentation, based on ARISE 217
Table D13.5: Age 0-1 presentation group patient counts, scenario with sebelipase alfa with market access in England 218
Table D13.6: Age 0-1 presentation group patient counts, scenario with sebelipase alfa without market access in England 219
Table D13.7: Age 1+ presentation group patient counts, scenario with sebelipase alfa with market access in England 219
Table D13.8: Age 1+ presentation group patient counts, scenario with sebelipase alfa without market access in England 220
Table D13.9: Total LAL Deficiency prevalent patients, by age presentation group and scenario 220
Table D13.10: Diagnosis rate of LAL Deficiency 221
Table D13.11: Treatment rate amongst diagnosed LAL Deficiency patients 222

Table D13.12: Total treated patients, by scenario, treatment type, and age presentation group 222
Table D13.13: Treatment continuation rate amongst treated patients, by years from start of treatment 223
Table D13.14: Compliance with recommended dosing 223
Table D13.15: Average annual drug costs per patient, by age group 225
Table D13.16: Non-drug direct medical costs, by treatment option and age of presentation group 226
Table D13.17: Total costs, scenario with sebelipase alfa with market access in England 229
Table D13.18: Total costs, scenario with sebelipase alfa without market access in England 229
Table D13.19: Net budget impact of sebelipase alfa with market access in England 229
Table D13.20: Net budget impact of sebelipase alfa with market access in England, assuming age of presentation according to ARISE clinical trial 231
Table D13.21: Net budget impact of sebelipase alfa with market access in England, assuming availability of only 20 mg vial 231
Table D13.22: Net budget impact of sebelipase alfa with market access in England, with annual per-patient cost cap of [redacted] 231
Table E14.1: Changes in hours of work and professions for carers (n=8) ... 235
Table 17.1: Databases searched in clinical systematic review 251
Table 17.2: Search strategy used in the Ovid platform for the clinical systemic review 252
Table 17.3: Search strategy used in the EBSCO host platform for the clinical systemic review 252
Table 17.4: Databases searched in economic systematic review 255
Table 17.5: Search strategy used in the Ovid platform for the economic systemic review 256
Table 17.6: Search strategy used in the EBSCO host platform for the economic systemic review 257

Figure B6.1: Cellular cholesterol homoeostasis in (A) healthy individuals and (B) patients with LAL Deficiency 41
Figure B6.2: Kaplan-Meier Estimate: Survival in Infants with LAL Deficiency with Growth Failure 42
Figure B6.3: Kaplan-Meier Estimate: Paediatric and Adult Patients with LAL Deficiency at Risk for Fibrosis, Cirrhosis, or Liver Transplant 43
Figure B6.4: Summary of Multi-Organ Damage and Various LAL Deficiency Disease Manifestations 46
Figure B7.1: Severity of symptoms among patients with LAL Deficiency 51
Figure B7.2: EQ-5D scores in children and adults with LAL Deficiency prior to and following sebelipase alfa treatment 52
Figure B7.3: Impact of LAL Deficiency on carers' daily and leisure activities compared with the mean EQ-5D score of patient cared for (n=7) 54
Figure B7.4: EQ-5D scores across patients with LAL Deficiency before and after sebelipase alfa treatment (n=10) 57
Figure B8.1: Care Pathway for Paediatric LSD Services in England 60
Figure B8.2: Proposed Diagnostic Pathway for Determining Patients with LAL Deficiency 66
Figure C9.1: PRISMA diagram of clinical systematic review 76
Figure C9.2: Patient disposition in LAL-CL02 97
Figure C9.3: Kaplan-Meier Plot of Survival from Birth to 12 Months of Age for Sebelipase alfa-Treated Subjects in Study LAL-CL03 (PES) vs. Untreated Patients in Study LAL-1-NH01 (Patients with Early Failure to Thrive Only) 105
Figure C9.4: Waterfall Plot of Change in ALT (U/L) from Baseline to the Last Time point in the Double-blind Treatment Period, by Subject (Study LAL-CL02, FAS) 108
Figure C9.5: Mean (±SE) Change from Baseline in ALT Values over Time (Study LAL-CL02, FAS, Double-blind Period and EAS, Open-label Period) 109
Figure C9.6: Mean Hepatic Transaminases Over Time (Studies LAL-CL01 and LAL-CL04) 110

Figure C9.7: Change from Baseline to the Last Time Point in the Double-blind Period in Morphometry Scores (Percent Steatosis), by Subject and Treatment Group 113
Figure C9.8: Mean Percent Change from Baseline in LDL-c and HDL-c over Time (Study LAL-CL02, FAS, Double-blind Period and EAS, Open-label Period) 115
Figure C9.9: Mean Percent Change from Baseline in Serum Lipids (Studies LAL-CL01 and LAL-CL04) 116
Figure C10.1: Frequency of symptoms among children with LAL Deficiency suffering from hepatomegaly (n=7) 147
Figure D11.1: PRISMA diagram for economic literature search 162
Figure D12.1: Cost-consequence model schematic 164
Figure D12.2: Time to compensated cirrhosis state in LAL-CL02 patients 171
Figure D12.3: Weight for age curve derived from RCPCH growth charts 187
Figure D12.4: Markov trace for best supportive care 196
Figure D12.5: Markov trace for sebelipase alfa 196
Figure D12.6: Accumulation of QALYs over time for best supportive care 197
Figure D12.7: Accumulation of QALYs over time for sebelipase alfa 197
Figure D12.8: Survival with sebelipase alfa and BSC in the base case 198
Figure D12.9: Survival with sebelipase alfa and BSC in the infant only analysis 198
Figure D12.10: Tornado diagram of incremental QALYs 201
Figure D12.11: Tornado diagram of incremental life years (undiscounted) 201
Figure D12.12: Tornado diagram of incremental costs 202
Figure D12.13: Resulting total costs from PSA 204
Figure D12.14: Resulting total QALYs from PSA 204
Figure D12.15: Resulting total life years from PSA 204
Figure D13.1: Prevalence Estimates for Age 1+ Presentation LAL Deficiency Patients 213
Figure D13.2: Age-to-weight correspondence by age of presentation group for LAL Deficiency patients receiving sebelipase alfa 215
Figure E14.1: Impact of LAL Deficiency on employment of carers 234

Glossary of terms

Term	Definition
ACAT	Acyl-Cholesterol Acyltransferase
ADA	Anti-drug antibody
AE	Adverse event
AE LALD	(Spanish LAL Deficiency support group)
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ApoB	Apolipoprotein B
APRI	Aspartate aminotransferase to Platelet Ratio Index
ARISE	Acid Lipase Replacement Investigating Safety and Efficacy
AST	Aspartate transaminase
ATU	Autorisation Temporaire d'Utilisation (Temporary Use Authorisation)
AWMSG	All Wales Medicines Strategy Group
BIM	Budget impact model
BSC	Best supportive care
CAD	Coronary artery disease
CC	Compensated cirrhosis
CV	Cardiovascular
CE	Cholesteryl Esters
CI	Confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CNS	Central nervous system
CRF	Case report form
CSR	Clinical study report
CVD	Coronary vascular disease
DBS test	Dried blood spot test
DCC	Decompensated cirrhosis
EMA	European Medicines Agency
ECG	Electrocardiogram
ERT	Enzyme replacement therapy
EU	European Union
FA	Fatty Acid
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FC	Free Cholesterol
FCH	Familial combined hyperlipidaemia
FFA	Free Fatty Acid
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
H&E stain	Haematoxylin and eosin stain
HBV	Hepatitus B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitus C virus
HDL/HDL-c	High density lipoprotein/ High density lipoprotein cholesterol
HELLP	Haemolysis; elevated liver enzymes; low platelet count
HeFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
HMG-CoAr	Hydroxymethylglutaryl-coenzyme A reductase
HRG	Health resource group
HRQL	Health related quality of life
HSCT	Haematopoietic stem cell transplantation
IAR	Infusion associated reaction
ICH	International Conference on Harmonisation of Technical Requirements

Term	Definition
	for Registration of Pharmaceuticals for Human Use
IMP	Investigational medicinal product
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LAL/ LAL Deficiency	Lysosomal acid lipase/ Lysosomal acid lipase deficiency
LDH	Lactate dehydrogenase
LDL/ LDL-c	Low density lipoprotein/ Low density lipoprotein cholesterol
LDLR	Low-Density lipoprotein receptor
LIPA	Lysosomal acid lipase gene
LLM	Lipid lowering medication
LLN	Lower limit of normal
LPLV	Last patient last visit
LSD	Lysosomal storage disorder
MEGE-MRI	Multiecho gradient echo sequence-magnetic resonance imaging
MPS	Mucopolysaccharide
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NNT	Number needed to treat
ONS	Office of Natioanl Statistics
PAS	Patient access scheme
PbR	Payment by results
PD	Pharmaco dynamic
PDFF	Proton density fat fraction
PedsQL™	Paediatric quality of life inventory questionnaire
PES	Primary efficacy set
PH	Proportional hazards
PK	Pharmaco kinetic
PLT	Platelet test
PNH	Paroxysmal nocturnal haemoglobinuria
PP /PPS	Per protocol/ per protocol set
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
QOW	Every other week
QW	Weekly
RCPCH	Royal College of Paediatrics and Child Health
rhLAL	Recombinant human lysosomal acid lipase
SAE	Serious adverse event
SD	Standard deviation
SMC	Scottish Medicines Consortium
SOLACE	Support Organization for LAL Deficiency - Advocacy, Care and Expertise
SRBEP	Sterol regulatory element binding proteins
SRT	Substrate reduction therapy
SVR	Sustained viral response
TEAE	Treatment-emergent adverse event
TFHN	Transfusion-free haemoglobin normalisation
TG	Triglyceride
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
WFA	Weight for age
WHO	World Health Organisation
VLDL-C	Very Low Density Lipoprotein Cholesterol

Executive Summary

Lysosomal acid lipase (LAL) Deficiency is an ultra-rare, genetic, life-threatening, progressive disease associated with early mortality and significant morbidity and caused by mutations in the LIPA gene, leading to a failure of normal lipid metabolism due to low or absent LAL enzyme activity. LAL Deficiency leads to disrupted lipid metabolism and results in cirrhosis with portal hypertension, liver failure, accelerated atherosclerosis, and other devastating systemic complications (Bernstein, 2013). LAL Deficiency affects people of all ages as clinical complications may manifest from infancy through to adulthood. Although the disease course is variable in children and adults, it predominantly manifests in childhood with median age of onset of 5 years (Bernstein, 2013). Serious liver complications often develop at an early stage of disease and progress at a faster rate than in most other liver diseases (Data on File, CSR LAL-2-NH01; Alkhouri, 2013; Angulo, 1999). Infants presenting with LAL Deficiency represent a medical emergency as they experience a rapidly progressive condition with the median age of death of 3.7 months. Untreated, infants with confirmed growth failure do not survive beyond 12 months (Jones, 2015a).

Sebelipase alfa (Kanuma®) is the first therapy to be approved for the treatment of LAL Deficiency. The significant limitations of the supportive therapies available prior to this innovative therapy highlight the urgent need for access to a targeted therapy that corrects the underlying cause of LAL Deficiency and changes the course of disease for affected patients.

Sebelipase alfa directly addresses the underlying cause of disease by replacing the missing or deficient enzyme, resulting in reduction of the accumulated substrates and restoration of normal lipid metabolism. Sebelipase alfa is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with LAL Deficiency.

The factors most important to consider when assessing the value of sebelipase alfa in the treatment of LAL Deficiency include: (1) the devastating and life-threatening nature of the condition; (2) the transformative clinical benefits of sebelipase alfa, including the potential to be life-saving; (3) the very small number of eligible patients; (4) the clear lack of effective treatment alternatives; and (5) the ethical imperative to provide access to treatment for these severely ill patients, and to ensure such access is provided fairly and without discrimination between patients with the rarest diseases and those with more common diseases.

Alexion seeks to continue its partnership and dialogue with NICE and the NHS to provide innovative medicines for patients with devastating ultra-rare diseases, and is confident that after examining the clinical benefits associated with sebelipase alfa, NICE will also recommend to the NHS in England that LAL Deficiency patients be provided access to sebelipase alfa. As explained in Sections 12 and 13, the dosage for sebelipase alfa is dependent on the weight of patients, and therefore the costs associated with treatment can vary significantly. Importantly, Alexion will bring

forward proposals in the form of a Patient Access Scheme (PAS) to cap the annual cost of treating an individual patient and ensure that overall cost remains consistent with clinical benefit and the value of sebelipase alfa, irrespective of patient weight. We intend to begin discussions with the relevant authorities about the parameters for a PAS as soon as possible.

Product characteristics (Section 2.2 and 2.3)

The European Commission granted marketing authorisation of Kanuma (sebelipase alfa) for long-term enzyme replacement therapy in patients of all ages with LAL Deficiency on August 28, 2015.

Table ES1: Summary of sebelipase alfa for LAL Deficiency Product Characteristics

Pharmaceutical Formulation	Concentrate for solution for infusion (sterile concentrate). Each vial contains 20 mg sebelipase alfa in 10 ml of solution (2 mg/ml).
Mechanism of Action	Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL). Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Replacement of LAL enzyme activity leads to reductions in liver fat content and transaminases, and enables metabolism of cholesteryl esters and triglycerides in the lysosome, leading to reductions in low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (HDL-c), triglycerides, and increases in HDL-c. Improvement in growth occurs as a result of substrate reduction in the intestine (Kanuma SPC, 2015).
Method of Administration	Intravenous infusion.
Doses /Dosing Frequency	*Infants (< 6 months of age):* The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL Deficiency is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response. *Children and adults:* The recommended dose in children and adults who do not present with rapidly progressive LAL Deficiency prior to 6 months of age is 1 mg/kg administered as an intravenous infusion once every other week.
Repeat Courses of Treatment	Long-term therapy per SmPC
Indication	Long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) Deficiency
Acquisition Cost	The NHS list price for sebelipase alfa is £6,286 per 20mg vial.

I. Nature of the Condition

Disease Morbidity (Section 6.1)

LAL Deficiency is caused by genetic mutations that lead to a decrease or loss in LAL enzyme activity. The reduction or absence of LAL results in marked build-up of cholesteryl esters (CEs) and triglycerides (TGs) in vital organs, blood vessels, and other tissue (Grabowski, 2012). In the liver, LAL Deficiency leads to hepatomegaly, steatosis, fibrosis, cirrhosis, and often progresses to liver failure requiring a liver transplant at an early age. LAL Deficiency also results in cirrhosis with portal hypertension, liver failure, accelerated atherosclerosis, and other devastating systemic complications, including splenomegaly, anaemia, and thrombocytopenia. An estimated 87% of LAL Deficiency patients experience manifestations in more than one organ (Bernstein, 2013). Lipid abnormalities and the associated risk of accelerated atherosclerosis are important clinical outcomes that contribute to morbidity and mortality in the broader LAL Deficiency population (Bernstein, 2013; Burton, 2015c).

LAL Deficiency affects people of all ages as clinical complications may manifest from infancy through adulthood. Infants with LAL Deficiency represent a medical emergency as they experience a rapidly progressive condition characterized by malabsorption, growth failure, and liver failure with the median age of death 3.7 months (Jones, 2015a). Although the age at onset and disease course is variable in children and adults, it is predominantly a childhood condition that can rapidly progress with serious complications occurring at an early age. The median age at first onset in children and adults is 5 years of age, with 83% presenting at 12 years of age or younger (Bernstein, 2013). It is estimated that approximately 50% of children and adults with LAL Deficiency progressed to fibrosis, cirrhosis, and liver transplant within 3 years from clinical manifestation onset (Data on File, CSR LAL-2-NH01).

Quality of Life for Patients and Carers (Section 7.1, 10.1.1)

LAL Deficiency has a substantial detrimental impact on the lives of patients, their families and those involved in their care. Patients that participated in a European LAL Deficiency patient/carer survey (EU LAL-D Survey) frequently suffered from 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 Deficiency was 0.76 (n=8); the mean score for adults was 0.34 (n=2) suggesting a severely reduced quality of life.

Caring for a patient with LAL Deficiency had a considerable impact on physical and mental health. The majority of carers that responded to the EU LAL-D Survey reported they were mentally exhausted, stressed and anxious due to providing care

(n=6). A lower patient health-related quality of life (HRQL) appeared to correlate with an increased burden on carers.

[redacted] Liver disease is the primary manifestation of LAL Deficiency (Bernstein, 2013); therefore, in light of limited published HRQL data in LAL Deficiency patients, data from patients with non-alcoholic fatty liver disease (NAFLD) provide the closest analogue. NAFLD patients have a utility of 0.92 with fibrosis and 0.82 with cirrhosis, which drastically deteriorates to 0.6 upon progression to decompensated cirrhosis. LAL Deficiency patients are likely to have lower HRQL than NAFLD patients in each of these stages due to the possible concurrent cardiovascular and gastrointestinal manifestations of LAL Deficiency. Furthermore, LAL Deficiency patients progress more rapidly through the stages of liver disease to eventual death than NAFLD patients and are typically much younger (Alkhouri, 2013; Angulo, 1999).

Infants and children can present with severe vomiting, malabsorption, diarrhoea, steatorrhea, and failure to thrive. These symptoms are known to have a negative impact on HRQL in patients with functional gastrointestinal disorders (Koloski, 2000). LAL Deficiency is a progressive disease and can be expected to be more severe than functional GI disorders; therefore, symptoms observed in infants and children are likely to significantly impact the HRQL of patients with this disease.

Affected infants with rapidly progressive disease require long-term hospitalisation, and often die before the age of 6 months after suffering from diarrhoea, vomiting, anaemia, thrombocytopenia (which may require transfusion support), and failure to thrive (Anderson, 1999; Mayatepek, 1999). The impact on the quality of life of the patients and parents and caregivers of these infants would be expected to be significant.

Extent and Nature of Current Treatment Options (Section 8)

Currently, there are no effective, regulatory-approved therapies available to treat patients with LAL Deficiency other than sebelipase alfa. Available options for patient management are only supportive in nature and include lipid-lowering therapies, vitamin E, haemaopoietic stem cell transplantation, and liver transplantation.

Supportive therapies do not address the underlying defect in LAL Deficiency. Rather, their main objective is to reduce the burden of LAL Deficiency related complications. Although some temporary stabilisation of the clinical condition has been described, these interventions do not appear to substantially modify the outcome in affected patients (Hoeg, 1984; Meyers, 1985).

Alexion is not aware of any NICE, NHS England or other national guidance or expert guidelines specifically relating to management of LAL Deficiency. An NHS Standard Contract for Lysosomal Storage Disorders Service (Children) is in place (NHS

England E06/S(HSS)/c, 2013). A clinical guideline from the children's lysosomal storage disorder (LSD) centres in England is currently in draft form (personal communication).

II. Impact of the New Technology

Clinical Effectiveness of Sebelipase Alfa (Sections 9.6 and 9.9)

Two pivotal studies focused on developing evidence of safety and efficacy across the clinical spectrum of LAL Deficiency. The first (LAL-CL03) was based on demonstrating a survival benefit in infants with the most rapidly progressive presentation of this disease where a placebo-controlled study would not be clinically or ethically acceptable. This was coupled with the second (LAL-CL02: ARISE), a randomised, double-blind, placebo-controlled study evaluating improvements in multiple clinically important disease-related abnormalities in children and adults where the rate of disease progression is more variable. Alanine aminotransferase (ALT) normalisation was selected as the primary endpoint in LAL-CL02, to demonstrate that sebelipase alfa can reduce the liver injury that occurs due to substrate accumulation and hence reduce the risk of serious hepatic complications. Additional clinically important endpoints in the clinical studies were evaluated to provide evidence supporting clinical benefit in this rare multisystem disease and confirming that effective enzyme replacement is addressing the root cause of disease pathogenesis. Key secondary endpoints focused on the importance of restoring normal homeostasis to lipid metabolism as evidenced by the correction of dyslipidaemia and demonstrating improvements in liver volume, fat content, and histopathology.

Sebelipase alfa is the first and only specific treatment to be approved for patients with LAL Deficiency that has been shown in two pivotal clinical studies to produce significant improvements in serum transaminases, disease-related lipid abnormalities, and liver fat fraction in children and adults and improvements in survival and growth in infants (Burton, 2015a; Data on File, CSR LAL-CL03). These marked improvements in transaminases and other hepatic disease markers reduce the risk of progression to fibrosis, cirrhosis, liver transplant, and death. Improvement in liver function parameters and dyslipidaemia was maintained over long-term treatment.

Overall Magnitude of Health Benefits to Patients and Carers (Section 9.6, 9.9)

Sebelipase alfa is a recombinant form of the human LAL enzyme designed to address the underlying cause of LAL Deficiency. By replacing the deficient enzyme, treatment with sebelipase alfa restores lipid metabolism, thereby preventing chronic lipid accumulation, multi-organ system damage, and premature death.

In clinical trials, sebelipase alfa treatment in LAL Deficiency patients led to significant improvements in markers of chronic liver injury compared to placebo. Treatment with sebelipase alfa produced a rapid decline in ALT and aspartate transaminase (AST)

levels in the majority of people treated in all sebelipase alfa studies regardless of their baseline levels.

Chronic liver injury leads to liver fibrosis and cirrhosis and complications associated with advanced liver disease such as portal hypertension, bleeding varices, hepatic encephalopathy, and requirement for liver transplant. Therefore, it is expected that sebelipase alfa treatment would prevent or reduce fibrosis and cirrhosis and long-term liver complications.

Sebelipase alfa restores lipid metabolism, addresses the liver disease, and corrects the dyslipidaemia associated with untreated LAL deficiency. In children and adults, significant reductions were observed in LDL-c, as well as non-HDL-c and triglycerides, with increases noted in HDL-c. These improvements in the lipid profile would be anticipated to lead to a reduction in cardiovascular risk across the disease spectrum. Decreases in LDL-c with sebelipase alfa were seen irrespective of baseline lipid-lowering medication status.

Sebelipase alfa extended survival in infants with LAL Deficiency. In infants with LAL Deficiency (<6 months of age) presenting with growth failure, sebelipase alfa markedly improved survival (67% survived to one year of age) (Jones, 2015b), representing a more than a 3-fold increase in life expectancy beyond the median age at death for all infants with LAL Deficiency included in the natural history study (Jones, 2015a). Twelve-month survival also represents a significant improvement in survival for infants who received haematopoietic stem cell transplantation (HSCT) or liver transplant.

The survival results demonstrate the clinical benefit of treatment with sebelipase alfa in a group of critically ill subjects with LAL Deficiency at high risk of early mortality who previously had no treatment options. The mortality benefit observed in infants can be extrapolated to the broader population since many clinically relevant disease manifestations are common across the disease spectrum, and therapy with sebelipase alfa results in common beneficial effects, particularly with respect to liver disease parameters.

Treatment with sebelipase alfa also led to improvements in growth, anaemia and gastrointestinal symptoms in infants (Jones, 2015b).

The safety and tolerability profile of sebelipase alfa is favourable. The most commonly reported types of adverse events (AEs) were gastrointestinal disturbances, headache, pyrexia/body temperature increases, and upper respiratory signs and symptoms. The majority of treatment-emergent adverse events (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. Review of the safety data across subgroups based on demographic and baseline characteristics did not reveal any group for which the risk of treatment would outweigh the benefits. The use of lipid-lowering medications by subjects receiving sebelipase alfa does not appear to impact the safety profile of sebelipase alfa.

Health Benefits across LAL Deficiency Populations (Sections 6.1 and 9.9)

Severely affected patients are present across the disease spectrum from infants to adults (Bernstein, 2013).

The clinical development programme for sebelipase alfa was designed to provide evidence of safety and efficacy across the full spectrum of patients with LAL Deficiency and is representative of the patients expected to be treated in clinical practice in England.

Clinical benefit in infants presenting with rapidly progressive disease was primarily demonstrated as an improvement in survival, which was compared to a historical control. Survival was accompanied by substantial and rapid improvements in liver disease parameters, growth, and haematological abnormalities.

The clinical benefit observed in these infants can be extrapolated to the broader population since many clinically relevant disease manifestations are common across the disease spectrum, and enzyme replacement therapy (ERT) with sebelipase alfa results in common beneficial effects, particularly with respect to liver disease parameters. In children and adults, as previously noted, the rate of disease progression in LAL Deficiency is more heterogeneous; this precluded designing or conducting a study of the size and duration that would be required to directly assess the impact of ERT on clinical events associated with progressive liver disease particularly in the context of the rarity of this disease. Thus, the design of the pivotal study in children and adults was based on evaluation of multiple endpoints, which particularly when taken together, demonstrate the efficacy of ERT across multiple clinically important disease abnormalities. The consistent and substantial effects on these assessments, including reduction and normalisation of transaminase levels, improvements in multiple lipid parameters in the direction of reduced cardiometabolic risk, and reduction in liver fat content, predict, with a reasonable degree of confidence, that patients will be at reduced risk of important clinical events associated with disease progression that would occur in the absence of effective intervention. These benefits are particularly important given the early age at which many patients present with significant liver damage. Further, analyses of efficacy endpoints demonstrate the effectiveness of sebelipase alfa across subgroups based on demographic and baseline characteristics.

These results demonstrate that sebelipase alfa can effectively address the underlying cause of disease across the full spectrum of patients affected with LAL Deficiency.

Robustness of the Current Evidence and the Contribution the Guidance Will Have

Sebelipase alfa is the first targeted therapy to be approved for treating patients with LAL Deficiency and studies LAL-CL03 and LAL-CL02 are the first registration studies in LAL Deficiency. The Alexion-sponsored studies comprise the largest-ever dataset

of patients with LAL Deficiency. A total of 84 subjects with LAL Deficiency have received treatment with sebelipase alfa, including 9 infants, 47 children and 28 adults. Fifty-six of 84 patients (67%) who received sebelipase alfa during clinical trials (LAL-CL01/LAL-CL04, LAL-CL02 and LAL-CL03) were in the paediatric and adolescent age range (1 month up to 18 years). The results clearly demonstrate the efficacy and safety of sebelipase alfa across the full spectrum of patients with LAL Deficiency.

The clinical study programme contributed a great deal in terms of study design and choice of endpoints in this ultra-rare and heterogeneous condition. In addition, two non-interventional studies completed by Alexion have provided invaluable knowledge on progression of the disease and the rate of clinically important events.

In England there are currently 29 known patients diagnosed with LAL Deficiency. This includes 11 patients receiving treatment with sebelipase alfa as part of a clinical trial. These patients and their families would benefit from the opportunity to initiate or continue treatment under a nationally commissioned service.

Treatment Continuation Rules (Section 10.1.16)

Sebelipase alfa is indicated for long-term ERT in patients with LAL Deficiency. LAL Deficiency is a genetic disease and not curable with ERT; sebelipase alfa treatment is intended to improve survival and health outcomes in patients, but the underlying disease remains. Evidence from the sebelipase alfa clinical trials indicates that patients continue to benefit from on-going ERT and, at present, there is no evidence to guide the development of treatment continuation rules. As with most drugs developed for ultra-rare diseases, Alexion plans to continue to study the impact of sebelipase alfa in all LAL Deficiency patients, by enrolling patients into the Alexion fully-funded global LAL Deficiency registry.

III. Cost to the NHS and Personal Social Services

Budget Impact in the NHS and PSS (Section 13.7)

Due to the ultra-rare nature of LAL Deficiency and therefore the limited number of patients who will benefit from treatment with sebelipase alfa, the drug is expected to have a limited overall five-year budget impact in England. The five-year estimated budget impact (rounded for simplicity) is as follows:

- Year 1 = £4.3 million
- Year 2 = £7.0 million
- Year 3 = £10.1 million
- Year 4 = £13.7 million
- Year 5 = £18.5 million

- Total 5-year Budget Impact = £53.5 million

Robustness of Costing and Budget Impact Information (Section 13.8)

There is uncertainty in the age and weight of patients that will receive sebelipase alfa in England. Consequently, Alexion will bring forward proposals in the form of a PAS to further limit the estimated budget impact by limiting the maximum annual cost of treating an individual patient and ensuring that overall cost remains consistent with clinical benefit and the value of sebelipase alfa, irrespective of patient weight. We intend to begin discussions with the relevant authorities about the parameters for a PAS as soon as possible.

As with the cost-consequence analysis described in Section 12, only direct medical costs for the primary manifestation of LAL Deficiency – liver disease – have been captured in the budget impact analysis. LAL Deficiency affects more than one organ in most patients (Bernstein, 2013), thus the substantial cost savings associated with sebelipase alfa reducing gastrointestinal and cardiovascular events have not been captured. The budget impact analysis therefore is likely to underestimate the cost savings for the NHS and therefore overestimate the total net budget impact.

IV. Value for money

As required by NICE, a cost consequence analysis was undertaken in order to allow NICE to assess the value for money of sebelipase alfa in the treatment of LAL Deficiency. Alexion presents the following analyses:

1) Incremental benefit of sebelipase alfa versus best supportive care (BSC)
2) Cost comparison of sebelipase alfa versus BSC.

A health state transition model was constructed to simulate lifetime benefit and costs with six health states: (1) LAL Deficiency without compensated cirrhosis (CC), decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC); (2) CC; (3) DCC; (4) HCC; (5) liver transplant; and (6) death. Importantly, the model excludes important aspects of LAL Deficiency and the therapeutic effect of sebelipase alfa owing to small sample sizes and of the very limited information available on the natural history of the disease. In particular, cardiovascular effects (high LDL-c, low HDL-c), marked failure to thrive (growth failure), severe malabsorption, other gastrointestinal symptoms, pulmonary hypertension associated with intimal lipid deposition in pulmonary arteries, severe hypersplenism, mesenteric lipodystrophy, anaemia, and thrombocytopaenia are excluded from the model owing to lack of data. Given that an estimated 87% of LAL Deficiency patients experience manifestations in more than one organ (Bernstein, 2013), this is a serious shortcoming of the model. By excluding these other severe disease manifestations associated with LAL Deficiency, it is likely that this model underestimates the value of sebelipase alfa in the treatment of LAL Deficiency.

The health state transition model was based on an existing model in the literature (Mahady, 2012) assessing treatment for NAFLD and non-alcoholic steatohepatitis (NASH), which clinical experts have deemed the most appropriate disease analogue for modelling LAL Deficiency. Model health states, potential transitions, BSC transition probabilities (with adjustments as necessary) and health utilities are based on this model. Sebelipase alfa transition probabilities are based on patient-level clinical trial data. Direct medical costs come from UK HCV studies (Backx, 2014; Shepherd, 2007).

Results from the model suggest that treatment with sebelipase alfa will result in the majority of LAL Deficiency patients transitioning into the least severe health state (LAL Deficiency without CC, DCC or HCC). BSC patients deteriorate and are expected to live substantially shorter lives. In the base case, which combined the child/adult study and infant study, sebelipase alfa patients were expected to live for 70.70 (undiscounted) years; BSC patients were expected to live for 29.99 years. Sebelipase alfa generated 39.73 (discounted) QALYs over a patient's lifetime versus 19.24 for BSC. The estimated incremental QALY gains with sebelipase alfa are therefore 20.48 QALYs, representing the transformative nature of sebelipase alfa treatment for patients with LAL Deficiency.

Direct medical costs were £19,755 lower per patient with sebelipase alfa compared to BSC. The lifetime cost of sebelipase alfa was estimated to be [redacted] per patient versus £46,748 for BSC. However, this number likely greatly overestimates the true patient lifetime costs due to the following reasons:

- No patient cost cap was factored into this analysis, yet Alexion intends to propose an annual cap on patient costs as part of a PAS to the Department of Health;
- Complete patient compliance and adherence was assumed in the cost-consequence model; and
- No rebates have been built into this projection, yet substantial price cuts and rebates have occurred regularly during PPRS negotiations in the last 10 years.

Overall, access to sebelipase alfa would result in substantial clinical benefit and value to the very few patients affected by LAL Deficiency in England, as well as their families. The magnitude of this value justifies the manageable cost of treatment with sebelipase alfa in a limited patient group.

Nonetheless, caution should be used when attempting to interpret these analyses due to the relatively small body of LAL Deficiency disease information used to estimate patient outcomes over a lifetime. Such analyses are inherently prone to high levels of uncertainty and bias regardless of the modelling approach. For this reason, Alexion encourages NICE to consider the economic analyses presented in this document as auxiliary to the clinical data presented in the other sections of the

submission, which provides strong evidence of a large therapeutic effect for sebelipase alfa based from well-conducted clinical trials in an ultra-rare disease.

V. Impact of the technology beyond direct health benefits

Significant Benefits beyond Health Outcomes (Section 7.2, 14)

In the EU LAL-D Survey, HRQL was reported to improve following sebelipase alfa treatment. Prior to treatment with sebelipase alfa, the mean EQ-5D score among children with LAL Deficiency was 0.76 (n=8) and for adults it was 0.34 (n=2). After treatment scores were higher at 0.84 for children (n=6) and 0.76 for adults (n=1) (see Section 7.2)

Without treatment, infants with early growth failure do not survive beyond 12 months of age (Jones, 2015a). 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 oldest patient in the infant study entered preschool at age 3 and has been attending school without any reported difficulties compared to his peers. Sebelipase alfa may also reduce the need for other invasive therapies such as blood transfusions and HSCT in infants. 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 very significant.

In paediatric and adult patients, sebelipase alfa is expected to prolong survival, reduce liver, gastrointestinal and cardiovascular complications and reduce the need for liver transplantation, therefore improving quality of life and allowing affected individuals to lead long and productive lives (further details in Section 10). Since carers of children with LAL Deficiency report a substantial burden of care, this in turn will free them to fully pursue their own careers, enjoy leisure activities and reduce the stress and anxiety that comes with caring for someone with such a serious condition.

Proportion of Costs Incurred Outside of the NHS and PSS (Sections 14.1 - 14.4)

It is likely that considerable per-patient costs are associated with a condition such as LAL Deficiency, beyond those incurred by the NHS and PSS, and that treatment with sebelipase alfa could reduce these costs. The findings of the European LAL Deficiency patient survey, indicate that the key costs borne by patients and their carers are:

- Loss of employment for adults suffering from LAL Deficiency
- Reduced working hours for carers of patients with LAL Deficiency; and
- Out-of-pocket expenses due, for example, for specialist dietary requirements and travel expenses

Although out-of-pocket travel expenses may be incurred initially for sebelipase alfa treatment, it is expected that this would lessen through uptake of homecare arrangements.

Long-term benefits to the NHS of research and innovation (Section 14.6)

Alexion believes that the clinical programme for sebelipase alfa and subsequent reimbursement and use in the NHS will advance knowledge, foster clinical leadership and encourage research initiatives in rare diseases in the UK as well as encourage investment in the UK biotechnology and pharmaceutical industry.

Sebelipase alfa represents the first effective treatment for an ultra-rare and devastating disease that affects patients all around the world. Whilst patient numbers are relatively small in England, we benefit from the expertise of specialist clinical centres. The UK is world-leading with 12 clinical trial centres in England all managing patients from inside and outside the UK who travel to the UK to receive treatment across the full age spectrum of the disease.

Three of the nine infant patients treated in LAL-CL03 were treated at St Mary's Hospital, Central Manchester Foundation Trust and the centre continues to gain experience having enrolled five infants into the LAL-CL08 study. Experience with paediatric and adult patients with LAL Deficiency was led by Cambridge University Hospitals & Evelina Children's Hospital, London where three patients were enrolled into LAL-CL02.

Following access in England to sebelipase alfa, Alexion will seek to enrol additional centres in England into the LAL Deficiency Registry. This project will enable the collection and sharing of data to inform clinicians and authorities about the progression of the disease and the impact of treatment. UK centres will likely continue to contribute to the global knowledge base for LAL Deficiency through the management of patients receiving treatment with sebelipase alfa.

As a result of the expertise in England related to LAL Deficiency, patients will have access to the most novel and innovative treatments and approaches through new research programmes.

VI. Impact of the technology on the delivery of the specialised service

Staffing and Infrastructure Requirements, Including Training and Planning for Expertise (Sections 8.2.2, 15.1-15.2)

Sebelipase alfa treatment should be supervised by an experienced healthcare professional experienced in the management of patients with LAL Deficiency, other

metabolic disorders, or chronic liver diseases. Sebelipase alfa is administered by intravenous infusion. Appropriate medical support must be readily available when sebelipase alfa is administered (Kanuma SPC, 2015). In England, it is expected that initiation of the infusions and stabilisation of the patient will occur at specialist LSD centres followed by transition to local hospital outpatient clinics or homecare arrangements, as is the case for currently available ERTs.

No additional infrastructure will be required, since sebelipase alfa will be administered and monitored within existing services for LSDs and the patient numbers will be small.

VII. Conclusion

The significant morbidities and mortality associated with LAL Deficiency, despite best available supportive care, represent an unmet medical need for patients with this potentially life-threatening disorder. As the only licensed treatment for LAL Deficiency, sebelipase alfa will fulfil this critical clinical need and dramatically improve the quality of life for patients and their families devastated by this ultra-rare disease. Therefore, Alexion urges NICE to recommend national commissioning for use of sebelipase alfa in LAL Deficiency for patients in England in need of treatment with this novel ERT.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1.1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Intervention	Sebelipase alfa	None	N/A
Population	People with lysosomal acid lipase deficiency	None	N/A
Comparator(s)	Established clinical practice without sebelipase alfa	None	N/A
Outcomes	The outcome measures to be considered include: • mortality • cholesterol level (total, LDL and HDL) • triglycerides level • transaminase level • liver synthetic function • liver disease progression • liver transplant • liver fat content • cardiovascular events • adverse effects of treatment • health-related quality of life (for patients and carers).	The outcome measures reported are: • mortality • cholesterol level (total, LDL and HDL) • triglycerides level • transaminase level • liver fat content • adverse effects of treatment • health-related quality of life (for patients and carers).	As indicated previously to NICE, there are no new interim data analysis for the following four efficacy outcomes for any of the ongoing sebelipase alfa clinical trials: • liver synthetic function, • liver disease progression, • liver transplant, and • cardiovascular events. As such, we will not have new or additional data on these four outcomes by the submission deadline of October 14, 2015 so minimal information will be included on these measures in our submission.

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	None	N/A
Impact of the new technology	• Clinical effectiveness of the technology • Overall magnitude of health benefits to patients and, when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Cost to the NHS and PSS, and Value for Money	• Budget impact in the NHS and PSS, including patient access agreements (if applicable) • Robustness of costing and budget impact information • Technical efficiency (the incremental benefit of the new technology compared to current treatment) • Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Impact of the technology beyond direct health benefits, and on the delivery of the specialised 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 • Staffing and infrastructure requirements, including training and planning for expertise.	None	N/A
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows the following subgroups will be considered • infants with very rapidly progressing lysosomal acid lipase deficiency • people who have had a liver transplant	Currently, all patients with LAL deficiency are being considered. Subgroup analysis will not be undertaken.	The clinical development program for sebelipase alfa has been focused on providing evidence of safety and efficacy across the full spectrum of patients with LAL deficiency and as such the evidence submission will reflect the entire licensed population. No data are available on patients with a liver transplant and therefore this subgroup analysis is not possible.
Related NICE recommendations and NICE pathways	• None	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Related National Policy	• NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf • NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf • NHS England Standard Contract for Metabolic Disorders (Adult), 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-metab-disorders-adult.pdf	None	N/A

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

- Kanuma® (sebelipase alfa)
- Pharmacotherapeutic group: Other alimentary tract and metabolism products, Enzymes
- ATC code: A16AB14 (proposed; expected to be confirmed in January 2016)

2.2 What is the principal mechanism of action of the technology?

LAL Deficiency is an autosomal recessive lysosomal storage disorder characterised by a genetic defect that results in a marked decrease or loss in activity of the lysosomal acid lipase (LAL) enzyme.

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL).

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Replacement of LAL enzyme activity leads to reductions in liver fat content and transaminases, and enables metabolism of cholesteryl esters and triglycerides in the lysosome, leading to reductions in low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol, triglycerides, and increases in HDL cholesterol. Improvement in growth occurs as a result of substrate reduction in the intestine (Kanuma SPC, 2015).

2.3 Please complete the table below.

Table A2.1: Dosing Information of technology being evaluated

Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate). Each vial contains 20 mg sebelipase alfa in 10 ml of solution (2 mg/ml).
Method of administration	Intravenous infusion. 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 0.2µm filter.

Doses	*Infants (< 6 months of age)* The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response. *Children and adults* The recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to 6 months of age is 1 mg/kg administered as an intravenous infusion once every other week.
Dosing frequency	Once every other week or, for infants (< 6 months of age) presenting with rapidly progressive LAL Deficiency, once weekly.
Average length of a course of treatment	As it is an enzyme-replacement therapy (ERT), patients with LAL Deficiency are expected to be treated with sebelipase alfa for the duration of their lives.
Anticipated average interval between courses of treatments	Not applicable – sebelipase alfa is a long-term therapy
Anticipated number of repeat courses of treatments	Not applicable – sebelipase alfa is a long-term therapy
Dose adjustments	Dose adjustments up to 3 mg/kg once weekly may be considered in infants with rapidly progressive disease. The safety and efficacy of sebelipase alfa in patients older than 65 years have not been evaluated and no alternative dose regimens can be recommended for these patients.

Source: Kanuma SPC, 2015

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On the 28th August 2015, the European Commission granted marketing authorisation of Kanuma (sebelipase alfa) for long-term enzyme replacement therapy in patients of all ages with LAL deficiency.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Sebelipase alfa is currently available in the UK.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Sebelipase alfa received marketing authorisation via the EMA centralised procedure for approval in the European Union. It is not licensed in any other country outside of the EU.

Sebelipase alfa is also undergoing review by the FDA. The FDA granted sebelipase alfa with a Fast Track procedure and designation of Breakthrough Therapy for children with LAL Deficiency.

3.4 If the technology has been launched in the UK provide information on the use in England.

In the UK there is one patient being treated with sebelipase alfa under a compassionate use protocol and 11 patients currently being treated within a clinical trial.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Overview of clinical programme

The clinical development program for sebelipase alfa has been focused on providing evidence of safety and efficacy across the full spectrum of patients with LAL Deficiency. This development strategy included generation of evidence of safety and effectiveness based on improvements in multiple disease-related abnormalities in children and adults where a placebo-controlled study was feasible, and demonstrating an impact on survival in infants where a placebo-controlled study would not be clinically or ethically acceptable because of the rapid progression and early mortality associated with this presentation of the disease.

An overview of the studies in support of the efficacy and safety of sebelipase alfa in the long-term treatment of subjects with LAL Deficiency is provided in Table A4.1; brief summaries of each of the studies follow the table.

Six clinical studies have been initiated to evaluate sebelipase alfa treatment in infants, children, and adults with LAL Deficiency. Across these studies, a total of 84 subjects with LAL Deficiency have received treatment with sebelipase alfa, including 9 infants, 47 children and 28 adults. In addition, Alexion has completed a natural history study in infants, which provides a historical control for interpretation of the results of the interventional study in infants. A further observational study in children and adults provides additional insights into the abnormalities associated with this disease across a broader population and is discussed in Section 6.

All studies have been conducted in accordance with International Conference on Harmonization and Good Clinical Practice consolidated guidelines and the ethical principles of the Declaration of Helsinki.

Table A4.1: Overview of Sebelipase Alfa Clinical Development Program

Study Identifier (Status)	Study Design	Study Objective(s)	LAL Deficiency Population	Dosage Regimen	Treatment Duration	No. of Subjects	Primary Efficacy Endpoint
LAL-1-NH01 (Complete)	Observational, non-interventional (provides natural history control group for LAL-CL03)	Chart review of children with LAL Deficiency	Paediatric (≤ 2 years)	N/A	N/A	35 (control group for LAL-CL03, n=21)	N/A
LAL-CL01 (Complete)	Phase 1/2, single-arm, open-label, dose escalation	Safety, PK, and PD	Adult (≥ 18 years)	3 cohorts: 0.35, 1, and 3 mg/kg qw IV	4 weeks	9 (3/cohort)	N/A
LAL-CL02 (Double-blind period complete; Open-label period ongoing)	Phase 3, randomised, double-blind, placebo-controlled; followed by open-label extension	Efficacy, Safety, and PK	Paediatric / adult (≥ 4 years)	1 mg/kg qow IV	20 weeks double-blind followed by open-label up to 130 weeks	66 (36 sebelipase alfa / 30 placebo)	Normalisation of ALT
LAL-CL03 (Primary analysis complete; Follow-up ongoing)	Phase 2/3, single-arm, open-label	Efficacy, Safety, and PK	Paediatric (≤ 2 years)	Dose escalation from 0.35 to 1 mg/kg qw IV; Up to 3 or 5 mg/kg qw IV	Up to 260 weeks	9	Survival at 12 months
LAL-CL04 (Enrolment; complete; Follow-up ongoing)	Phase 2, single-arm, open-label extension for subjects who completed LAL-CL01	Efficacy and Safety	Adult (≥ 18 years)	0.35, 1, or 3 mg/kg, qw IV for 4 weeks; 1 or 3 mg/kg qow IV	Up to 260 weeks	8	N/A
LAL-CL06 (Enrolment complete; Follow-up ongoing)	Phase 2, single-arm, open-label	Efficacy, Safety, and PK	Paediatric / adult (> 8 months)	1 mg/kg qow IV	Up to 96 weeks	31	N/A
LAL-CL08 (Ongoing)	Phase 2, single-arm, open-label	Efficacy, Safety, and PK	Paediatric (< 8 months)	1 mg/kg qw IV; Up to 3 or 5 mg/kg qw IV	Up to 156 weeks	Up to 10 planned	N/A

ALT = alanine aminotransferase; IV = intravenous; LAL = lysosomal acid lipase; N/A = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; qow = once every other week; qw = once weekly

The natural history study, LAL-1-NH01, evaluated data on 35 infants with confirmed LAL Deficiency (mean age at onset of disease, 1.5 months). The study provided the first systematic evaluation of the natural history of LAL Deficiency 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, Study 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).

The initial clinical study of sebelipase alfa, LAL-CL01, was a Phase 1/2 dose-finding, safety, pharmacokinetic (PK) and pharmacodynamic (PD) study conducted in adults with documented LAL Deficiency and evidence of liver dysfunction. Overall, 9 subjects were treated with sebelipase alfa in rising dose cohorts of 0.35, 1.0 or 3.0 mg/kg (3 subjects each) administered intravenously (IV) once weekly (qw) for 4 weeks. Subjects who completed treatment were permitted to enrol in Study LAL-CL04, designed to provide long-term efficacy and safety data. The extension study is currently ongoing, as of the data cut-off for reporting of 05 Feb 2014, all 8 subjects who entered the study remain on long-term treatment with sebelipase alfa.

The pivotal Phase 3 study in children and adults with LAL Deficiency, LAL-CL02, was designed to investigate the effects of sebelipase alfa relative to placebo on a broad range of important disease-related abnormalities. The study includes a 20-week double-blind, placebo-controlled treatment period followed by an open-label extension period of up to 130 weeks where subjects randomized to placebo are permitted to cross over to sebelipase alfa. The study has completed enrolment with 66 subjects randomized. Final results from the double-blind treatment period are included in this submission. A total of 65 subjects remain on treatment in the open-label extension period as of the data cut-off for reporting of 30 May 2014.

The pivotal Phase 2/3 study in infants, LAL-CL03, is designed to evaluate the safety, tolerability, efficacy, PK and PD of sebelipase alfa in subjects with LAL Deficiency who developed growth failure before 6 months of age. The study has completed enrolment with 9 infants treated. Final results for the primary analysis of survival to 12 months are included in this submission. Six subjects remain on treatment as of the data cut-off for reporting of 10 Jun 2014.

The clinical development program also includes 2 studies initiated in 2014 which are anticipated to conclude in 2017 with a full safety and efficacy data set. Study LAL-CL06 is an open-label Phase 2 study in paediatric and adult subjects with LAL Deficiency who are not eligible for other current sebelipase alfa clinical studies due to age, disease progression, previous treatment by HSCT or liver transplantation, or less common disease manifestations. Subjects 2 to 4 years of age are specifically targeted in this study as part of the European Union (EU) Paediatric Investigation Plan. The second study, LAL-CL08, is an open-label Phase 2 study in infants with

LAL Deficiency who have clinical evidence of rapidly progressive disease before 8 months of age. This study differs from Study LAL-CL03 in allowing subjects with an expanded set of disease complications to be included, rather than requiring growth failure in all subjects, and initiating treatment at a dose of 1 mg/kg weekly (in Study LAL-CL03, the initial 2 doses were 0.35 mg/kg prior to escalation to 1 mg/kg).

Timing of the Clinical Studies

As of August 2015, all sebelipase alfa clinical studies, with the exception of Study LAL-CL01, were ongoing to obtain long-term safety and efficacy data and to allow subjects access to sebelipase alfa for uninterrupted ERT. Table A4.2 summarises the clinical data cut-off points for the ongoing studies. These cut-offs reflect a clinically meaningful milestone for each study: the completion of the primary efficacy assessments for Studies LAL-CL02 and LAL-CL03, and the completion of 2 years of study treatment and follow-up (Week 104) for subjects enrolled in Study LAL-CL04. No additional data is expected in the next 12 months.

Table A4.2: Data Cut-off Points for Ongoing Sebelipase Alfa Clinical Studies

Study	Timing	Date	Final Data
LAL-CL02	All data through the Primary Completion Date (LPLV for Week 20 of study)	30 May 2014[c]	April 2017
LAL-CL03	All data through the Primary Completion Date (LPLV for assessment of survival at 12 months of age)	10 Jun 2014[c]	Aug 2018
LAL-CL04	All data through completion of 2-year (Week 104) assessment[a]	05 Feb 2014[c]	Oct 2017
	Cumulative safety data through 27 June 2014[b]	27 Jun 2014[c]	
LAL-CL06	Any SAE, withdrawals due to an AE, or moderate or severe IAR information available as of 08 Sep 2014[b]	08 Sep 2014	Jun 2017
LAL-CL08	Any SAE, withdrawals due to an AE, or moderate or severe IAR information available as of 08 Sep 2014[b]	08 Sep 2014	Dec 2018

AE = adverse event; IAR = infusion-associated reaction; LPLV = Last Patient Last Visit; SAE = serious adverse event
Primary Completion Date = The date that the final subject was examined for the purposes of final collection of data for the primary outcome of the study
[a] One subject from Study LAL-CL04 has Week 90 data.
[b] Included in the Summary of Clinical Safety; not in a clinical study report
[c] Summary of Clinical Safety includes any SAE, withdrawals due to an AE, or moderate or severe IAR information available as of 08 Sep 2014 for these studies

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

Alexion is currently evaluating timing for submissions to the Scottish Medicine Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). It is

anticipated that submissions to these two groups likely will occur after the NICE submission is complete.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Alexion has not identified any issues relating to equity or equality that are specific to this evaluation.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Disease Overview

Lysosomal acid lipase (LAL) Deficiency is an ultra-rare, life-threatening, progressive disease associated with early mortality and significant morbidity. It is caused by a genetic mutation that leads to a marked decrease or loss in LAL enzyme activity. The marked reduction or absence of LAL results in marked build-up of cholesteryl esters (CEs) and triglycerides (TGs) in vital organs, blood vessels, and other tissues. LAL Deficiency results in cirrhosis with portal hypertension, liver failure, accelerated atherosclerosis, and other devastating systemic complications. An estimated 87% of LAL Deficiency patients experienced manifestations in more than one organ; 79% of those patients were 19 years of age or younger (Bernstein, 2013).

In the liver, LAL Deficiency leads to hepatomegaly, steatosis, fibrosis, cirrhosis, and often progresses to liver failure requiring a liver transplant at an early age. Other clinical manifestations may include splenomegaly, anaemia, and thrombocytopenia. Additionally, older patients often have dyslipidaemia, which is associated with an increased risk of cardiovascular disease and accelerated atherosclerosis. Similar to other liver diseases, many patients may be asymptomatic until they experience a severe consequence of the disease.

LAL Deficiency is caused by a marked decrease or complete loss in LAL enzyme activity and affects people of all ages with clinical complications that manifest from infancy through adulthood. Infants presenting with LAL Deficiency represent a medical emergency as they experience a rapidly progressive condition characterized by malabsorption, growth failure, and liver failure with the median age of death 3.7 months (Jones, 2015a). Although the age at onset and disease course is variable in children and adults, it is predominantly a childhood condition that can rapidly progress with serious complications occurring at an early age. In a review of 135 children and adult cases, the median age at first onset was 5 years, with 83% presenting at 12 years of age or younger (Bernstein, 2013). In a subset of patients from an observational study in LAL-deficient children and adults, it is estimated that approximately 50% of children and adults with LAL Deficiency progressed to fibrosis,

cirrhosis, and liver transplant within 3 years from clinical manifestation onset (Data on File, CSR LAL2-NH01).

Etiology

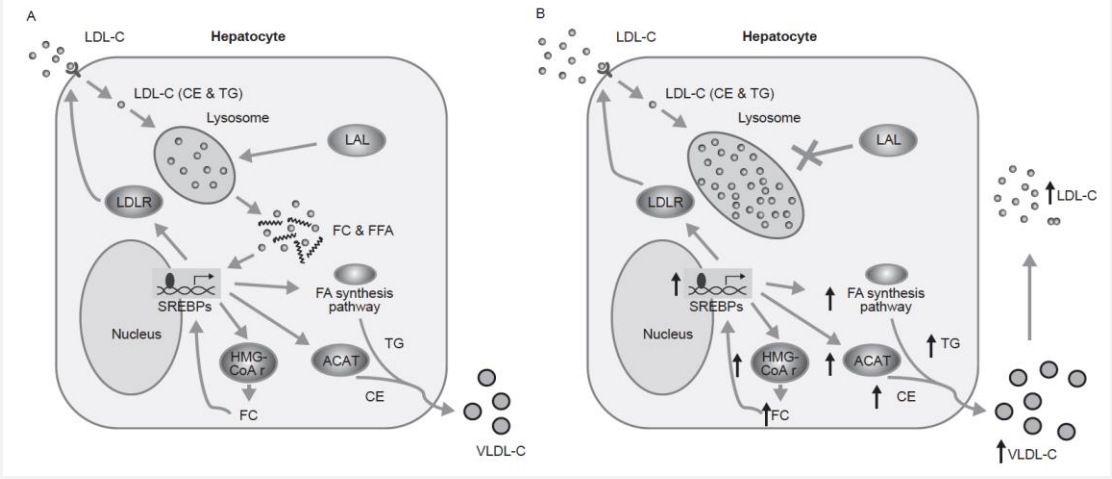
Inheritance and genetics

LAL Deficiency is an autosomal recessive disease and affected individuals are typically either homozygous or compound heterozygous for *LIPA* gene mutations. LAL Deficiency is caused by LIPA mutations encoding LAL located on chromosome 10q23.2-q23.3. The gene mutations associated with LAL Deficiency lead to a marked decrease or loss in LAL enzyme activity. The most commonly inherited defect is the exon 8 splice site mutation, c.894G > A (E8SJM), which is found in more than 50% of children and adults with LAL Deficiency (Reiner, 2014).

Disruption of lipid metabolism

LAL plays a key role in lipid metabolism by degrading LDL-derived neutral lipids (cholesteryl esters and triglycerides). In healthy individual, LDL- -c is transported by endocytosis from the cell membranes of hepatocytes to the lysosome (cell organelles containing hydrolytic enzymes) where LAL breaks down the LDL-c to free cholesterol and free fatty acid (Figure B6.1). In a LAL deficient patient, the enzyme is deficient and the LDL-c particles accumulate within the lysosome causing cellular dysfunction and disruption of normal lipid homeostasis.

Figure B6.1: Cellular cholesterol homoeostasis in (A) healthy individuals and (B) patients with LAL Deficiency



A) As LDL-derived neutral lipids (cholesteryl esters and, to a lesser extent, triglycerides) are degraded by LAL, the resulting free cholesterol and fatty acids act as critical mediators in cellular cholesterol homoeostasis. These lipids or their oxidized derivatives interact with transcription factors (SREBPs) that directly modulate the expression of genes involved in the synthesis and uptake of cholesterol andlipogenesis.

B) When LAL activity is absent or reduced, cholesteryl esters and triglycerides are not degraded and accumulate within lysosomes. The consequent scarcity of intracellular free cholesterol causes the SREBP-mediated up-regulation 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). Enhanced expression of HMG-CoA reductase is the primary outcome of SREBP-2 sensing intracellular cholesterol depletion, leading to an increase in free cholesterol levels.

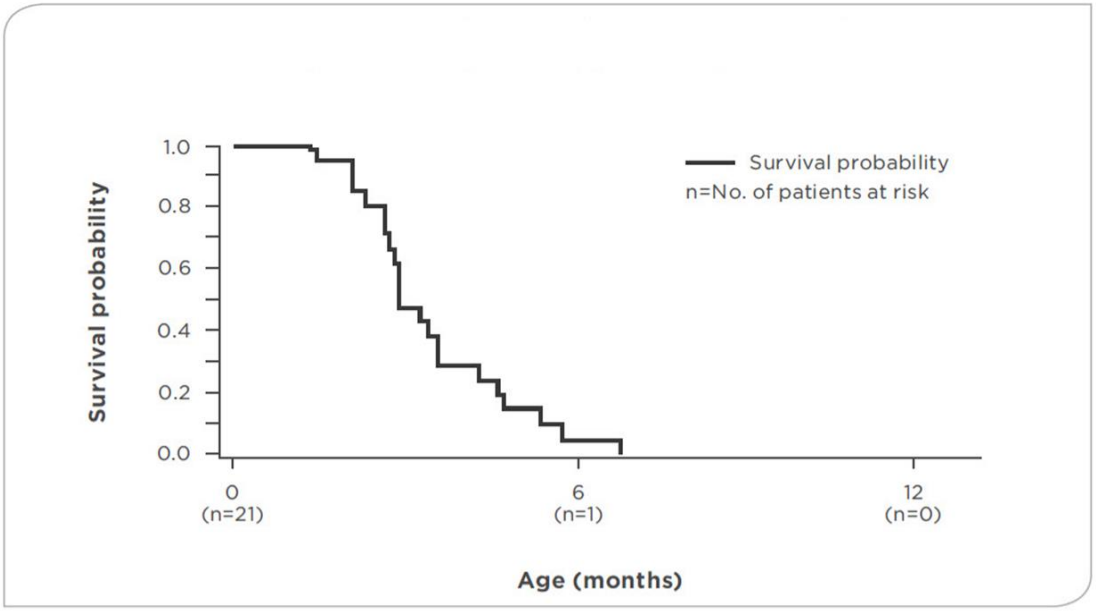
ACAT, acyl-cholesterol acyltransferase; CE, cholesteryl esters; FA, fatty acid; FC, free cholesterol; FFA, free fatty acid; HMG-CoA r, hydroxymethylglutaryl-coenzyme A reductase; LAL, lysosomal acid lipase; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; SREBPs, sterol regulatory element binding proteins; TG, triglyceride; VLDL-C, very-low-density lipoprotein cholesterol.

Source: Reiner, 2014

Mortality and Morbidity

As noted above, LAL Deficiency in infants is a medical emergency. Early and severe symptom onset is observed at a median age of 1 month. Infants with LAL Deficiency experience a rapidly progressive condition characterized by malabsorption, growth failure, and liver failure with the median age of death 3.7 months (Jones, 2015a). In infants with rapidly progressive LAL Deficiency with growth failure, there is a nearly 100% mortality shortly after birth (Figure B6.2).

Figure B6.2: Kaplan-Meier Estimate: Survival in Infants with LAL Deficiency with Growth Failure

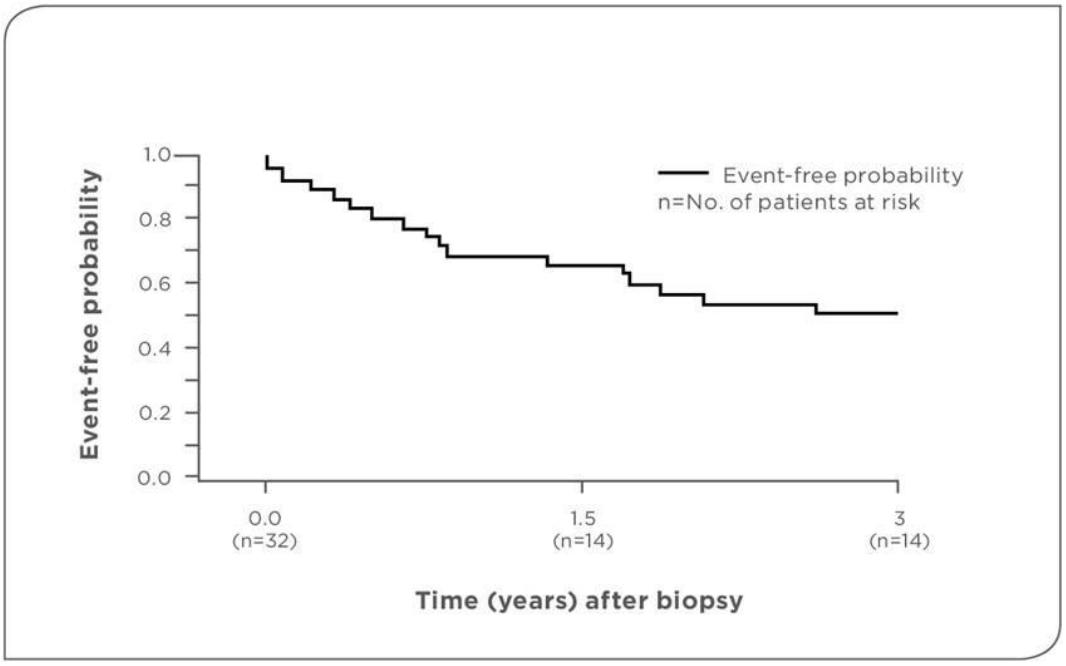


Source: Jones, 2015a
Notes: Data based on a retrospective chart review and data extraction of 35 patients diagnosed with LAL Deficiency before age 2 (26 with growth failure before 6 months of life, 9 without). Of the 26 patients with growth failure, 21 patients shown in the graph did not undergo haemaopoietic stem cell transplant (HSCT) or liver transplant. Growth failure is defined as either weight decrease across 2 major centiles or weight below tenth percentile with no weight gain for ≥2 weeks or loss of ≥5% birth weight after 2 weeks of age within the first 6 months of life.

Marked storage of cholesteryl esters and triglycerides occurs primarily in the liver, intestines and adrenal glands, and causes hepatosplenomegaly, liver dysfunction, diarrhoea, vomiting, anaemia, failure to thrive and adrenal calcifications (Anderson, 1999; Mayatepek, 1999). Liver fibrosis and cirrhosis is also seen (Marshall, 1969; Konno, 1966; Crocker, 1965). Although lipid abnormalities and the associated cardiovascular complications are important clinical outcomes leading to mortality in the broader LAL deficient patient population, as noted above, early death in infants is largely attributed to severe failure to thrive and/or rapidly progressive liver disease often precluding development of longer-term cardiovascular risk (Reiner, 2014).

Children and adults with LAL Deficiency face early and significant morbidity from progressive disease complications with a median age of first clinical manifestation at 5-6 years of age (Bernstein, 2013; Burton, 2015c). In an observational study, approximately 50% of paediatric and adult LAL Deficiency patients progressed to fibrosis, cirrhosis, or liver transplant within 3 years of clinical manifestation onset (Data on File, CSR LAL-2-NH01) (Figure B6.3).

Figure B6.3: Kaplan-Meier Estimate: Paediatric and Adult Patients with LAL Deficiency at Risk for Fibrosis, Cirrhosis, or Liver Transplant



Source: Data on file, CSR LAL-2-NH01
Notes: Based on modelling using a subset of 31 patients (≥5 years of age) in an observational study who received a liver biopsy, and 1 additional patient with no biopsy who received a liver transplant. Patients selected by their clinical for liver biopsy are expected to have more evidence of disease progression than patients with LAL Deficiency overall.

In addition, in a review of 135 paediatric and adult patients with LAL Deficiency, the median age of clinical manifestation onset was at 5 years of age. Furthermore, 83% of patients were ≤12 years old at onset. This review also revealed that 51% of patients progressed to fibrosis, cirrhosis, or death (Bernstein, 2013).

An observational study confirmed previously published findings that LAL Deficiency is predominantly a paediatric disease. In this observational study, the median age at the first report of disease related abnormalities was 5.8 and 81% of the cases (n=48) were younger than 18 years (Burton, 2015c).

Multi-organ Damage

Patients with LAL Deficiency face damage and complications related to involvement of multiple vital organs including the liver, intestines (gastrointestinal [GI]), spleen, and heart. It is estimated that 87% of LAL Deficiency patients experience manifestations in more than one organ; 79% of those patients were 19 years of age or younger (Bernstein, 2013).

Liver Manifestations

Liver manifestations typically dominate the clinical presentation of LAL Deficiency. Overall, approximately 86% of LAL deficiency patients have been reported to have liver manifestations (Bernstein, 2013). Hepatomegaly is common, and persistent elevation of serum transaminases is an early indicator of liver injury in these patients.

The intra-lysosomal accumulation of lipid results in microvesicular steatosis with foamy macrophages in the liver which is prominent in LAL Deficiency patients. Additionally, MEGE-MRI (multiecho gradient echo sequence-magnetic resonance imaging: a non-invasive method to quantify liver fat content) estimates a proton density fat fraction (PDFF) of approximately 8.5% in LAL Deficiency patients (Balwani, 2014; Valayannopoulos, 2014a; Thewall, 2013); however, additional work is need to assess the toxicity of the lipid accumulation in comparison to that in NAFLD which has a higher PDFF.

Overall, 44% of LAL Deficiency subjects (n=66) in a phase 3 trial had a history or evidence of medically important chronic liver disease at baseline, including cirrhosis, portal hypertension, and/or coagulopathy (Balwani, 2014). Hepatic fibrosis progressing to cirrhosis and the expected clinical complications of liver failure, including portal hypertension, bleeding oesophageal varices, ascites, and hepatic encephalopathy also are often observed. In a comprehensive review of the literature, 9 of 12 patients with reported oesophageal varices were between 5 and 20 years of age (Bernstein, 2013).

Fibrosis was also common in affected infants being present in 6 of 9 infants including 4 who were less than 6 months of age (Jones, 2015a; Data on File, CSR LAL-1-NH01). Histologically confirmed cirrhosis has been described in subjects as young as 4 years of age (age range: 4-21) with many not having any past medical history/documentation of cirrhosis or portal hypertension underscoring the progressive nature of this disease (Balwani, 2014).

In addition to complications related to hepatic failure and portal hypertension, hepatobiliary malignancies have also been described in patients with LAL Deficiency, including those as young as 12 years of age. Lastly, as further evidence of the early and significant liver manifestations observed in LAL Deficiency, Bernstein and colleagues reported that death due to liver failure occurred in patients as young as 7 years of age with 50% of the reported deaths due to this cause occurring in patients younger than 21 years (Bernstein, 2013).

Dyslipidaemia and Cardiovascular Manifestations

Along with liver manifestations, dyslipidaemia is also prominent in the clinical picture and is a result of the disruption of lipid metabolism that occurs with LAL Deficiency. Elevations in total cholesterol, triglycerides, and LDL-c, and decreased levels of HDL-c are common in patients with LAL Deficiency and have been associated with accelerated, premature atherosclerosis. Lipid abnormalities and the associated risk of accelerated atherosclerosis are important clinical outcomes that contribute to morbidity and mortality in the broader LAL Deficiency population.

In LAL deficient patients, the resulting absence of intracellular free fatty acid and free cholesterol is expected to lead to an up-regulation of 1) endogenous cholesterol production by HMG-CoA reductase (via SREBP pathways), 2) Lipid particle endocytosis via LDL receptors, 3) increased synthesis of apolipoprotein B (ApoB),

and 4) markedly increased production of very-low-density lipoprotein cholesterol (VLDL-C) which also add to the increases in serum lipids noted in many patients (Reiner, 2014).

Although adverse cardiovascular (CV) outcomes, such as myocardial infarction and stroke, have been described in case reports of patients with LAL Deficiency, understanding of the cardiovascular risk is still incomplete and under-recognized. While dyslipidaemia with elevated LDL-c and triglycerides and low HDL-c is a prominent manifestation in children and adults leading to greater CV risk with age, there is limited information about lipid abnormalities in affected infants. Since infants face early death due to severe failure to thrive and/or rapidly progressive liver disease, longer-term cardiovascular risk from dyslipidaemia is not currently relevant in these patients. In LAL-CL02, dyslipidaemia was present at baseline irrespective of age and despite lipid lowering medication usage in 40% of patients: mean LDL-C 207.9 mg/dL (65.9 SD) overall population. Overall, 87% of LAL Deficiency patients have been reported to have cardiovascular manifestations (Bernstein, 2013).

Failure to Thrive and Gastrointestinal Manifestations

The initial symptoms of marked failure to thrive (growth failure) in infants typically include vomiting and diarrhoea associated with accumulation of lipid substrates in the intestine, leading to severe malabsorption and malnutrition.

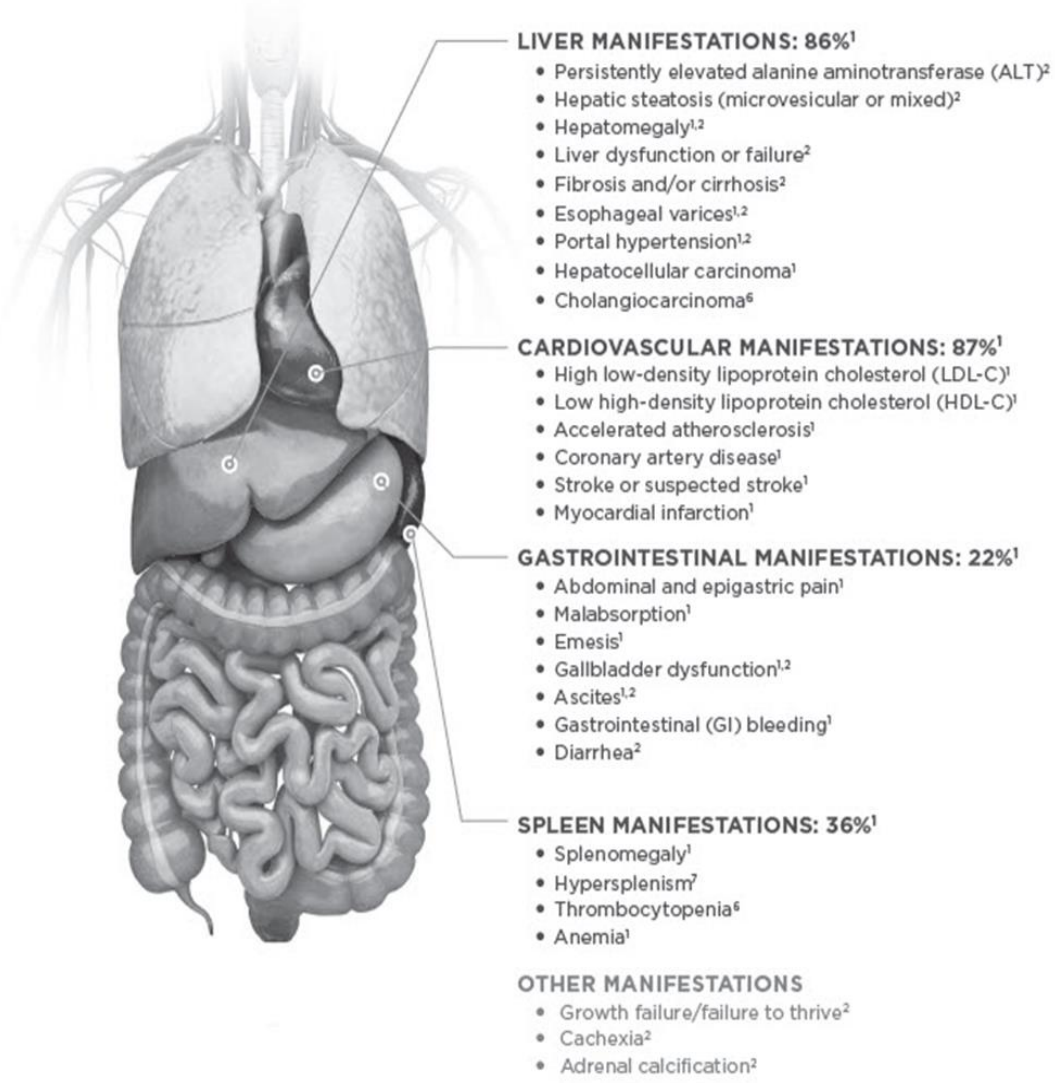
Undernourishment with loss of subcutaneous fat and muscle has been noted. In infants, growth failure is often observed within the first 6 months of life. In contrast, the impact of LAL Deficiency on growth is not widely appreciated in affected children although a recent review by Zhang et al has highlighted failure to thrive, vomiting, diarrhoea, and other gastrointestinal symptoms in ~30% of children with LAL Deficiency (Zhang, 2013). Similarly in LAL-CL02, 12% (6 of 50 patients under 18 years old) were less than the 5th centile, and therefore, the proportion of subjects with short stature is more frequent than expected.

Other Clinical Manifestations

In addition to the more common manifestations of LAL Deficiency, other clinical presentations and complications have been described including pulmonary hypertension associated with lipid deposition in pulmonary arteries, severe hypersplenism (can enlarge to 20 times its normal size by 2 to 3 months of age (Reiner, 2014) and splenic infarcts leading to splenectomies in children, mesenteric lymphadenopathy, anaemia, and thrombocytopenia (Bernstein, 2013).

A summary of the multi-organ damage and various disease manifestations is summarized in Figure B6.4.

Figure B6.4: Summary of Multi-Organ Damage and Various LAL Deficiency Disease Manifestations



Sources: 1. Bernstein, 2013 2. Reiner, 2014 6. Rockey, 2009 7. Ferry, 1991

Disease Progression for Patients with LAL Deficiency

Given the rarity of the disease, there are limited published data regarding its clinical progression over time. Although LAL deficient patients are at risk of cardiovascular and gastrointestinal complications, liver disease progression is often the most prominent and is likely more aggressive than other more common liver diseases. Additionally, in contrast to many other liver diseases, given that LAL Deficiency is a genetic disease, the defect is present from birth and symptoms may manifest very early in life as noted below where many clinical manifestations were first noted in childhood (median age of clinical onset was 5 years of age).

Alexion has completed an observational study in children and adults with LAL Deficiency which provides additional insights into the abnormalities associated with this disease across a broader population (LAL-2-NH01). LAL-2-NH01 was designed to characterize the key aspects of clinical presentation and progression of the disease in order to improve the understanding of the clinical phenotype. This study focused on centres with living patients and, as all patients were alive at the time of data collection, this study provided very little insight into end-stage disease and mortality associated with LAL Deficiency. An associated, prospective sub-study was conducted to assess hepatic and splenic volume and fat content using standardized methodologies. This study represents the largest case record review of patients with LAL Deficiency, and is the first that combined both retrospective and prospective data collection. Overall, retrospective chart data were collected from 48 living patients with LAL Deficiency and prospective data were generated in a subset of 24. Data from this study confirm previously published findings that the disease is predominantly a paediatric disease that results in liver injury and persistent dyslipidaemia, with serious complications that can require liver transplant or lead to either early death.

NAFLD and non-alcoholic stepatohepatitis (NASH) have been frequently studied with published long-term outcomes data. These diseases can provide some insights into prediction of liver disease progression in LAL Deficiency as there are some commonalities across a range of liver diseases in the progression from fibrosis to cirrhosis to hepatocellular carcinoma (HCC) or liver transplant. Preliminary analysis indicates that LAL Deficiency may progress more rapidly than other liver diseases:

LAL Deficiency:

- LAL-CL02 (ARISE) baseline data (Balwani, 2014)
    - 100% fibrosis
    - 47% bridging fibrosis (Ishak 3 or 4)
    - 31% showed cirrhosis
    - Mean age at time of biopsy was 12 years of age
- LAL-2-NH01 (Quinn, 2014a)
    - 68% fibrosis and/or cirrhosis
    - 16.1% cirrhosis
    - Mean age at the time of biopsy was 13 years of age

NAFLD and NASH:

- NAFLD (Alkhouri, 2013)
    - 14.7% fibrosis
    - 0% cirrhosis
    - Cross-sectional studies of 67 consecutive biopsy-proven paediatric patients with NAFLD had clinically significant fibrosis; cirrhosis was not seen in any cases
- NASH (Angulo, 1999)
    - 17% cirrhosis

- Patients with NASH had a median age of 50.5 years

Liver Transplantation:

- LAL-2-NH01 (Quinn, 2014a)
  - 13% had liver transplant (2/3 <18 years)
- NAFLD (Feldstein, 2009)
  - 3% had liver transplant
  - 20-year follow-up of a cohort of children (n = 66) with NAFLD with a mean age of 13.9±3.9 years; only 3% (n = 2) subjects required liver transplant

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

As is the case with most ultra-rare diseases, published information about the incidence and prevalence of LAL Deficiency is limited. As such, determining accurate patient numbers for those impacted by LAL Deficiency is difficult. The actual prevalence of patients impacted by LAL Deficiency is unknown; however, literature and database searches suggest 8-12 patients per million have the disease (Scott, 2013). These estimates can vary given assumptions about the frequency of the common mutation and may not reflect the early mortality in patients with LAL Deficiency. In a recent observational study of patients with LAL Deficiency, the proportion of older patients (>40 years of age) identified was substantially lower (18.7%) in comparison to the proportion of the normal population over 40 years of age (46.7%) (Burton, 2015c). These findings are consistent with a recent extensive case report review where less than 10% of the 135 reported patients were older than 40 years of age (Bernstein, 2013). This discrepancy, which suggests a lower prevalence of LAL Deficiency, could be the result of the early mortality due to the cardiovascular risk associated with dyslipidaemia, but further investigation is needed (Burton, 2015c).

The prevalence of LAL Deficiency patients aged 1 and over is estimated to be 4.38 per million (or 1:228,311), based on internal Alexion modelling (see section 13.1). This equates to 237 prevalent LAL Deficiency patients in England after 1 and over in 2016. It is estimated that there will be between 5 and 8 incident patients aged 1 and over per year.

Incidence of LAL Deficiency in infants is estimated to be 1.52 per million (or 1:657,895); this estimate is based on the frequency analysis from Scott et al. combined with null-allele assessment from Reiner et al., which enable an assessment of incidence of presentation of symptoms at birth (Scott, 2013; Reiner, 2014). This equates to an incidence of 1 patient with LAL Deficiency per year.

For the purposes of the budget impact analysis, there are estimated to be 237 patients in England with LAL Deficiency eligible for treatment with sebelipase alfa in the first year.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

As noted above, LAL Deficiency in infants is a medical emergency. Early and severe symptom onset is observed at a median age of 1 month. Infants with LAL Deficiency experience a rapidly progressive condition characterized by malabsorption, growth failure, and liver failure with the median age of death 3.7 months (Jones, 2015a). In infants with rapidly progressive LAL Deficiency with growth failure, there is a nearly 100% mortality shortly after birth (Figure B6.2).

Limited data exist on the life expectancy in paediatric and adult patients. In a review of 135 paediatric and adult patients with LAL Deficiency, Bernstein et al reported that death due to liver failure occurred in patients as young as 7 years of age with 50% of the reported deaths due to this cause occurring in patients younger than 21 years (Bernstein, 2013).

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

Due to the rarity and nature of the condition, quality of life data for people with LAL Deficiency is extremely limited and minimal information is available in published literature. Health-related quality of life (HRQL) data from three sources is provided:

1) European LAL Deficiency Patient/Carer Survey (EU LAL-D Survey);
2) The sebelipase alfa LAL-CL02 study (ARISE); and
3) Published data on HRQL in patients with related conditions.

European LAL Deficiency Patient/Carer Survey

In the absence of published literature specifically relating to quality of life in patients with LAL Deficiency, Alexion invited patients and their families to complete an online questionnaire from the 8th of September 2015 until the 18th of September 2015 (see Appendix 5 for questionnaires). Adults, children and families were recruited from the

UK through the UK Society for Mucopolysaccharide Diseases (MPS). However, due to the rarity of the condition the scope was expanded to gather insights from other European based patients and carers; the survey was sent to the only LAL Deficiency specific patient organisation in Europe, AE LALD (Spanish LAL Deficiency support group) and a US based LAL Deficiency patient organisation, SOLACE (Support Organization for LAL Deficiency - Advocacy, Care and Expertise) which has some European based members. The survey was designed in collaboration with physicians and was approved by the patient associations working with patients affected by LAL Deficiency. This helped identify the major domains of importance regarding the burden of LAL Deficiency on HRQL. Two versions of the questionnaire were created: a child-carer version consisting of 44 items and an adult version consisting of 50 items. In instances where patients were currently treated with sebelipase alfa, in terms of the physical impact of LAL Deficiency they were asked to think about their experience before their treatment.

The survey was completed directly by adult patients. For child patients (≤17 years of age), responses were completed on their behalf by a parent / carer; alternatively, patients completed it with parental assistance. Parents or family members responsible for the care of a patient with LAL Deficiency were also invited to answer “carer” specific questions about the impact of the disease on their own lives. The carer survey consisted of 19 questions.

Due to the very low sample size of the survey and the fact that not all patients answered all questions, the results must be interpreted with caution. In this patient survey, none of the responders had had any spleen surgery or had received a liver or stem cell transplant at any time. Therefore the sample may not be representative of the wider spectrum of patients with LAL Deficiency.

Impact on patients

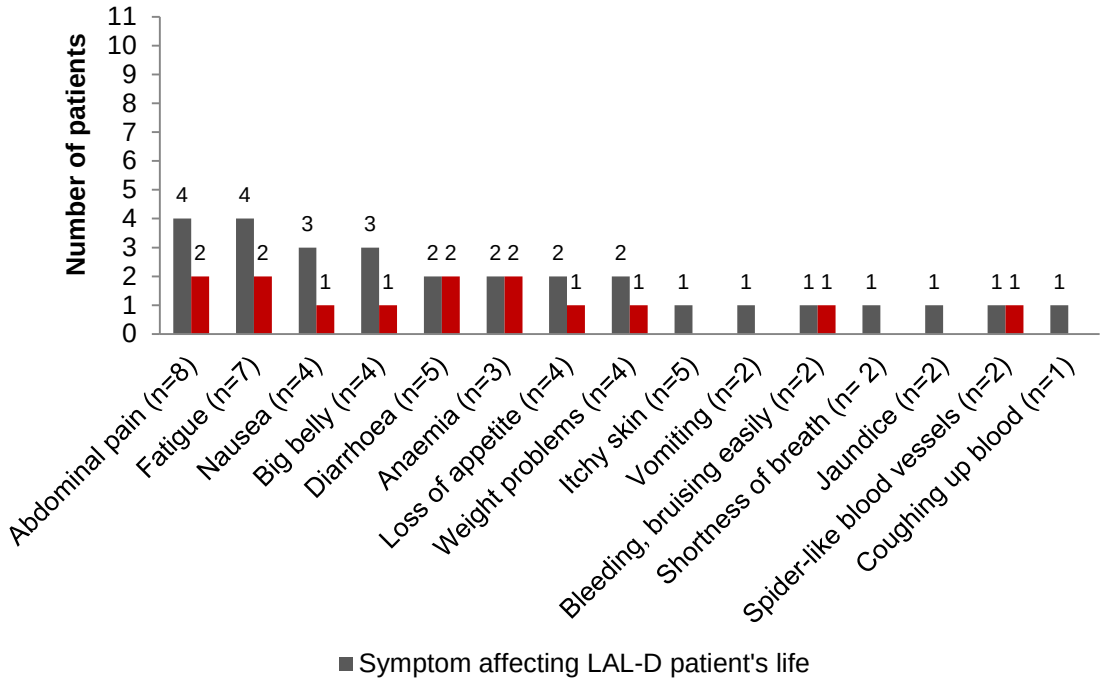
Eleven patients participated in the EU Survey; the mean patient age was 17 years (median: 11 years; range: 3-49). Most participants were children (n=8, 73%) and most participants were treated with sebelipase alfa (n=7, 64%). The mean age of patients when diagnosed with LAL Deficiency was 5.6 years for children and 33.5 years for adults. The mean age when patients experienced their first LAL Deficiency symptom was 3.3 years for children and 16 years for adults. The majority of children were from Spain (six of eight children; 75%), one from the UK and one from the Netherlands, while all adult patients were from the UK; none of the adult participants had children.

Abdominal pain was the most commonly reported symptom in almost all LAL Deficiency patients (91%). The other symptoms mentioned by more than half of the survey sample were fatigue, diarrhoea, nausea, loss of appetite, itchy skin and having a swollen abdomen (“big belly”). Swollen abdomen, weight problems and itchy skin were symptoms experienced mainly by children.

The physical burden of LAL Deficiency was further assessed by asking patients to consider the level of severity of the symptoms they experience – responses are summarised in Figure B7.1 Several patients reported that abdominal pain and fatigue, were symptoms affecting their lives; of these, half reported these symptoms to be very burdensome. Other symptoms cited as very burdensome were a swollen abdomen, nausea, diarrhoea and anaemia.

There were some differences in the assessment of disease severity between children and adults. Having a swollen abdomen and anaemia were mainly reported as very burdensome symptoms by children, while adults mainly indicated nausea as a very burdensome symptom.

Figure B7.1: Severity of symptoms among patients with LAL Deficiency



Notes: n corresponds to the number of patients responding to a given question. Weight problems include weight loss and weight gain problems. The "big belly" symptom was defined to patients as not related to fluid accumulation.

Parents of children suffering from LAL Deficiency highlighted that the disease had a substantial physical and emotional impact on the daily life of their children before starting treatment with sebelipase alfa. Some of their quotes are reported below:

"First he looked like a child with severe hunger problems: big belly and skinny arms and legs."

"She often complained of abdominal pain."

"My child had mood swings, she felt tired easily, looked pale with black marks around eyes. She lost appetite, and needed a lot of encouragement to eat. She could not take part in physical activities with other children."

Living with LAL Deficiency may be difficult, imposing a substantial burden and affecting the ability of adults to manage their everyday activities. An adult patient stressed:

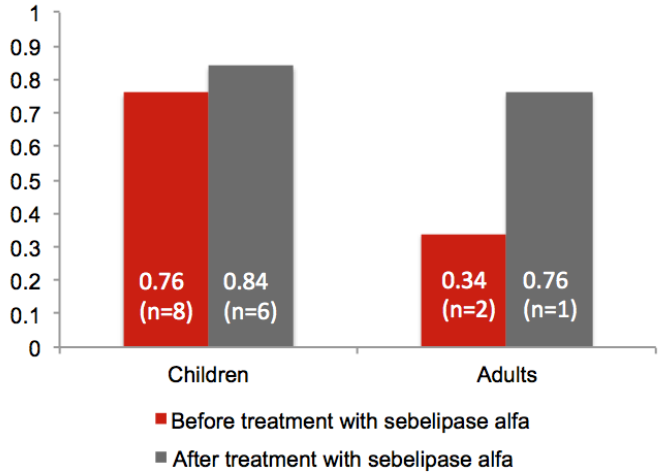
"Simple everyday tasks and activities were difficult due to the pain and discomfort I was experiencing. I suffered nausea after eating."

The parents of two boys indicated that they had to undertake many medical tests and had frequent hospital visits, which, as a result, affected the everyday lives of their children and of the whole family.

HRQL was measured in the patient survey using the 5 level version of the EQ-5D instrument. Patients were asked to rate their current mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For patients who were receiving treatment with sebelipase alfa, they were also asked to estimate their quality of life before commencing treatment using the same EQ-5D scale. It is recognised that such retrospective evaluation of quality of life is potentially subject to recall bias, however given the high proportion of LAL Deficiency patients receiving sebelipase alfa, this was the only way to understand the pre-treatment burden in patients who would be eligible for treatment.

HRQL was reported to improve following sebelipase alfa treatment. Prior to treatment with sebelipase alfa, the mean EQ-5D score among children with LAL Deficiency was 0.76 and for adults it was 0.34 (Figure B7.2). After treatment scores were higher at 0.84 for children and 0.76 for adults (see Section 7.2)

Figure B7.2: EQ-5D scores in children and adults with LAL Deficiency prior to and following sebelipase alfa treatment



Six children who participated in the survey were of school age (≥5 years old), and five had parents who completed the schooling questions. LAL Deficiency does not appear to have a major impact on patients' schooling; the majority of children of school age (80%) were able to follow a full-time education. Most parents (80%) also reported that their child was able to keep up with schoolwork. However, most children (80%) were required to miss days at school for hospital and doctor visits. In addition,

it was highlighted that in an 11 year old girl with LAL Deficiency from the UK with very low EQ-5D scores (0.30 before treatment), she had trouble keeping up with school and, in addition, felt sad not only about missing days from school, but the disease itself. After therapy with sebelipase alfa her EQ-5D improved to 0.56.

Most children of school age (4 out of 5) were treated with sebelipase alfa. However based on the survey results; it is unclear whether schooling status and performance at school are affected by treatment:

- The untreated child did not report any schooling issues
- Two of four treated children did not report any impact of the treatment on their schooling ability
- One of four treated children reported better mood and being more active while at school following treatment, however the situation before treatment was not specified
- One of four treated children reported missing lessons as a result of sebelipase alfa treatment, however the situation before treatment was not specified.

Only two adult patients indicated their working status and provided information about the impact of the disease on their employment situation. One patient indicated LAL Deficiency had a moderate impact on her ability to work, while the other patient had to retire as a result of the disease (see Section 14 for further details). The retired patient stressed:

"I was very limited in my work situation due to physical nature of the role and the fact that physical activity exaggerated my extreme pain and discomfort further."

Impact on carers

Seven carers of children with LAL Deficiency and one carer of an adult patient took part in the carer survey. All carers were parents of the LAL Deficiency patient. Two carers were from the UK. Most of the patients being cared for were being treated with sebelipase alfa (7 of 8).

Carers reported that caring for a patient with LAL Deficiency had a considerable impact on their physical and mental health. The majority of carers (75%) reported they were mentally exhausted, stressed and anxious due to caring.

Respondents often reported experiencing feelings of stress and anxiety regarding their child's future or for their child's disease course. Some parents reported:

"I do feel anxious sometimes thinking about what will happen to my child, how she will be able to cope with this long life condition, and what the future would hold."

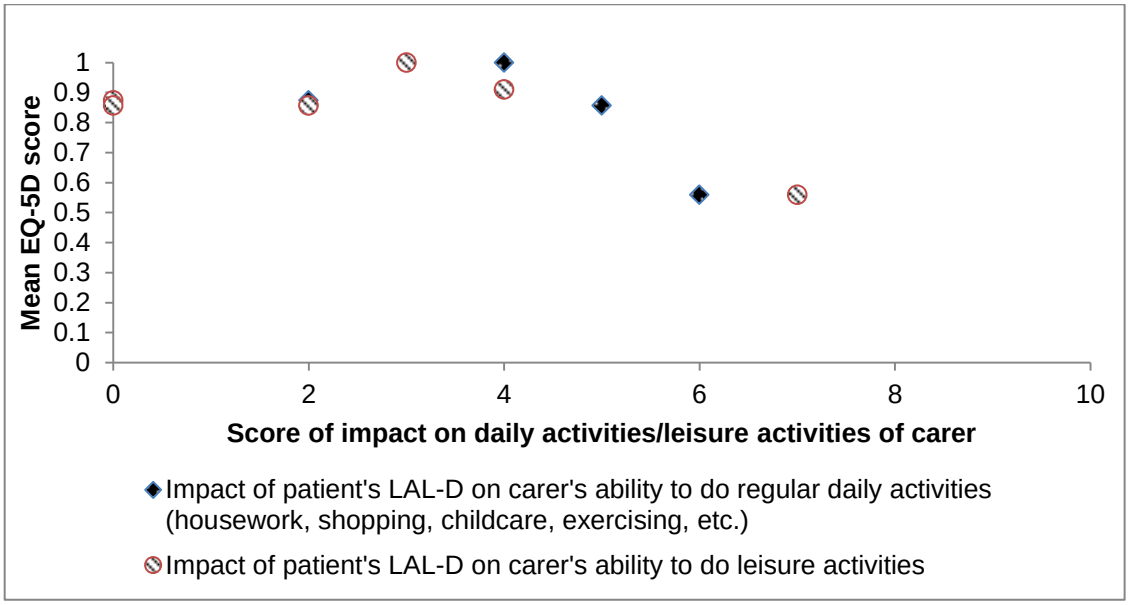
"I am not peaceful in the course of the disease. I have the fear of accelerated development of pathologies associated."

The impact of LAL Deficiency on the ability of carers to engage in daily activities and leisure activities was moderate (scores of 3.8 and 3, respectively, on a scale of 0 to

10, where 0 means no effect and 10 means completely prevented activities). The carer of the adult patient (n=1) indicated the heavy burden of the patient's LAL Deficiency on her daily activities (score 7) and leisure activities (score 8). The overall scores were comparable with data provided by those caring for patients with paroxysmal nocturnal haemoglobinuria (PNH).

The results indicate a correlation between decreased patient HRQL and the burden on carers. The impact on daily activities and leisure activities of carers was greater when patient's EQ-5D score was lower (Figure B7.3). However, EQ-5D scores were available only for seven patients; therefore, these data should be interpreted with caution.

Figure B7.3: Impact of LAL Deficiency on carers' daily and leisure activities compared with the mean EQ-5D score of patient cared for (n=7)



Impact score range 0 to 10, where 0-no impact and 10-completely preventing activities; LAL-D = LAL Deficiency

Results suggested LAL Deficiency had a wider impact on families as a whole. Most of the carers (63%) highlighted that they took fewer holidays due to their child's LAL Deficiency and that they had reduced their time spent with other family members.

LAL Deficiency also affected carers' employment – the majority of carers (88%) were working part-time or were unemployed. When working, most carers had to reduce hours of work or had to change their work in order to take care of the patient with LAL Deficiency (for further detail see Section 14).

LAL-CL02 (ARISE)

Quality of life data were collected in the sebelipase alfa study LAL-CL02 (ARISE), which enrolled paediatric and adult patients aged 5 years or older. HRQL in the patients enrolled in LAL-CL02 is sufficiently maintained such that at baseline, as a result of the study inclusion/exclusion criteria, their HRQL was similar to that of unaffected individuals (for detailed results see Section 10). The enrolled population

included patients with substantial pathological liver damage at baseline, [redacted] Consistent with other chronic liver diseases, the significant impact on HRQL comes with progression to more severe liver disease states such as decompensated cirrhosis/liver failure, liver cancer and liver transplantation (see below and Section 10 for further discussion).

Quality of life associated with complications of LAL Deficiency

Liver involvement is common in LAL deficient patients and it frequently leads to progressive hepatic complications and the need for liver transplantation at an early age. Importantly there is evidence of rapid disease progression in younger patients leading to liver transplantation or sometimes death within the first or second decade of life (Elleder, 2000). Affected individuals are likely to have experienced complications associated with cirrhosis (for example oesophageal varices, gastrointestinal bleeding, ascites and portal hypertension), liver transplantation. The presence of jaundice, and the severe symptoms associated with liver disease progression and liver transplantation have been strongly documented to have very deleterious HRQL impact in patients with other liver disease (Levy, 2008).

LAL Deficiency patients are also at a much higher risk of coronary vascular disease (CVD) events (Shah, 2015). The impact of coronary artery disease (CAD) on HRQL is well established and HRQL in CAD patients is also correlated very strongly with mortality risk (Abdallah, 2013). This is discussed further in Section 10.1.1.

Conclusion

Despite limited data, it is likely that LAL Deficiency has a detrimental impact on the lives of patients, family, and caregivers impacted by the disease. Patients who participated in the EU LAL-D Survey frequently suffered from abdominal pain as well as fatigue, diarrhoea, nausea, loss of appetite, itchy skin and a swollen abdomen, and these symptoms were in some cases reported to be very burdensome. The mean EQ-5D score among children with LAL Deficiency was 0.76; the mean score for adults before treatment with sebelipase alfa was 0.34.

The majority of carers that responded to the EU LAL-D Survey reported they were mentally exhausted, stressed and anxious due to caring. A lower patient HRQL appeared to correlate with an increased burden on carers.

[redacted] There is no literature yet on HRQL of LAL Deficiency patients who have suffered decompensated cirrhosis, liver transplant, and/or a serious cardiovascular event. However, it is expected that LAL Deficiency patients who have

suffered these serious events will have markedly reduced HRQL, as one would expect given the experience of patients with similar health conditions.

There are further aspects of the condition that could not be captured in the available sources. The age range of patients participating in the survey was 3-21 years, therefore the survey may not have captured the impact of caring for an infant with rapidly progressive LAL Deficiency. Affected infants with rapidly progressive disease require long-term hospitalisation and die before the age of 6 months after suffering from diarrhoea, vomiting, anaemia and thrombocytopenia (which may require transfusion support), and failure to thrive (Anderson, 1999; Mayatepek, 1999; Jones, 2015a). The impact on the quality of life of the parents and caregivers of these infants would be expected to be extremely substantial. Additionally, affected families receive genetic counselling and potentially have the further burden of undergoing genetic testing and managing the implications.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

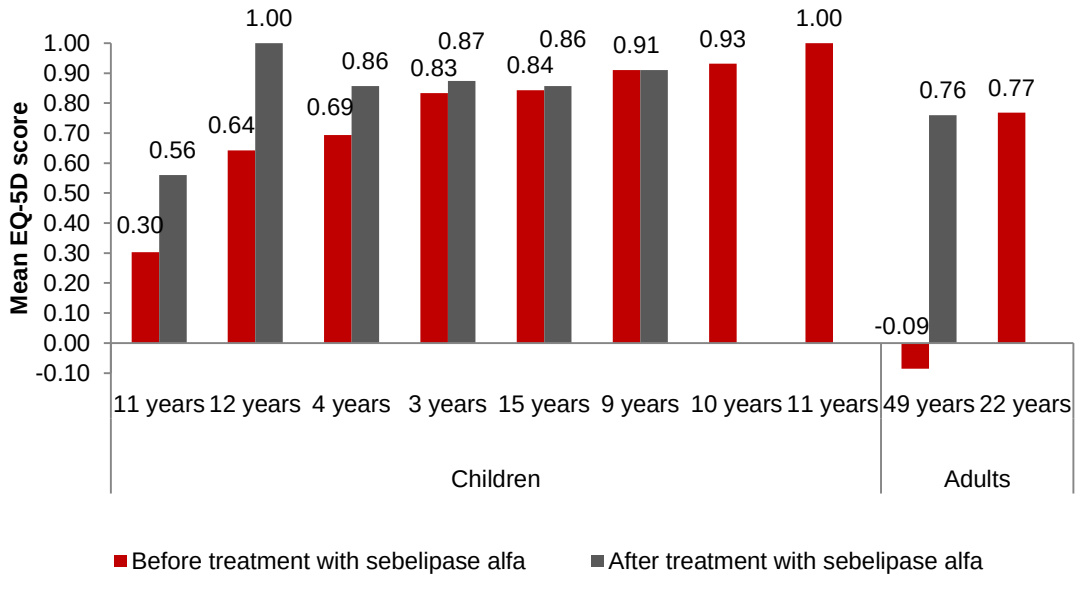
Sebelipase alfa is a recombinant form of the human LAL enzyme designed to address the underlying cause of LAL Deficiency. By replacing the deficient enzyme, treatment with sebelipase alfa restores lipid metabolism, thereby preventing chronic lipid accumulation, multi-organ system damage, and premature death. In clinical studies, sebelipase alfa produced significant improvements in serum transaminases, disease-related lipid abnormalities, and liver fat fraction in children and adults and improvements in survival and growth in infants. These marked improvements in transaminases and other hepatic disease markers reduce the risk of progression to fibrosis, cirrhosis, liver transplant, and death.

Sebelipase alfa is expected to have wider benefits, for instance it will reduce the need for other invasive therapies such as blood transfusions, parenteral nutrition and HSCT in infants (Data on File, CSR LAL-CL03). 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. Indeed one infant from the UK with rapidly progressive disease treated with sebelipase alfa in the clinical trial has survived to over 3 years of age with normal development. 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. In paediatric and adult patients, sebelipase alfa is expected to prolong survival, reduce liver and cardiovascular complications and reduce the need for liver transplantation, therefore improving quality of life and allowing affected individuals to lead long and productive lives (further details in Section 10).

Overall, and as expected given the inclusion/exclusion criteria, subjects enrolled in [redacted] The EU LAL-D Survey showed that the mean EQ-5D scores among children (non-infant onset) calculated from parent's reports thinking about the child condition before (n=8) and after treatment (n=6) were 0.76 and 0.84, respectively (Figure B7.2 and Figure B7.4). Among adults, the mean EQ-5D score (estimated retrospectively) was 0.34 before treatment (n=2) and 0.76 after treatment (n=1). As noted above, although the limitations of retrospective evaluation are recognised, this was the only way to understand the pre-treatment burden in patients who would be eligible for treatment. Overall, it appears that HRQL is good in patients treated with sebelipase alfa; the scores approach, or even exceed, the average score of the healthy UK population (0.86) (Janssen, 2014).

Figure B7.4: EQ-5D scores across patients with LAL Deficiency before and after sebelipase alfa treatment (n=10)



Note: The children aged 10 and 11 years and the 22 year old adult were not treated with sebelipase alfa; as such, their current HRQL was captured.

The parents of children with LAL Deficiency underlined the obvious improvements observed in their children's physical health and emotional well-being after treatment with sebelipase alfa. Some of their quotes are reported below:

"My child looks better than before the treatment, although she still needs a lot of comfort and emotional support and extra care especially during the treatment day and day after. She needs encouragement to carry daily tasks such as get up, getting dressed and having medication."

"His body is a little bit stronger (muscles and duration). Also he is not so skinny anymore."

"His health has greatly improved. The analytical exam results showed also improvement."

"My child showed increased growth and improved appetite. He also has less general fatigue."

"She is a much more physically active girl. She has less abdominal swelling. She also showed proper growth and weight / height."

An adult patient who was treated with sebelipase alfa had obvious improvement in his everyday life and was more capable of undertaking daily activities. He underlined:

"I am now able to perform simple everyday tasks and activities due to the pain & discomfort being less than what I was experiencing before. The incidences of suffering nausea after eating are now far less than what I experienced previously."

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are no relevant NICE, NHS England or other national guidance or expert guidelines available relating to management of LAL Deficiency. A clinical guideline from the children's LSD centres in England is currently in draft form and will be submitted to NICE for review (personal communication).

The following policy documents are relevant to patients with LAL Deficiency:

- 2013/14 NHS Standard Contract For Lysosomal Storage Disorders Service (Children) (NHS England, 2013a)
- 2013/14 NHS Standard Contract for metabolic Disorders (Adult) (NHS England, 2013b)

- NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), (NHS England, 2012)

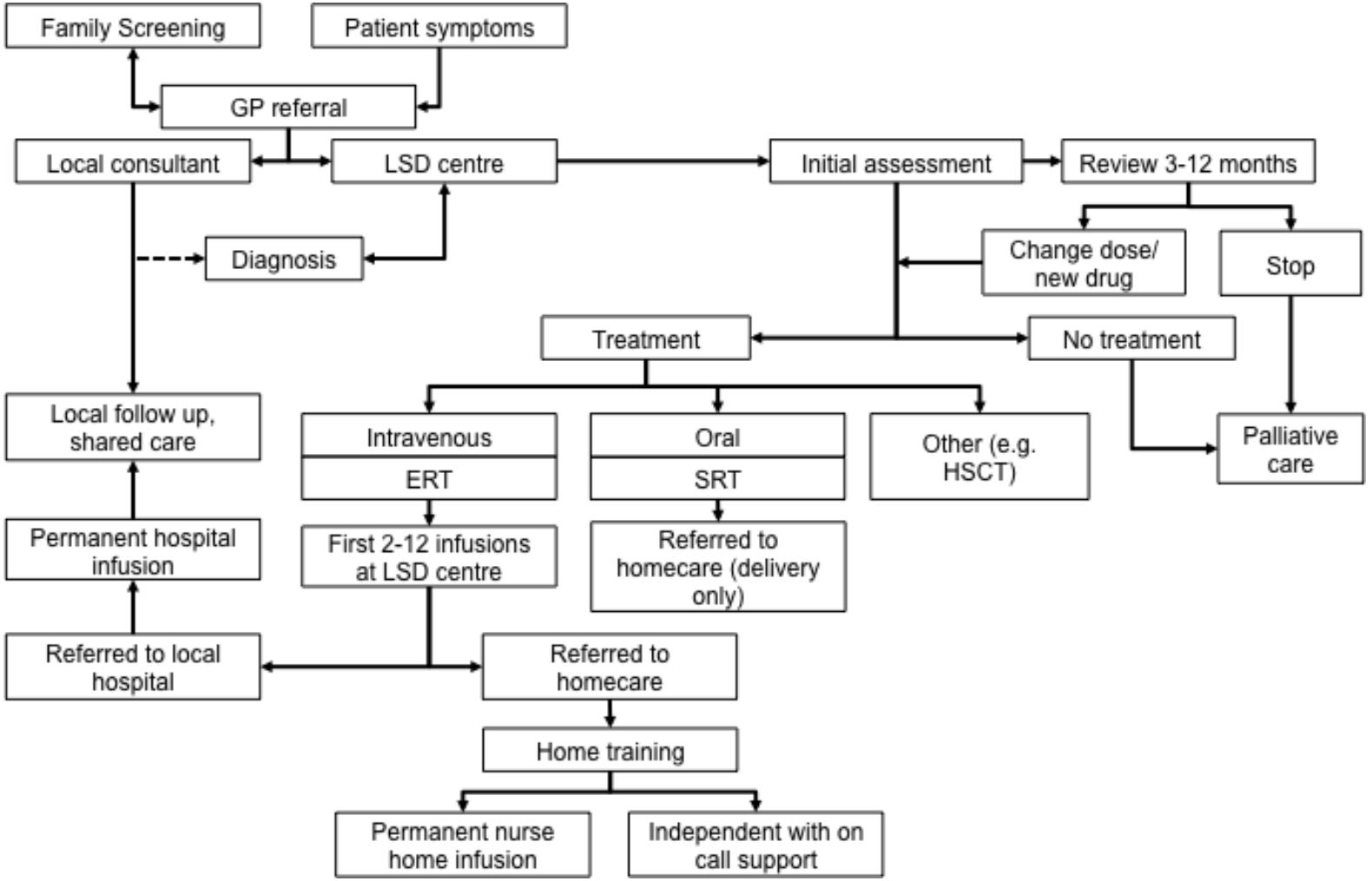
8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

National centres of excellence

Birmingham, Cambridge, London and Manchester are all designated national centres for the diagnosis and management of LSDs in either children or adults, and have extensive experience of ERTs. These regional centres all have an ongoing commitment to managing paediatric or adult patients in dedicated outpatient and inpatient facilities.

The clinical pathway of care for paediatric LSD services incorporating enzyme replacement therapy is shown in Figure B8.1.

Figure B8.1: Care Pathway for Paediatric LSD Services in England



Source: Adapted from NHS England, 2013a (2013/14 NHS standard contract for lysosomal storage disorders service, children); ERT = enzyme replacement therapy; HSCT = haematopoietic stem cell transplantation; LSD = lysosomal storage disorder; SRT = substrate reduction therapy

Diagnosis

A diagnosis of LAL Deficiency can be obtained by demonstration of deficient LAL activity via enzyme-based assays. Mutational analysis is not essential but can be very helpful for pre-natal counselling/ testing and carrier testing. Biopsy findings and radiological findings are not considered diagnostic, but help raise the suspicion of LAL Deficiency (Reiner, 2014).

The accuracy and timeliness of the diagnosis of LAL Deficiency is important to avoid both unnecessary clinical interventions and more invasive diagnostic procedures (e.g. liver biopsy) when diagnosis can be made through a dried blood spot (DBS) test, or leucocyte enzyme analysis, the preferred diagnostic tests to confirm a LAL Deficiency diagnosis. DBS LAL enzyme testing was the primary methodology used in the clinical development program (including the pivotal trials).

The most relevant diagnostic tools are described below.

Dried Blood Spot (DBS) Test

Measurement of LAL activity can be performed with a DBS test using the fluorimetric substrate 4-methylumbelliferyl palmitate.

Because lipases in whole blood may interfere with the measurement of LAL activity in DBS, an assay has been developed in which a LAL inhibitor is used to increase specificity. The method was assessed using DBS samples from 140 controls, 11 samples from LAL-deficient patients, and 15 carriers.

LAL deficient samples showed significantly reduced activity with results close to zero activity in all 11 samples tested. Carriers show activity grouped neatly between normal and LAL deficient cases, with all results below the reference range. Therefore, the method can differentiate clearly between normal activity, carriers and patients with LAL Deficiency (Hamilton, 2012).

Laboratory results can vary, because the assay is considered a Laboratory Developed Test; it is designed, manufactured and used within a single laboratory. Assay validation is performed within each laboratory with inherent differences based on methods utilized (for example, fluorimeter manufacturer, source of reagents, etc.). Additionally, based on laboratory experience/preference/sample type, the unit of measure of LAL activity may be reported differently but is generally reported as either "n_{mol} or p_{mol} per punch per hour" or "per hour per spot". Reference ranges (normal ranges) and affected cut-offs vary depending on LAL enzyme activity results obtained from the specific quantity of samples available during the validation phase. In the majority of the laboratories utilizing the DBS method, the affected cut-off is a LAL enzyme activity that is essentially "non-detectable".

The DBS test has practical advantages as well. It requires a small sample volume (50µl whole blood) that can be transported at ambient temperature to specialized laboratories. Sample short-term stability falls by only 15% in LAL activity after 7 days.

Long term stability at -20°C shows 87% LAL activity remaining after 100 days (Hamilton, 2012). DBS testing has also a high degree of sensitivity and specificity.

Leucocyte Testing

Some labs still perform LAL Deficiency confirmation via measurement of lysosomal acid lipase activity in peripheral blood mononuclear cells or cultured fibroblasts.

Genetic Testing

Suspected LAL-deficient patients may be tested by complete sequencing of the coding regions of LIPA. Although this is not essential for diagnosis, it can be very helpful for pre-natal counselling/ testing and carrier testing. There are some limitations to this type of genetic testing. Some patients may have functionally important mutations that go undetected in routine genetic screening. Genetic testing for LAL Deficiency may not be easily accessible and may be expensive.

Liver Biopsy

Liver biopsy is considered to be the most reliable test to evaluate liver abnormalities (Reiner, 2014) particularly the development of fibrosis and cirrhosis. However, there are morbidity and mortality risks associated with this invasive and expensive procedure (Chalasani, 2012). Blood tests should be used to obtain a diagnosis if possible, prior to obtaining a biopsy in suspected patients (Chalasani, 2012, Vajro 2012).

Moreover, it is not possible to make a definitive diagnosis of LAL Deficiency through analysis of a biopsy specimen. For example, the presence of microvesicular steatosis is not unique to LAL Deficiency. It can be attributed to Reye's syndrome, acute fatty liver of pregnancy, HELLP (haemolysis; elevated liver enzymes; low platelet count) syndrome, and use of medications (e.g., valproate or anti-retroviral medicines) (Reiner, 2014).

Radiological Imaging

One evolving method to identify and quantify the hepatic lipid in LAL Deficiency is hepatic magnetic resonance spectroscopy using a 3T magnetic resonance imaging (MRI) scanner. It is worth noting that this does not provide a definitive diagnosis. This approach, however, may be preferable to repeat biopsy sampling for diagnosis and disease monitoring (Thelwall, 2013).

Differential Diagnosis and Diagnostic Pathway

Differential Diagnosis

Due to low disease awareness and the similarities between manifestations of LAL Deficiency and other metabolic, liver, and cardiovascular diseases, misdiagnosis of

LAL Deficiency may occur resulting in inappropriate management and delayed treatment. The most common misdiagnoses in children and adults patients include:

a) Non-alcoholic steatohepatitis (NASH)

b) Non-alcoholic fatty liver disease (NAFLD)

c) Heterozygous familial hypercholesterolemia (HeFH)

d) Familial Combined Hyperlipidaemia (FCH)[1]

e) Metabolic Syndrome

Table B8.1 describes the characteristics of liver diseases including NAFLD and NASH and LAL Deficiency.

[1] In ROC analysis, used to determine the optimal cutoff values for ApoB, TC, and triglyceride levels, investigators have determined the following absolute cutoff values for FCH criteria: Apolipoprotein B>1200 mg/L; Triglycerides>1.5 mmol/L (135 mg/dL). Total cholesterol>6.0 mmol/L (240 mg/dL).

Table B8.1: Description of Other Liver Diseases (NAFLD and NASH) and LAL Deficiency

	NAFLD	NASH	LAL Deficiency (Children and Adults)
Liver Effects			
ALT (U/L)	30.3 ± 19.9[1]	49 ± 33.3[1]	87.0[7] (50-237)
AST (U/L)	22.9 ± 11.3[1]	37.6 ± 26.2[1]	73.5[7] (39-220)
Fibrosis (%)	39[4]	78[4]	68.8[7]
Cirrhosis (%)	0[4]	4[4]	31.2[7]
Liver Transplant		30-40%[6]	Unknown
CV Effects			
LDL-c (mg/dL)	108.6 ± 35.4[1]	116.5 ± 38.9[1]	204.0[7]
HDL-c (mg/dL)	48.7 ± 13.5[1]	42.4 ± 9.9[1]	32.5[7]
TG (mg/dL)	164.3 ± 121. 9[1]	180.3 ± 87.5[1]	159.5[7]
Cholesterol (mg/dL)	193 ± 40.2[1]	194.6 ± 35.6[1]	261.5[7]
Prevalence	2-9%[2]	20-50%[2]	1:130,000[8]
Age of onset	40-50[3]	Not available	Genetic birth defect with variable onset[9]
Clinical Signs and Symptoms	Hepatic Steatosis, Hepatic Inflammation, Fatigue, Elevated Transaminases	Hepatic Steatosis, Fibrosis, Elevated Transaminases	Microvesicular Steatosis, Elevated Transaminases, LDL≥160 MG/dL
Other Organs	Cardiovascular	Cardiovascular	Spleen, Gastrointestinal tract, Cardiovascular
Death	Liver: 1.6-6.8%; Cardiovascular: 12.6-36%[5]	Liver: 0%; Cardiovascular: 8.6%[5]	Unknown

[1]Clinical characteristics of NAFLD/NASH patients over 18 years (Hossain, 2009)

[2]Estimated prevalence in the general population (Bugianesi, 2013)

[3]Most patients are diagnosed with NAFLD in their 40s or 50s (Sheth, 2014)

[4]Distribution of fibrosis scores in adult patients (Singh, 2015)

[5]Mortality from liver causes and cardiovascular causes (LaBrecque, 2012)

[6]30-40% of patients with NASH-related cirrhosis require liver transplantation (LaBrecque, 2012)

[7]Data on file, CSR LAL-CL02

[8]Scott, 2013

[9]Bernstein, 2013

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDL-c = low density lipoprotein cholesterol; HDL-c = high density lipoprotein cholesterol; TG = triglyceride

It is possible to distinguish LAL Deficiency from the above conditions by following a few simple principles:

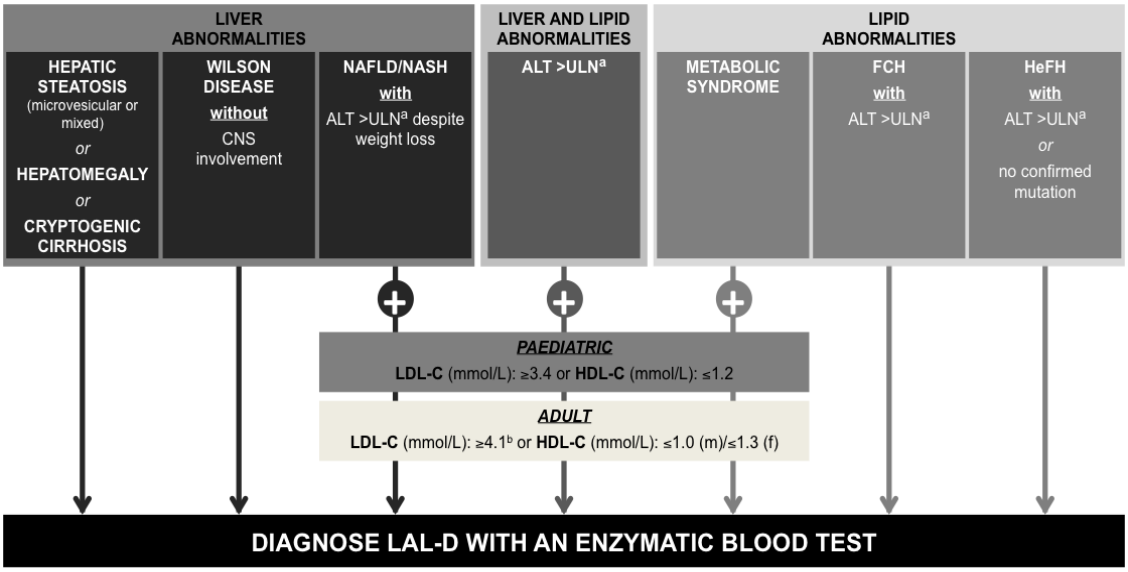
1. Conduct a detailed family history to distinguish autosomal dominant disorders (HeFH and FCH) from autosomal recessive disorders (LAL Deficiency).
2. A thorough physical exam to identify hepatomegaly, which can be only mildly enlarged in LAL deficient patients, but may be an early sign of disease.
3. Rule out common disorders via full viral immunological profile.
4. Compare levels of total cholesterol and HDL-c.
5. HDL-c levels are usually lower in LAL Deficiency than in HeFH, but may overlap with levels seen in patients with HeFH.
6. LDL-c levels may also be higher in LAL Deficiency compared to those commonly seen in NAFLD.
7. Follow current guidelines that indicate patients with microvesicular steatosis should be ruled out for secondary causes of steatosis (Chalasani, 2012).
8. Test for LAL Deficiency using a simple blood spot test.

The proposed diagnostic pathway for detecting patients with LAL Deficiency is described in more detail below.

Diagnostic Pathway

Taking into account the frequent misdiagnosis that may occur with LAL Deficiency, the following proposed pathway highlights high risk groups for which LAL Deficiency should be suspected (Figure B8.2).

Figure B8.2: Proposed Diagnostic Pathway for Determining Patients with LAL Deficiency



Abbreviations: ALT, alanine aminotransferase; CNS, central nervous system; FCH, familial combined hyperlipidaemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LAL-D, Lysosomal Acid Lipase Deficiency, LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ULN, upper limit of normal; m= males; f= females.
Notes: [a] Age- and gender-specific. [b] LDL-C is > 130mg/dL in patients on lipid-lowering medications

Current Supportive Options and Therapies in Development

Currently, there are no safe and effective, regulatory-approved therapies available to treat patients with LAL Deficiency. Most therapies available are only supportive in nature and include lipid-lowering therapies, vitamin E, haemaopoietic stem cell, and liver transplantation.

Supportive therapies do not address the underlying defect in LAL Deficiency. Their main objective is to lessen the burden of LAL Deficiency related complications. Although some temporary stabilisation of the clinical condition has been described, these interventions do not appear to substantially modify the outcome in affected patients (Hoeg, 1984; Meyers, 1985).

Lipid-lowering Therapies

Lack of Efficacy of Statins and Other Lipid Lowering Therapies in LAL Deficiency

Though statins reduce cholesterol synthesis, they also increase LDL receptor expression. This increased expression would reduce plasma LDL-C levels, but, in view of the higher receptor-mediated uptake of plasma LDL-C, it would also be expected to accelerate lysosomal accumulation of cholesteryl esters, with potentially deleterious effects on liver function.

Results from a systematic review (Bernstein, 2013), observational study (LAL2-NH01) (Quinn, 2014a) and the Phase 3 ARISE trial (Data on File, CSR LAL-CL02)

are summarised below and suggest a lack of efficacy of lipid lowering medications (LLM) in LAL Deficiency.

- Bernstein et al (2013): In a systematic review of 135 LAL deficient cases reported in the literature, statin use was documented in 35 subjects including some of the cases above. Eight of these 35 patients did not undergo liver biopsy. Fifteen demonstrated histological features of LAL deficiency, fibrosis or cirrhosis. Twelve patients underwent repeat liver biopsies on statins. In these 12 patients where this information was available, histological improvement was not seen in any case and in all 12 patients liver histology showed progressive liver disease. In 6 of 12 cases there was documentation that progression resulted in either liver transplantation or death.
- Observational study (Quinn, 2014a; Data on File, CSR LAL-2-NH01): Out of 48 LAL Deficiency patients, 34 (81%) reported prior LLM use. Of these, statins were the most common (27 subjects; 60%). Eight subjects received ezetimibe (18%) and 10 (22%) received an unspecified LLM.
    - LDL-c Levels: LDL-c was consistently elevated to > 100 mg/dL for most (83%; 24 of 29) subjects with at least 4 LDL-c values reported. A relatively small number (5) of subjects with at least 4 LDL-c values reported had at least 3 LDL-c values ≤ 100 mg/dL after initiation of LLM.
    - Serum Transaminases: Intervention with LLMs had limited effectiveness in normalizing serum transaminases (ALT and AST). The majority (458 of 499 values; 92%) ALT values were above the ULN (43 U/L), with only a small proportion (41 of 499 values; 8%) of values being ≤ 43 U/L at any time. Review of AST data over time on a per-subject basis showed that most (59%), but not all, subjects had AST values above the ULN, set as 59 U/L.
- Phase 3 ARISE trial (Data on File, CSR LAL-CL02): Thirty-nine percent of subjects overall were receiving LLM, including 42% and 37% of subjects in the sebelipase alfa (n=14) and placebo (n=11) groups, respectively, at baseline. Review of LDL-c levels among subjects receiving and not receiving LLM at baseline showed that mean LDL-c was lower, yet still abnormally high, in subjects receiving LLM compared to those who were not [redacted]

In summary, based on the case reports and studies above, although statins appear to reduce plasma cholesteryl levels and triglycerides to a variable degree these biochemical changes are not accompanied by substantial improvements of serum transaminases which are a marker of liver injury. Although cholesterol and/or LDL cholesterol levels are reduced they are not consistently maintained at desirable target concentrations even when combined with additional lipid lowering agents. The biochemical improvements are accompanied in some cases by evidence of reduction in hepatomegaly although this has not been studied in a rigorous setting. In the one

case where liver cholesterol ester content was assessed this showed a small reduction with statin therapy but remained substantially elevated relative to levels seen in liver samples from normal controls.

Vitamin E (Tocopherols)

In an *in vitro* study, Tocopherol was found to promote lysosomal exocytosis and reduce lipid accumulation in fibroblasts harvested from infants with LAL Deficiency. However *in vivo*, very high concentrations of Tocopherol would be needed to have a similar effect, due to the rapid oxidation of vitamin E derivatives by the cytochrome P450 enzyme CYP4F (Reiner, 2014).

Haemaopoietic Stem Cell Transplantation

HSCT has been used to treat LAL Deficiency presenting in infancy as a medical emergency with rapid disease progression. HSCT is frequently limited in use and/or associated with high mortality due to the condition of the infants at the time of diagnosis and to the rapidly progressive nature of the disease. Additionally, HSCT carries its own inherent risks, including toxicity of the conditioning regimens, multi-organ failure, sepsis, graft failure and graft-versus-host disease. Furthermore, HSCT has had limited success in addressing the multi-organ nature of LAL Deficiency (Krivit, 2000; Stein, 2007; Tolar, 2009; Yanir, 2013).

In the natural history study LAL-1-NH01, median survival was noted to be longer for patients who received HSCT (and/or liver transplant) compared to those who did not; however, median age at death was still short at 8.6 months and 100% of patients died before 4 years of age (Jones, 2015a).

Liver Transplantation

Liver transplantation has shown inconsistent success as a strategy to help LAL deficient patients. In a 2013 review of the findings in 135 reported patients with diagnosed LAL Deficiency, Bernstein et al reported liver transplantation in nine patients who were aged 5 to 14 years at transplantation. At least three additional patients developed liver failure requiring transplantation, two of whom subsequently died (Bernstein, 2013).

There is limited information on the long-term follow-up for the majority of transplanted patients. In this review however, six liver-transplanted patients were followed from 10 months to three years, reportedly without complications. An additional patient who was transplanted at five years of age experienced transplant rejection and developed progressive, congestive heart failure (Bernstein, 2013).

Only two transplanted patients had documented follow-up for over five years. One, transplanted at 14 years of age, had a subsequent biliary infection and obstruction requiring surgery. She developed end-stage renal failure seven years post-transplant and required chronic haemodialysis by 21 years of age. The transplant may have

ameliorated only the liver disease, but not the systemic lysosomal cholesteryl ester accumulation. The second patient for whom long term follow-up was reported had no renal involvement six years after transplant (Bernstein, 2013).

In England, 664 liver transplants were carried out from April 2014 to March 2015, accounting for 24% of all transplants (NHS Blood and Transplant, 2015). Furthermore, in April 2015, 596 patients remained on the waiting list for a liver transplant and 80 patients died while waiting for a transplant between April 2014 and March 2015. A recent report considers liver transplant the third most expensive organ transplant after heart transplant and double lung transplant (Bentley, 2011).

Generally, it is also recognised for systemic metabolic diseases (such as LAL Deficiency) that liver transplant does not represent a cure given the presence and development of extrahepatic damage (Mazariegos, 2014).

In summary, liver transplantation does not address the multi-organ nature of LAL Deficiency, has variable efficacy, and can be associated with serious complications.

Sebelipase alfa

The limitations of supportive therapies discussed in this section highlight the urgent need for a therapy that addresses the root cause of LAL Deficiency.

Sebelipase alfa is the first treatment to undergo regulatory approval for the treatment of LAL Deficiency. Sebelipase alfa is a recombinant form of the human LAL enzyme designed to address the underlying cause of LAL Deficiency. By replacing the deficient LAL, treatment with sebelipase alfa reduces substrate accumulation and restores lipid metabolism, thereby preventing chronic lipid accumulation, multi-organ system damage, and premature death. It is the first and only specific treatment to be approved for patients with LAL Deficiency that has been shown in two pivotal clinical studies (LAL-CL02 and LAL-CL03) to produce significant improvements in serum transaminases, disease-related lipid abnormalities, and liver fat fraction in children and adults and improvements in survival and growth in infants (Burton, 2015a; Jones, 2015b). These marked improvements in transaminases and other hepatic disease markers reduce the risk of progression to fibrosis, cirrhosis, liver transplant, and death.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

LAL Deficiency may be misdiagnosed

As discussed in section 8.2, due to low disease awareness and the similarities between manifestations of LAL Deficiency and other metabolic, liver, and cardiovascular diseases, misdiagnosis of LAL Deficiency may occur resulting in inappropriate management and delayed treatment.

Currently available therapies are supportive in nature and do not treat the underlying cause of disease

Prior to sebelipase alfa, there had been no approved drug therapies, and very limited supportive care options for patients with LAL Deficiency. Supportive care options used in clinical practice do not address the underlying cause of the disease.

Due to their mode of action, the benefit of LLM therapies for patients with LAL Deficiency is limited; LLM treatment has demonstrated variable effects on cholesterol levels and triglycerides with no improvement on markers of liver injury. Due to the variable efficacy and risks of liver transplantation and HSCT as well as limitations in terms of donor availability, there is uncertainty regarding their benefit in LAL Deficiency.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Sebelipase alfa is licensed for long-term ERT in patients of all ages with LAL Deficiency. Due to the lack of therapeutic alternatives, sebelipase alfa should be considered in any patient diagnosed with LAL Deficiency.

As with other ERTs in rare genetic diseases, initiating treatment as soon as possible after diagnosis is expected to provide maximal benefit to patients, both by improving existing symptoms and minimising further disease-related impairments. The severe progressive nature of LAL Deficiency and the absence of an effective alternative highlight the importance of treating early with sebelipase alfa. Clearly, in infants with rapidly progressive disease who would otherwise not survive beyond 12 months, initiation of treatment should occur immediately on diagnosis. Although in rare cases LAL Deficiency is not diagnosed until adulthood, it predominantly presents as a paediatric disease with a mean age at symptom onset of five years old (Reiner, 2014). The accumulation of lipids begins early in life and is progressive and life limiting. Patients typically present with hepatomegaly and liver dysfunction or dyslipidaemia including markedly elevated LDL-c at an early age (Bernstein, 2013). Providing sebelipase alfa as early as possible would maximise the potential to limit or prevent liver damage and reverse dyslipidaemia with a resultant lowered risk of liver-related complications and cardiovascular events.

Sebelipase alfa is well tolerated and results in prolonged survival in infants and improvement of multiple markers of liver injury and dyslipidaemia in children and adults. The clinical development programme and the licensed indication demonstrate that sebelipase alfa is suitable for all patients diagnosed with LAL Deficiency, subject to clinical judgement. The combination of study populations in the programme reflects the spectrum of disease seen in the overall patient population.

In clinical studies (LAL-CL02) there were no clinically meaningful differences noted in the effectiveness of sebelipase alfa based on gender, race, ethnicity, or genetic mutation category. Sebelipase alfa was effective relative to placebo in all age categories. In addition, treatment with sebelipase alfa was effective across subgroups by baseline disease characteristic (Data on File, CSR LAL-CL02). In clinical studies patients treated with sebelipase alfa received best supportive care, which included treatment with LLMs (in LAL-CL02, 42% of patients were on LLM at baseline) (Data on File, CSR LAL-CL02).

In rare cases people with LAL Deficiency survive into their forties and fifties. Although disease appears to have progressed more slowly in these patients it is likely that cumulative liver damage, fibrosis and cirrhosis put them at risk of sudden, serious and potentially fatal liver complications and that they are also at risk of serious cardiovascular events.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

LAL Deficiency is a serious, debilitating and multi-systemic disease that results in early mortality. Onset of LAL Deficiency is from birth, and affects all ages, but it mainly presents as a paediatric disease. In the absence of an effective therapy, infants with this condition die before the age of 6 months. Liver failure is the main cause of death, though patients are also at risk of fatal cardiovascular events (Bernstein, 2013).

The disease represents a significant unmet medical need because there are currently no available treatment options that specifically correct the biological cause of the condition. Current therapies are supportive in nature and consist of lipid-lowering therapies, haematopoietic stem cell, and liver transplantation. These therapies do not address the underlying defect in LAL Deficiency and do not appear to substantially modify the outcome in affected patients (Hoeg, 1984; Meyers, 1985; Data on File, CSR LAL-1-NH01). Surgical interventions in particular are associated with complications and increased morbidity/mortality.

Sebelipase alfa is innovative and represents a step-change in the management of this multi-systemic, life-limiting condition because:

- It is the first pharmacological treatment approved for the treatment of LAL Deficiency
- It is approved for use in LAL Deficiency patients of all ages

- It is the first treatment option (pharmacological or otherwise) that addresses the underlying biological cause of LAL Deficiency. Sebelipase alfa is an ERT: therapy aims to replace deficient enzyme and prevent the damage caused by accumulation of its substrate, cholesteryl esters and triglycerides
- Sebelipase alfa substantially improves survival in infants compared to current supportive care
- Sebelipase alfa significantly improved markers of chronic liver injury compared to placebo, potentially reversing liver damage and improving liver outcomes in children and adults thus improving quality of life and survival
- Sebelipase alfa significantly improved dyslipidaemia compared to placebo, supporting its role in treating the underlying cause of disease and reducing cardiovascular risk.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

The introduction of sebelipase alfa is not expected to change the way that existing services that provide and administer ERTs are organised or delivered.

LAL deficiency is a lysosomal storage disorder and most individuals with this diagnosis will already be known to a designated LSD centre in England. All such centres are familiar with the administration of ERT and managing multisystem disorders. The delivery of treatment for LAL deficiency fits in well to this service framework, however the intensity of management required for the infants may require extra resource for the multidisciplinary teams. Newly diagnosed patients may be identified through hepatology services and so will need to referred to the relevant local LSD centre.

Alexion anticipates that, following specialist initiation and stabilisation of the patient on sebelipase alfa, the infusion would be delivered either in local hospital outpatient clinics or in a homecare setting by a trained nurse, as is standard practice for the administration of other ERTs in the UK.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests are required to select patients for treatment. As discussed in Section 8.2, diagnosis can be achieved through a specific enzymatic DBS test or the

leucocyte test. The DBS test is currently undertaken at the Queen Elizabeth University Hospital in Glasgow, but is expected to be available in several centres in the UK.

Sebelipase alfa is administered by intravenous infusion. It is expected that initiation of the infusions and stabilisation of the patient will occur at specialist centres followed by transition to local hospital outpatient clinics or homecare arrangements, as is the case for currently available ERTs in the UK.

No additional monitoring is required. Patients and caregivers should be advised that reactions related to administration and infusion may occur during and after sebelipase alfa treatment (Kanuma SPC, 2015).

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure are required.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Not applicable.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A search of the Cochrane Database of Systematic Reviews yielded no existing published literature reviews of efficacy or safety data for sebelipase alfa. Consequently, a systematic search of the literature was conducted on 1st June 2015 with the aim of identifying all published evidence on the efficacy and safety of sebelipase alfa for the treatment of patients with LAL Deficiency. Two reviewers assessed the publication title and abstracts for inclusion in the review, followed by review of the full text articles (where available). A third reviewer resolved contradictory decisions and areas of any remaining uncertainty. The complete search strategies for each database are presented in Appendix 17.1.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Unpublished studies were identified through the manufacturer (Alexion) as well as clinical trial registries. Alexion provided clinical study reports relating to each of the relevant clinical trials.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C9.1: Selection criteria used for published studies

Inclusion criteria	
Population	Lysosomal Acid Lipase Deficiency Wolman's disease Cholesteryl Ester Storage disease
Interventions	Sebelipase alfa
Outcomes	Clinical efficacy Disease progression Safety
Study design	Randomised controlled studies, Controlled studies, Observational studies
Language restrictions	No restrictions
Search dates	No restrictions
Exclusion criteria	
Population	No restrictions
Interventions	No restrictions
Outcomes	No restrictions
Study design	Animal Individual case study reports Letters Comment articles
Language restrictions	No restrictions
Search dates	No restrictions

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

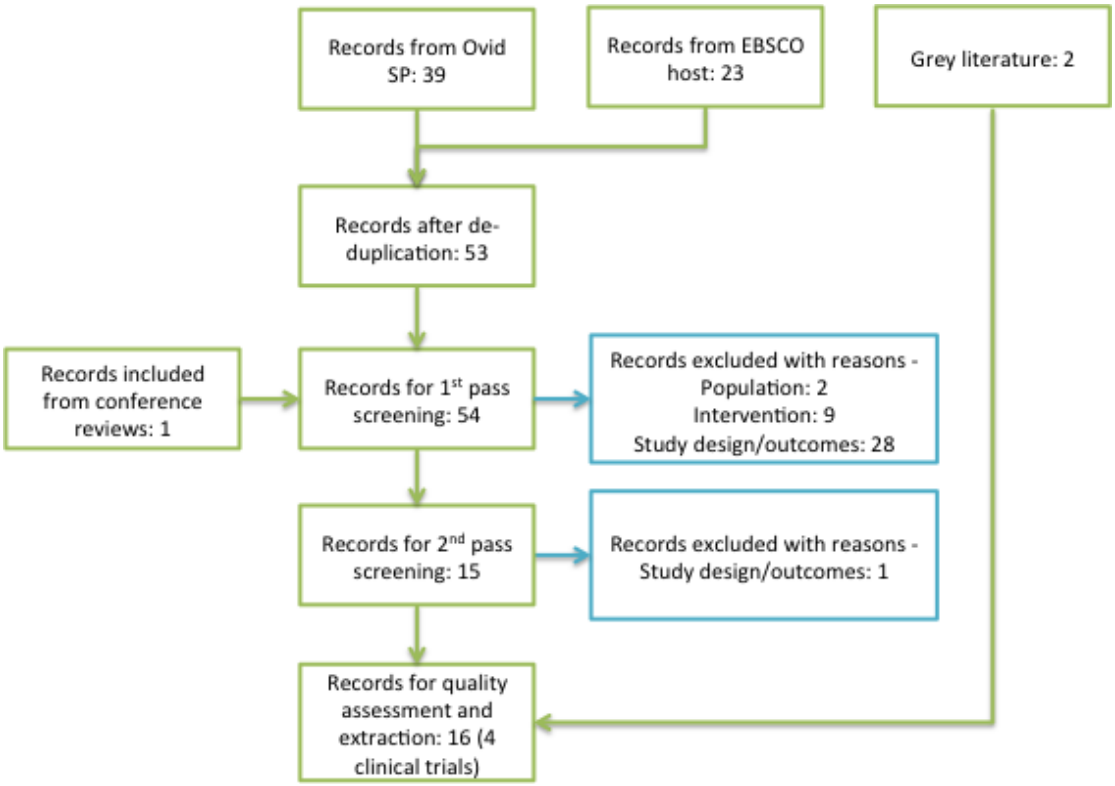
A total of 54 publications were screened of which 15 were assessed as relevant according the inclusion/ exclusion criteria (Figure C9.1). Following a second review

one of these publications was excluded due to publication type. An additional two publications were identified through grey literature searching giving a total of 16 relevant publications. These 16 publications relate to 4 clinical trials: LAL-CL01, LAL-CL02, LAL-CL03 and LAL-CL04 (Table C9.3 and Table C9.8).

Following completion of the literature review study LAL-CL03 has been published as a full manuscript (Burton 2015a).

Alexion has completed a natural history study in infants, which provides a historical control for interpretation of the results of the interventional study in infants (LAL-CL03). This study has therefore been described in detail in this submission (Jones, 2015a).

Figure C9.1: PRISMA diagram of clinical systematic review



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C9.2: Selection criteria used for unpublished studies

Inclusion criteria	
Population	Lysosomal Acid Lipase Deficiency Wolman's disease Cholesteryl Ester Storage disease
Interventions	Sebelipase alfa
Outcomes	Clinical efficacy Disease progression Safety
Study design	Randomised controlled studies, Controlled studies, Observational studies
Language restrictions	None
Search dates	No restrictions
Exclusion criteria	
Population	No restrictions
Interventions	No restrictions
Outcomes	No restrictions
Study design	Animal Individual case study reports Letters Comment articles
Language restrictions	No restrictions
Search dates	No restrictions

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Two ongoing unpublished studies, LAL-CL06 and LAL-CL08 with expected completion dates of June 2017 and December 2018 respectively, were identified through a search of the clinicaltrials.gov database. The efficacy results from these studies are not included in this submission due to lack of availability and therefore these studies have not been described in detail in the following sections, however where possible, available safety data has been included in the submission.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured

abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

Table C9.3: List of relevant studies

Study Name (Status)	Study Design	Study Objective(s)	Population	Intervention/ Comparator	Treatment Duration	Primary Study reference/ Data source
LAL-CL03 (Primary analysis complete; Follow-up ongoing)	Phase 2/3, single-arm, open-label	Efficacy, Safety, and PK	Paediatric (≤ 2 years) patients with LAL Deficiency, n=9	Sebelipase alfa: Dose escalation from 0.35 to 1 mg/kg once weekly IV; Up to 3 or 5 mg/kg once weekly IV	Up to 208 weeks	Data on File, CSR LAL-CL03
LAL-1-NH01 (Historical control group for LAL-CL03, Complete)	Observational, non-interventional	Chart review of children with LAL Deficiency	Paediatric (≤ 2 years), n=35	N/A	N/A	Jones, 2015a
LAL-CL02, ARISE (Double-blind period complete; Open-label period ongoing)	Phase 3, randomised, double-blind, placebo-controlled; followed by open-label extension	Efficacy, Safety, and PK	Paediatric / adult (≥ 4 years) patients with LAL Deficiency, n=66 (36 sebelipase alfa / 30 placebo)	Sebelipase alfa 1 mg/kg every other week IV, Placebo	20 weeks double-blind followed by open-label up to 130 weeks	Data on File, CSR LAL-CL02
LAL-CL01 (Complete)	Phase 1/2, single-arm, open-label, dose escalation	Safety, PK, and PD	Adults (≥ 18 years) with LAL Deficiency, n=9 (3/cohort)	3 cohorts: 0.35, 1, and 3 mg/kg once weekly IV	4 weeks	Balwani, 2013a; Data on File, CSR LAL-CL01
LAL-CL04 (Enrolment; complete; Follow-up ongoing)	Phase 2, single-arm, open-label extension for subjects who completed LAL-CL01	Efficacy and Safety	Adults with LAL Deficiency (≥ 18 years), n=8	Sebelipase alfa: 0.35, 1, or 3 mg/kg, once weekly IV for 4 weeks; 1 or 3 mg/kg once every other week IV	Up to 156 weeks	Balwani, 2013a; Data on File, CSR LAL-CL04

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

No relevant published studies were excluded.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

Table C9.4: Summary of methodology for randomised controlled trials

Study name	LAL-CL02 (ARISE)
Objectives	To evaluate the safety, efficacy, and PK of sebelipase alfa in subjects ≥4 years of age with LAL Deficiency
Location	A total of 55 study centres were initiated in this study, including 49 during the recruitment period and 6 after recruitment, to allow transfer of subjects for local treatment. Study centres were initiated in 17 countries, including Australia; Europe (Croatia, Czech Republic, France, Germany, Greece, Italy, Poland, Russia, Spain, United Kingdom); Middle East (Turkey); North America (United States and Canada); and South America (Argentina), as well as Japan and Mexico. Subjects were screened at a total of 41 of the 55 study centres in all of these countries, with the exception of Greece.
Design	Multicentre, randomised, placebo-controlled study. Subjects in the placebo group could crossover to receive sebelipase alfa upon entry into the open-label period. Randomisation was stratified by the following parameters: age at randomisation (< 12 years, ≥ 12 years); average screening ALT level (< 3 × ULN, ≥ 3 × ULN); and use of lipid-lowering medications (LLM) (yes, no).
Duration of study	The study consisted of a screening period of up to 6 weeks, a 20-week double-blind treatment period, an open-label period of up to 130 weeks, and a follow-up phone call at least 4 weeks after the last dose of study drug. The duration of each subject's treatment was expected to be at least 78 weeks, and subjects may continue to receive treatment in the study for up to 150 weeks.
Sample size	n=66
Key inclusion criteria	≥ 4 years of age Deficiency of LAL enzyme activity confirmed by dried blood spot (DBS) testing at screening, based on the definition of deficiency provided by the central laboratory performing the assay. ALT ≥ 1.5 × the upper limit of normal (ULN) (based on the age- and gender specific normal ranges of the central laboratory performing the assay) on 2 consecutive screening ALT measurements obtained at least 1 week apart. If receiving LLM, subject was receiving a stable dose of the medication for at least 6 weeks prior to randomisation and was willing to remain on

	a stable dose for at least the first 32 weeks of treatment in the study. If receiving medications for the treatment of non-alcoholic fatty liver disease (NAFLD) (e.g., glitazones, high-dose vitamin E, metformin, ursodeoxycholic acid [UDCA]), subject was receiving a stable dose for at least 16 weeks prior to randomisation and was willing to remain on a stable dose for at least the first 32 weeks of treatment in the study.
Exclusion criteria	Subject had severe hepatic dysfunction (Child-Pugh Class C). Subject had other medical conditions or comorbidities that, in the opinion of the Investigator, would have interfered with study compliance or data interpretation, including but not restricted to severe intercurrent illness, known causes of active liver disease other than LAL Deficiency (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease, or physician concerns about excess alcohol consumption), human immunodeficiency virus (HIV), poorly-controlled diabetes, or cancers other than non-melanoma skin cancer. Subject had previous haematopoietic or liver transplant procedure. Subject received treatment with high-dose corticosteroids (acute or chronic) within 26 weeks prior to randomisation. (Note: Subjects receiving maintenance therapy with low-dose oral, intranasal, topical, or inhaled corticosteroids were considered eligible for the study.) Subject participated in a study employing an investigational medicinal product (IMP) within 4 weeks prior to randomisation. Subject had a known hypersensitivity to eggs.
Method of randomisation	Subjects were randomised via an interactive voice response system (IVRS) or interactive web response system (IWRS). Subjects were randomly allocated in a 1:1 ratio stratified by the following parameters: age at randomisation (< 12 years, ≥ 12 years); average screening ALT level (< 3 × ULN, ≥ 3 × ULN); and use of LLM at baseline (yes, no).
Method of blinding	During the double-blind period, subjects either received sebelipase alfa 1 mg/kg or matched placebo (buffered solution identical in composition to the formulation buffer for sebelipase alfa) via IV infusion every other week.
Intervention(s) (n =) and comparator(s) (n =)	Sebelipase alfa (n=36) and placebo (n=30)
Baseline differences	Groups were well matched by demographic and baseline disease characteristics. Levels of non-HDL-c and cholesterol were lower in the sebelipase group.
Duration of follow-up, lost to follow-up information	All but 1 subject (65 of 66 subjects; 98%) completed the double-blind period and continued into the open-label period. As of the data cut-off date for the CSR (30 May 2014), all 65 subjects who entered the open-label period were currently continuing in the study.
Statistical tests	All efficacy analyses of data from the double-blind period were performed for the Full Analysis Set (FAS). The analyses of the primary and secondary efficacy endpoints were repeated using the Per Protocol (PP) Set and for the FAS for all subgroups. Proportions of subjects who met the primary endpoint were compared using Fisher's exact test at α=0.05. Secondary efficacy endpoints were compared using a Wilcoxon rank sum test, based on the fixed hypothesis sequence (at α=0.05).
Primary outcomes (including	The primary efficacy outcome measure was the proportion of subjects who achieved ALT normalisation at Week 20 (i.e., ALT below the age- and gender-specific ULN provided by the central laboratory performing

scoring methods and timings of assessments)	the assay) at the last visit in the double-blind treatment period.
Secondary outcomes (including scoring methods and timings of assessments)	Changes (improvement or normalisation rates, as applicable) from baseline to the end of the double-blind treatment period (Week 20): (1) relative change in LDL-c; (2) relative change in non-HDL-c; (3) the proportion of subjects with an abnormal baseline AST (i.e., > ULN) who achieved AST normalisation, based on age- and gender-specific normal ranges provided by the central laboratory performing this assay; (4) relative change in triglycerides; (5) relative change in HDL-c; and, in the subset of subjects for whom the assessments were performed, (6) relative change in liver fat content; (7) the proportion of subjects who showed improvement in liver histopathology; and (8) relative change in liver volume. Safety, tolerability, and immunogenicity of sebelipase alfa therapy. Further characterise the PK of sebelipase alfa

Table C9.5: Summary of methodology for uncontrolled studies: LAL-CL03

Study name	LAL-CL03
Objective	To evaluate the effect of sebelipase alfa (SBC-102) therapy on survival at 12 months of age in children with growth failure due to LAL Deficiency.
Location	There were 9 primary centres in the UK, United States (US), France, Turkey, Saudi Arabia, Taiwan, Italy, and Egypt, and 3 qualified local medical centres in the UK, France, and Ireland where subjects who were medically stable could be transferred for long-term treatment.
Design	Open-label, repeat-dose, intra-subject dose escalation study The study consisted of a screening period of up to 3 weeks, a treatment period of up to 4 years, and a follow-up visit at least 30 days after the last dose of sebelipase alfa.
Duration of study	Up to 4 years
Patient population	Subjects with LAL Deficiency who presented as infants and were considered to have rapidly progressive disease based primarily on the presence of growth failure within the first 6 months of life.
Sample size	n=9
Key Inclusion criteria	Male or female child with a documented decreased LAL activity relative to the normal range of the lab performing the assay or documented result of molecular genetic testing (2 mutations) confirming a diagnosis of LAL Deficiency. Growth failure* with onset before 6 months of age, as defined by: • 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); OR • 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; OR • Loss of > 5% of birth weight in a child who is older than 2 weeks of age.

	*NOTE: In the unusual circumstance where a subject had a rapidly progressive course of LAL Deficiency 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.
Exclusion criteria	Clinically important concurrent disease or co-morbidities which, in the opinion of the Investigator and Sponsor, would interfere with study 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 under nutrition or rapidly progressive liver disease. Subject was > 24 months of age. (Note: Subjects > 8 months of age on the date of first infusion were not eligible for the primary efficacy analysis.) Had received an IMP other than sebelipase alfa within 14 days prior to the first dose of sebelipase alfa in this study. Myeloablative preparation, or other systemic pre-transplant conditioning, for haematopoietic stem cell or liver transplantation. Previous haematopoietic stem cell or liver transplant. Known hypersensitivity to eggs.
Intervention(s) (n =) and comparator(s) (n =)	Sebelipase alfa, n= 9 All subjects who initiated treatment under LAL-CL03 protocol received a starting dose of 0.35 mg/kg weekly (qw), and were escalated to a dose of 1 mg/kg qw once acceptable safety and tolerability had been demonstrated during at least 2 infusions at the dose of 0.35 mg/kg. One subject initiated treatment with sebelipase alfa 0.2 mg/kg under a Temporary Use Authorisation (Autorisation Temporaire d'Utilisation; ATU) prior to enrolling in LAL-CL03; this subject received a gradual dose escalation from 0.2 mg/kg to 1 mg/kg over a period of 4 weeks under the ATU and thereafter continued on a dose of 1 mg/kg qw and was transitioned into extension study LAL-CL05* (Week 40) and then into study LAL-CL03 (Week 85) at this dose. *NOTE: Study LAL-CL03 was originally designed as a safety trial with a limited 4-month treatment period. After nonclinical chronic toxicology data and extended clinical experience in adults became available, the Sponsor opened LAL-CL05 as an extension study to evaluate the long-term efficacy and safety of sebelipase alfa (including a survival analysis) in subjects who had initiated treatment in LAL-CL03 or under an expanded access programme. Study objectives were modified in Protocol Amendment 6, which merged study LAL-CL03 with its extension study, LAL-CL05, under a single protocol. With the merger of the 2 studies, survival at 12 months of age was established as the primary objective of LAL-CL03.
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Nine subjects, all of whom were ≤ 8 months of age on the date of their first infusion, were enrolled, treated, and analysed. No subject discontinued from the study prior to 12 months of age for reasons other than death. As of the data cut-off, all 6 surviving subjects were continuing to receive treatment with sebelipase alfa in this study.

Statistical tests	Efficacy was analysed for the Primary Efficacy Set (PES). As at least one subject in the PES was excluded from the Per Protocol Set (PPS), all efficacy analyses were also repeated for the PPS, in accordance with the Statistical Analysis Plan. The proportion of subjects surviving to 12 months of age was calculated, along with an exact 95% CI based on the Clopper-Pearson method. As a complementary analysis, Kaplan-Meier survival curves were generated from birth to 12 months of age and from first infusion of sebelipase alfa to 12 months of age, as well as a Kaplan-Meier estimate and exact 95% CI for median survival past the first infusion of sebelipase alfa. To support a comparison of survival rates between treated subjects in study LAL-CL03 and untreated infants with LAL Deficiency in natural history study LAL-1-NH01, the proportion (exact 95% CI) of subjects in LAL-1-NH01 surviving to 12 months of age was calculated using the Clopper-Pearson method, and Kaplan-Meier survival curves were constructed for LAL-1-NH01.
Primary outcomes (including scoring methods and timings of assessments)	The proportion of subjects surviving to 12 months of age
Secondary outcomes (including scoring methods and timings of assessments)	Safety and tolerability Effect on survival beyond 12 months of age Effect on growth parameters Effect on hepatomegaly, splenomegaly, and liver function Effect on haematological parameters The pharmacokinetics (PK) of sebelipase alfa delivered by intravenous (IV) infusion.

PES, Primary Efficacy Set; PPS, Per Protocol Set; PK, pharmacokinetics; WFA, weight-for-age

Table C9.6: Summary of methodology for uncontrolled studies: LAL-1-NH01

Study name	LAL-1-NH01
Objective	The objectives of this study were (1) to characterise patient survival and key aspects of the clinical course of LAL Deficiency presenting in infancy and (2) to serve as a historical reference for efficacy studies of enzyme replacement therapy (ERT) in patients with LAL Deficiency presenting in infancy
Location	21 sites were initiated in the United States (US), UK, Canada, Egypt, France, and Italy, with 18 sites enrolling at least 1 patient
Design	This was a multinational, multicentre natural history study of patients diagnosed with LAL Deficiency presenting in infancy (historically called Wolman disease or LAL Deficiency/Wolman phenotype). All patients were diagnosed after 01January 1985. Specified demographic and clinical data from eligible patients were extracted through clinical chart review and entered on case report forms (CRFs) for further analysis. For any patient alive as of the last chart record reviewed, their physician was contacted prior to database lock to determine the patient's survival status. No clinic visits or prospective assessments were required of patients enrolled in this study. All data were collected by referencing a patient's

	medical records.
Duration of study	2.5 years
Patient population	Subjects who were diagnosed with LAL Deficiency presenting in infancy (under the age of 2 years)
Sample size	N=36 Note * only 35 eligible patients were included in the analysis (1 patient who received sebelipase alfa in LAL-CL03 was excluded)
Key Inclusion criteria	Clinical diagnosis of LAL Deficiency within the first 2 years of life that was confirmed by either LAL enzyme activity testing (i.e., an abnormal result relative to the testing laboratory's reference range) or LIPA gene mutation analysis (i.e., loss-of-function mutations in both alleles), and if the following minimum data were available in the patient's medical records: a. Date of birth; b. Gender; c. Date of death (or age at death), if deceased; d. Weight at birth (or first recorded weight) and at least 1 other weight measurement obtained a minimum of 4 weeks later and prior to the initiation of HSCT or ERT; e. Test date, result, and name of testing center for LAL enzyme activity and/or LIPA gene mutation analysis; f. Date of initiation of HSCT, if applicable g. Date of initiation of ERT for LAL Deficiency, if applicable. Note: Patients with a known family history of LAL Deficiency (i.e., an affected sibling) may have been diagnosed in the absence of any clinical symptoms.
Exclusion criteria	Patients whose medical history did not contain all required data Patients who had received ERT (sebelipase alfa) in a clinical study, LAL-CL03 for which LAL-1-NH01 is intended to serve as a historical control.
Intervention(s) (n =) and comparator(s) (n =)	Not applicable
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	40 patients were enrolled, and 36 patients met all study eligibility criteria. Data were analysed for 35 patients. All 35 patients were deceased at time of enrolment so no follow up necessary.
Statistical tests	All data were listed, and selected data were descriptively summarized and plotted. Anthropometric data were standardized to Z-scores according to age -gender normative data gathered by the World Health Organization

	(WHO), and percentiles were computed from the z-scores. Anthropometric data were also represented according to the number and percentage of patients meeting criteria for dichotomous indicators of under nutrition (underweight, wasting, and stunting) and combinations of these indicators. With the exception of survival data, all data for treated patients were summarised only through the date of transplant initiation or first dose of ERT. Kaplan-Meier (K-M) curves were used to estimate time from birth to death and proportions alive at selected ages (e.g., 12 and 18 months). If unavailable, date of death was estimated from age at death. No survival data were censored. Standard life tables and plots of median (95% confidence interval [CI]) time to death were generated overall and by treatment. Comparison of the time to death between patients who had and had not received treatment was performed using log-rank tests. Cox Proportional Hazards (PH) regression modelling was also performed to examine the association of time to death with factors including gender, country of origin, receipt (yes/no) of a HSCT and/or liver transplant, and receipt (yes/no) of a supportive intervention such as a blood transfusion, an enteral supplement, a parenteral supplement, or steroid replacement therapy. All models included gender and supportive interventions; the model for all eligible patients also included treatment. Other factors were considered for inclusion in the model and retained via a stepwise selection process, with a significance level 0.2 as the criterion for entering an explanatory factor and a significance level of 0.05 for removing a factor. Interactions between factors were not to be considered. As appropriate, summary statistics and statistical analyses were performed for subgroups of patients with and without early growth failure, and for treated patients (i.e., those receiving a haemaopoietic stem cell transplant [HSCT] and/or liver transplant) and untreated patients.
Outcomes (including scoring methods and timings of assessments)	This study was a retrospective chart review and there were no pre-specified outcome measures. The objectives were to characterise patient survival and key aspects of the clinical course of LAL Deficiency presenting in infants. This study also characterises the presentation and progression of LAL Deficiency in a subgroup of patients who had early growth failure within the first 6 months of life, and did not receive HSCT or ERT.

Table C9.7: Summary of methodology for uncontrolled studies: LAL-CL01/04

Study name	LAL-CL01/ *LAL-CL04*
Objective	To evaluate the safety, tolerability and pharmacokinetics of sebelipase alfa in adult patients with liver dysfunction due to lysosomal acid lipase deficiency
Location	The study was conducted at a total of 7 sites in the United States (US), United Kingdom (UK), France, and the Czech Republic.
Design	LAL-CL01 is a Phase 1/2 open-label, multicentre, dose-escalation study. The study comprised a screening period, a treatment period, and a post-treatment follow-up period (including an End of Study visit). *LAL-CL04 is an open-label, extension study evaluating the long-term safety, tolerability, PK, and efficacy of sebelipase alfa in patients who completed LAL-CL01.*

Duration of study	LAL-CL01: 52 days. Subjects were administered infusions of sebelipase alfa on Day 0, Day 7, Day 14, and Day 21. Following the fourth infusion, subjects continued to be monitored at follow-up visits conducted at approximately 7 days and 14 days (optional) post-infusion. An End of Study visit was conducted at 30 days after the fourth infusion or, for subjects who prematurely withdrew from the study, no sooner than 7 days after their last infusion. *LAL-CL04: The duration of each subject's treatment in the study varied but was expected to be at least 26 weeks. Subjects can continue receiving sebelipase alfa infusions for up to 3 years.*
Patient population	Adult patients with liver dysfunction due to LAL Deficiency
Sample size	n=9
Key Inclusion criteria	Male or female subjects ≥18 and ≤65 years of age. Documented decreased LAL activity relative to the normal range of the lab performing the assay or documented result of molecular genetic testing confirming diagnosis of LAL Deficiency. Evidence of liver involvement based on clinical presentation (hepatomegaly) and/or laboratory test results (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 1.5x upper limit of normal [ULN]). If on a statin or ezetimibe, had to be on a stable dose for at least 4 weeks prior to screening. *LAL-CL04: male or female subjects, 18 to 65 years of age, inclusive, who received all 4 scheduled doses of sebelipase alfa in study LAL-CL01 with no life threatening or unmanageable study drug toxicity.*
Exclusion criteria	Clinically significant concurrent disease, serious inter-current illness, concomitant medications or other extenuating circumstances that, in the opinion of the Investigator, would either interfere with study participation or the interpretation of the effects of sebelipase alfa. Clinically significant abnormal values on laboratory screening tests, other than liver function or lipid panel tests. Subjects with an abnormal laboratory value that was of borderline significance could be allowed to undergo repeat testing once within a 30 day period. Subject participated in a study employing an investigational drug within 30 days of the screening. Child-Pugh Class C or AST and/or ALT persistently elevated >3x ULN at screening (2 or more occasions). Previous haemaopoietic bone marrow or liver transplant. Subject received prior treatment with enzyme replacement therapy. Subject had a total score of 8 or more on a screening Alcohol Use Disorders Identification Test (AUDIT). Subject had a known hypersensitivity to eggs.
Intervention(s) (n =) and comparator(s) (n =)	3 sequential dose cohorts: 0.35 mg/kg/week (Cohort 1, n=3), 1 mg/kg/week (Cohort 2, n=3), and 3 mg/kg/week (Cohort 3, n=3). *LAL-CL04: Each subject initiated treatment in the extension study at the same weekly dose of sebelipase alfa that he/she received in study LAL-CL01, i.e., 0.35 mg/kg weekly, 1 mg/kg weekly, or 3 mg/kg weekly for 4 weeks. After the initial 4 weekly doses, all subjects moved to dosing at 1 mg/kg every other week (subjects who initiated dosing at 0.35 or 1 mg/kg weekly) or 3 mg/kg every*

	other week (subjects who initiated dosing at 3 mg/kg weekly).
Baseline differences	The age of subjects at the time of diagnosis of LAL Deficiency was variable (range 4.1 to 42.4 years), as was the time between diagnosis and enrolment in LAL-CL01 (0.8 to 36.3 years).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Participants were actively monitored and followed up until the End of Study visit (Day 52 or at least 7 days from last infusion). All 9 (100%) subjects completed the study as planned. The 9 treated subjects each received 4 complete infusions of sebelipase alfa at their allocated dose. *LAL-CL04: This is an ongoing study; a follow-up visit will be conducted for all subjects at 30 days after the last dose of sebelipase alfa.*
Statistical tests	The study was not powered to detect differences between cohorts and therefore no statistical comparisons of cohorts were performed. Exploratory statistical analyses were performed to examine the effects of sebelipase alfa on key activity parameters in both LAL-CL01 and LALCL04. Wilcoxon's sign-rank test was used for statistical tests of change from baseline, without adjustment for multiplicity.
Primary outcomes (including scoring methods and timings of assessments)	LAL-CL01: The primary objective was to evaluate the safety and tolerability of sebelipase alfa in patients with liver dysfunction due to LAL Deficiency. *LAL-CL04: to evaluate the long-term safety and tolerability of sebelipase alfa in subjects with liver dysfunction due to LAL Deficiency*
Secondary outcomes (including scoring methods and timings of assessments)	The secondary objective of LAL-CL01 was to characterise the pharmacokinetics of sebelipase alfa delivered by IV infusion after single and multiple doses (pre and post infusion Day 0 and 21). Biological activity of sebelipase alfa was assessed by analysis of hepatic transaminases (ALT, AST), lipid parameters (total cholesterol, triglycerides, HDL, LDL), and serum ferritin.

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transferase; IRRs Infusion-related reaction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PD, pharmacodynamics; TEAEs, treatment-emergent adverse event; SAEs, serious adverse events

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Table C9.8: Sebelipase alfa clinical trial publications

Study reference	Key Publication/ Data sources	Additional Publications (Conference abstracts)
LAL-CL01 and open-label extension LAL-CL04	Balwani, 2013a Data on File, CSR LAL-CL01 Data on File, CSR LAL-CL04	Valayannopoulos, 2014a; Valayannopoulos, 2014b; Rojas-Caro, 2015; Whitley, 2014; Balwani, 2013b; Abel, 2014; Jones, 2012a; Valayannopoulos, 2013; Tripuraneni, 2013; Jones, 2012b; Enns, 2012
LAL-CL02 (ARISE)	Burton, 2015a Data on File, CSR LAL-CL02	Balwani, 2014*; Burton, 2015b; Quinn, 2014b
LAL-CL03	Data on File, CSR LAL-CL03	Valayannopoulos, 2014c Jones, 2015b

*Abstract not identified in literature review and provided by Alexion

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

Patient demographics

An overview of the demographic characteristics for the 84 subjects with LAL Deficiency enrolled in Studies LAL-CL03, LAL-CL02 and LAL-CL01 is provided in Table C9.9 below.

The eligibility criteria for the pivotal sebelipase alfa studies were designed to select subjects likely to receive sebelipase alfa therapy and represent the full spectrum of patients with LAL Deficiency. All subjects enrolled in Studies LAL-CL01, LAL-CL02 and LAL-CL03 were required to have a confirmed diagnosis of LAL Deficiency based on residual LAL activity. Due to the medically emergent nature of the presentation of this disease in infants, diagnosis could be confirmed in Study LAL-CL03 by either documented decreased LAL activity relative to the normal range of the laboratory performing the assay or documented result of molecular genetic testing (2 mutations).

Among infants with the most rapidly progressive disease, median age at onset of LAL Deficiency symptoms was <1 month. Median age at symptom onset in children and

adults with the disease was 4 years in Study LAL-CL02. At the time of first dose of study treatment, median age was 3 months in Study LAL-CL03, 13 years in Study LAL-CL02, and 30 years in Study LAL-CL01.

Baseline Disease Characteristics

An overview of the baseline disease characteristics for the patients enrolled in Studies LAL-CL03, LAL-CL02 and LAL-CL01 is provided in Table C9.9 below.

Growth Failure / Failure to Thrive

All 9 infants in Study LAL-CL03 presented with growth failure prior to 6 months of age (n = 8) or had rapidly progressive disease requiring urgent medical intervention (n = 1) (Data on File, CSR LAL-CL03). [redacted]

Although less prominent compared with the Baseline findings in infants, evidence of impairment of growth was also noted in Study LAL-CL02. A higher than expected proportion of subjects were shorter than the 5th centile for height (12% versus [redacted] (Data on File, CSR LAL-CL02).

Liver Dysfunction

All subjects across the sebelipase alfa program had evidence of liver dysfunction at study Baseline.

Marked abnormalities in liver biochemical parameters were observed at Baseline in all 9 infants in Study LAL-CL03: AST was elevated in all subjects (median = 125 U/L) and ALT was elevated in 7 (median = 145 U/L) (Data on File, CSR LAL-CL03). Elevations in GGT, total bilirubin, and ALP were reported [redacted]. All of the 9 subjects had a finding of hepatomegaly and/or splenomegaly on Baseline physical examination.

As required for entry into Study LAL-CL02, all 66 subjects had abnormal ALT levels (i.e., ALT ≥ 1.5 × the ULN) at Baseline (median 87 U/L) with ALT ≥ 3 × ULN in 27% of subjects. All but 1 subject had abnormal AST levels (median 73.5 U/L) and AST was ≥ 3 × ULN in 14% (Data on File, CSR LAL-CL02). Overall, 41%, 38%, 21%, and 14% of the 66 subjects had ALP, GGT, total bilirubin, and indirect bilirubin, respectively, > ULN at Baseline. The liver was palpable on physical examination in 73% of subjects. Mean Baseline liver fat content based on MEGE-MRI was 8.5%.

Review of Baseline liver biopsies obtained in 32 subjects in Study LAL-CL02, including 14 subjects < 18 years of age and 8 subjects < 12 years of age, revealed significant liver disease with evidence of fibrosis (Ishak fibrosis scores ≥ 1) in all 32 (Data on File, CSR LAL-CL02). Ten (31%) of the 32 subjects had Ishak fibrosis scores of 5 or 6, indicating either early or incomplete cirrhosis or probable or definite cirrhosis, respectively. Among the 10 subjects with cirrhosis, the youngest was 4 years of age with 5 subjects < 12 years old, indicating significant progression of disease early in life. More than half (6 of 10) had no documented medical history of cirrhosis. Biopsy evidence of microvesicular steatosis at Baseline was reported in all but 1 subject (a placebo subject whose biopsy only showed cirrhotic scar without hepatocytes), with the majority (88%) having fat vacuoles replacing all or nearly all of the hepatocytes.

In Studies LAL-CL01/LAL-CL04, all 9 subjects had evidence of liver involvement at study entry: 8 had hepatomegaly on physical examination and 8 had AST or ALT > ULN (Data on File, CSR LAL-CL01).

Dyslipidaemia

Evidence of dyslipidaemia was noted at Baseline across the disease spectrum.

Serum lipid abnormalities were observed at Baseline in most infants in Study LAL-CL03 with data available: triglycerides were elevated in [redacted], HDL-c was [redacted] and total cholesterol and LDL-c were [redacted](Data on file, CSR LAL-CL03). These findings, low HDL-c with often normal LDL-c and total cholesterol, are consistent with the serum lipid abnormalities observed in the historical control cohort from Study LAL-1-NH01 and the literature (Grabowski, 2012; Data on file, CSR LAL-1-NH01).

In Study LAL-CL02, Baseline assessments of lipids demonstrated marked dyslipidaemia (Data on file, CSR LAL-CL02). More than half (58%) of the subjects had LDL-c in the very high range (≥ 190 mg/dL [4.9 mmol/L]) with only 6% having LDL-c < 130 mg/dL (3.4 mmol/L); 24% of subjects with Baseline LDL-c ≥ 190 mg/dL were on LLMs. Low HDL-c levels were common: all 33 females had HDL-c < 50 mg/dL (1.3 mmol/L) and 70% of males had values < 40 mg/dL (1.0 mmol/L). Hypertriglyceridemia (≥ 200 mg/dL [2.3 mmol/L]) was seen in 21% of subjects. Review of LDL-c levels among subjects receiving and not receiving LLMs at Baseline showed that mean LDL-c was lower, yet still abnormal, in subjects receiving LLMs compared to those who were not (173.6 mg/dL versus 230.2 mg/dL [4.5 mmol/L versus 6.0 mmol/L]).

In Studies LAL-CL01/LAL-CL04, 8 of the 9 subjects had lipid abnormalities (mean HDL-c 35 mg/dL (SD 10mg/dL), LDL-c of 144mg/dL (SD 71mg/dL) and triglyceride of 152 mg/dL (SD 79mg/dL) despite the fact that 7 were receiving LLMs at study entry (Data on file, CSR LAL-CL01).

Summary

In summary, review of Baseline characteristics, including medical history and concomitant supportive therapies, indicate that the infants enrolled in Study LAL-CL03 presented with an immediately life-threatening disease requiring urgent medical intervention. Further, the Baseline characteristics for this group are consistent with those reported among the patients in the natural history study LAL-1-NH01, supporting the comparison of survival data and outcomes between the subjects in these 2 studies.

The Baseline disease characteristics in children and adults in Study LAL-CL02, which are consistent with those reported by Bernstein, et al (Bernstein, 2013), indicate that LAL Deficiency is a multisystem disease in this population with serious complications, including ongoing liver injury, advanced liver fibrosis and cirrhosis occurring at an early age, and marked disturbances of lipid metabolism.

Table C9.9: Baseline Demographic and Disease Characteristics

Characteristics	LAL-CL03	LAL-1-NH01	LAL-CL02			LAL-CL01
	All (N = 9)	All (n=35)	All (n=66)	Sebelipase alfa (n=36)	Placebo (n=30)	All (N = 9)
Males, n (%)	5 (56)	19 (54.3)	33 (50)	18 (50)	15 (50)	6 (67)
White, n (%)	[redacted]	17 (48.6)	55 (83)	27 (75)	28 (93)	9 (100)
Not Hispanic or Latino, n (%)	[redacted]	26 (74.3)	56 (85)	30 (83)	26 (87)	9 (100)
Age at Onset of LAL Deficiency-related abnormality (years) Mean ± SD (Median)	[redacted]	0.12 ± 0.11 (0.08)	6.5 ± 7.12 (4.0)	7.5 ± 8.36 (5.0)	5.4 ± 5.16 (4.0)	13.1 ± 11.19 (9.8)
Age at Randomisation/First Dose (years) Mean ± SD (Median)	[redacted]	N/A	16.1 ± 10.93 (13.0)	16.8 ± 11.52 (13.5)	15.2 ± 10.24 (13.0)	32.2 ± 10.54 (29.9)
Age < 12 years, n (%)	9 (100)	35 (100)	24 (36)	14 (39)	10 (33)	0
Mutation						
Homozygous Common	0	1 (8.3[c])	21 (32)	11 (31)	10 (33)	1 (11)
Heterozygous Common	0	2 (16.7[c])	35 (53)	17 (47)	18 (60)	8 (89)
Other[b]	6 (100[c])	4 (33.3[c])	10 (15)	8 (22)	2 (7)	0
Baseline transaminases (U/L) Mean ±SD						
ALT	[redacted]	NR	102.4±43.71	105.1±45.31	99.0±42.23	76±29
AST	[redacted]	NR	82.8±34.15	86.6±33.49	78.2±34.93	56±12
Baseline serum lipids (mg/dL) Mean ±SD						
LDLc	[redacted]	NR	207.9±65.85	189.9±57.16	229.5±69.95	144±71
Non-HDL-c	[redacted]	NR	240.2±71.06	220.5±61.48	263.8±75.48	NR
TG	[redacted]	NR	162.6±60.42	174.4±65.90	174.4±65.90	152±79
HDL-c	[redacted]	NR	32.8±7.22	32.4±7.09	33.4±7.46	35±10
Liver fat content (%) at baseline, Mean ±SD	NR	NR	8.50±3.50	8.75±3.95	8.16±2.80	NR
Baseline LLM use, n (%)	NA	NA	26 (39)	15 (42)	11 (37)	7 (78)

LAL = liposomal acid lipase; SD = standard deviation, NA = not applicable, NR = not reported

[a] Ethnicity was not reported in the other 3 subjects

[b] 'Other' mutation: at least one of the alleles has a defined mutation, nether allele has the common mutation

[c] Only 6 of the 9 patients in LAL-Cl03 and 12 of the 35 patients in LAL-1-NH01 had data on LIPA genetic testing

Sources: Data on file, CSR LAL-CL01; Data on file, CSR LAL-CL02; Data on file, CSR LAL-CL03; Data on file, CSR LAL-CL04

Choice of comparator

A placebo-controlled study design was employed in Study LAL-CL02. This is appropriate and in line with the scope of this submission since no alternative effective treatments exist. Patients in LAL-CL02 could continue other medical management for LAL Deficiency at a stable dose (prior to and for at least the first 32 weeks of treatment) while participating in this study.

LAL-CL03 was single-arm in design. An active comparator was not employed as no safe or effective alternative therapy is currently available for the treatment of LAL Deficiency. Further, a placebo control was not considered appropriate given the life threatening complications of LAL Deficiency presenting in infants, the rapidity of disease progression, and the extreme implausibility of spontaneous improvement in the absence of disease-modifying treatment. For this reason, a retrospective natural history study was undertaken to provide a historical control for Study LAL-CL03 (*for further discussion see Section 9.9.2*).

LAL-CL01 is an open-label, multicentre, dose-escalation study primarily designed to investigate safety and tolerability of sebelipase alfa. No active or placebo control was included.

Dose

In LAL-CL02 patients received 1 mg/kg sebelipase alfa or placebo every other week (qow) during the 20-week double-blind treatment period; no dose modifications were permitted during this period. After completing double-blind treatment, all subjects began open-label treatment with sebelipase alfa at a dose of 1 mg/kg qow. During open-label extension, dose increases to 3 mg/kg qow are permitted in the event of inadequate clinical response, and a dose reduction to 0.35 mg/kg qow is permitted in the event of poor tolerability.

In LAL-CL03 subjects initiated treatment at 0.35 mg/kg administered IV once weekly, and were escalated to a dose of 1 mg/kg once weekly once acceptable safety and tolerability had been demonstrated. Subjects with suboptimal clinical response could be considered for further dose escalation to 3 mg/kg once weekly. Further escalation to 5 mg/kg once weekly could be considered if there was suboptimal response in association with the presence of neutralising antibodies.

A small cohort of infants has received treatment with sebelipase alfa at a dose of 5mg/kg once weekly in clinical trials. This dose is not approved for use in the EU and data are evolving on this dosing strategy. Currently 3 children are receiving this dose in the UK clinical trial centre in Manchester.

LAL-CL01 was a dose ranging study investigating three doses of sebelipase alfa: 0.35 mg/kg/week, 1 mg/kg/week and 3 mg/kg/week.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Primary and key secondary efficacy analyses were conducted on data from Study LAL-CL02 for the following pre-specified subgroups:

- Age at randomisation (< 12 years, ≥ 12 years to < 18 years, ≥ 18 years)
- Gender (male, female)
- Race
- Ethnicity
- Baseline BMI, rounded to 1 decimal place (normal/low [< 25.0 kg/m2], overweight [25.0 to 29.9 kg/m2], obese [≥ 30.0 kg/m2])
- Tertiles of baseline liver volume
- Tertiles of baseline liver fat content
- Baseline LDL-c (normal/low [< 130 mg/dL], high [≥ 130 mg/dL to < 190 mg/dL], very high [≥ 190mg/dL]
- Baseline TG (normal/low [< 200 mg/dL], high [≥ 200 mg/dL to < 500 mg/dL], very high [≥ 500 mg/dL]
- Average screening ALT level (< 3 × ULN, ≥ 3 × ULN) (amended to baseline ALT)
- Baseline use of LLM (yes, no)

The effects of genotype and the presence of cirrhosis on liver biopsy were also investigated in LAL-CL02.

The effects of dose and regimen as well as anti-drug antibody (ADA) status were also investigated in LAL-CL01, LAL-CL02, LAL-CL03 and LAL-CL04.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Study LAL-CL03

[redacted] Overall, 9 infants with confirmed LAL Deficiency were enrolled in this study [redacted] (Data on file, CSR LAL-CL03); all 9 subjects received treatment with sebelipase alfa and were <6 months of age at the time of first infusion. As of the data cut-off for reporting (10 Jun 2014), 6 (67%) subjects had received treatment with sebelipase alfa through to at least 12 months of age and 3 (33%) died prior to 12 months of age (Data on file, CSR LAL-CL03). All 6 subjects who survived to 12 months of age were ongoing on

treatment at the time of the data cut-off; the maximum duration of exposure at that time was [redacted] (Data on file, CSR LAL-CL03).

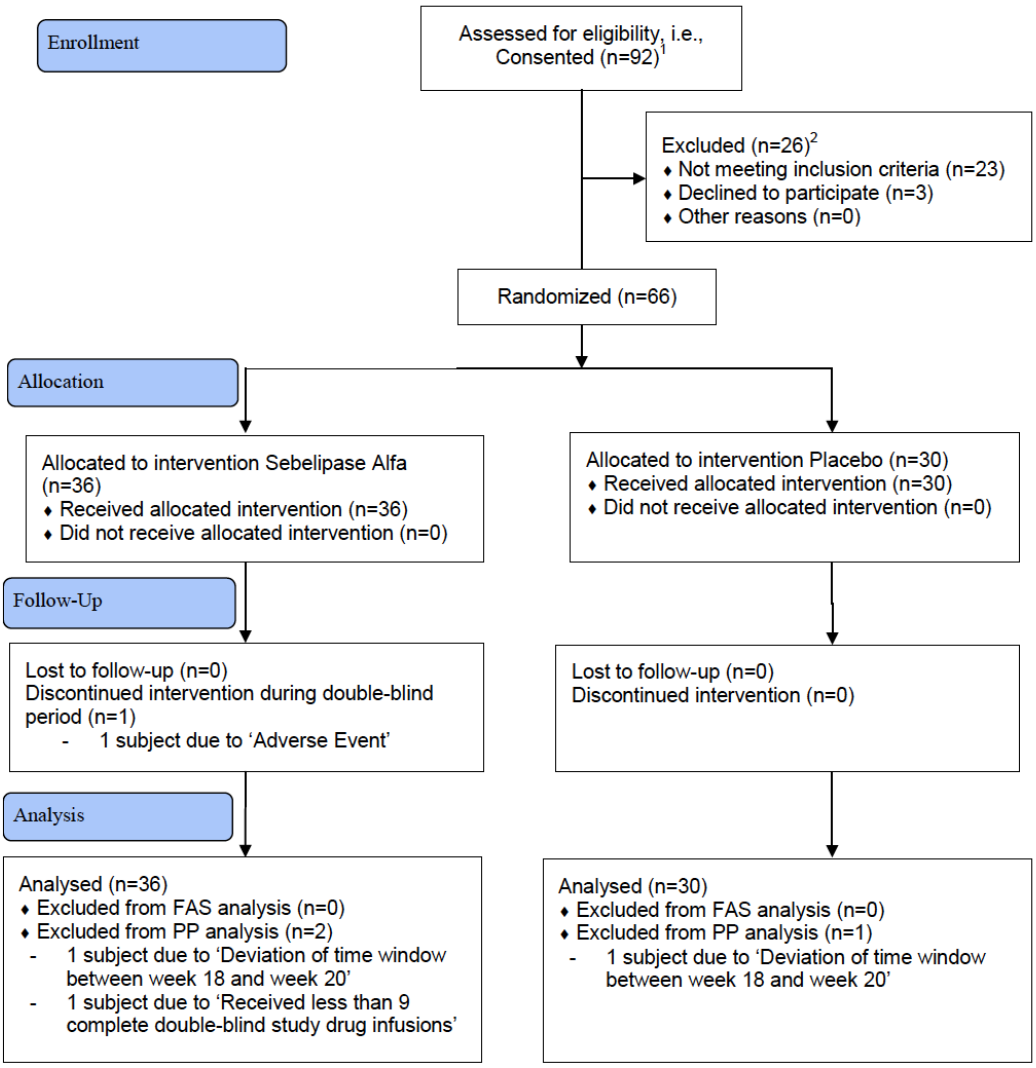
36 patients were included in the historical control study (LAL-1-NH01). Data were analysed for 35 eligible patients (excluding 1 eligible patient who received sebelipase alfa in LAL-CL03). The 35 eligible patients were already deceased at the time of enrolment. A subpopulation of 21 infants with growth failure within the first 6 months of life based on objective criteria similar to those used in Study LAL-CL03 and, like subjects in Study LAL-CL03, who had not received prior HSCT or liver transplant, was used for the primary comparison.

Study LAL-CL02

In Study LAL-CL02, 55 study centres were initiated in 17 countries. Overall, 66 subjects with confirmed LAL Deficiency were randomised over a 9-month period (Data on file, CSR LAL-CL02); 36 subjects were randomised to receive sebelipase alfa and 30 to receive placebo (Figure C9.2). All 66 subjects received at least 1 dose of study treatment (Data on file, CSR LAL-CL02).

Sixty-five (98%) of the 66 randomised subjects completed the double-blind treatment period and continued into the open-label period. One sebelipase alfa subject was discontinued from dosing during the double-blind period due to an infusion-associated reaction (IAR) after receiving 2 study treatment infusions. This subject may enter the open-label period upon rechallenge. As of the data cut-off, all 65 subjects who entered the open-label period were continuing in the study receiving sebelipase alfa at 1 mg/kg once every other week; maximum exposure at that time was ~16 months (68 weeks) (Data on file, CSR LAL-CL02).

Figure C9.2: Patient disposition in LAL-CL02



1 There were 92 screenings across 86 unique subjects.
2 There were 26 exclusions across 20 unique subjects.

Studies LAL-CL01 and LAL-CL04

In Study LAL-CL01, 9 subjects were allocated to 1 of 3 dose cohorts (3 subjects per cohort at 0.35, 1.0 and 3.0 mg/kg); all 9 subjects completed the study receiving 4 infusions of sebelipase alfa once weekly (Data on file, CSR LAL-CL01). 8 of 9 subjects who completed Study LAL-CL01 entered the extension study LAL-CL04 between 9 and 28 weeks after their last dose of sebelipase alfa in Study LAL-CL01 (Data on file, CSR LAL-CL04). As of the data cut-off, all 8 subjects who entered Study LAL-CL04 remained on treatment with 7 of the 8 subjects having completed the Week 104 visit (i.e., ~2 years of treatment on sebelipase alfa).

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

No patients were lost to follow-up or withdrew from LAL-CL01, LAL-CL02 or LAL-CL03. The majority of patients from LAL-CL01 entered the extension study and 7 of 8 of those completed the Week 104 visit. 5 of 6 subjects who survived to 12 months of age in LAL-CL03 were ongoing on treatment at the time of data cut-off.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

Table C9.10: Quality assessment of sebelipase alfa clinical trials

Study name	**LAL-CL02 (randomised controlled trial)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Each subject was assigned an enrolment number at screening. Subjects were randomised via an interactive voice response system (IVRS) or interactive web response system (IWRS).
Was the concealment of treatment allocation adequate?	Yes	The study was double-blinded. During the double-blind treatment period (Week 0 to Week 20), subjects randomly assigned to placebo received matched placebo (buffered solution identical in composition to the formulation buffer for sebelipase alfa) via IV infusion every other week.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Groups were similar in terms of baseline demographics, onset of LAL Deficiency-related abnormality, serum transaminases, liver fat content and volume and history of lipid-lowering medication. Levels of Non-HDL-c and cholesterol were significantly lower in the sebelipase group. HDL-c and LDL-c were not significantly different.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The study included a 20-week double-blind period, followed by an open-label period of up to 130 weeks. The subjects (and their parents or legal guardians), Investigators, and all Sponsor personnel (except those required to report assigned study medication to regulatory authorities in the case of suspected unexpected serious adverse reactions [SUSARs]) and designees involved in the conduct of the clinical study were blinded to the identity of the study infusions. No dose modifications were permitted during the double-blind treatment period. Subjects who demonstrated evidence of significant clinical progression on blinded study drug were permitted to discontinue from the

		double-blind treatment period and transition to open-label treatment with sebelipase alfa at a dose of 1 mg/kg. Subjects may also have been considered for a further dose escalation to 3 mg/kg every other week in the event of inadequate clinical response during open-label treatment, as described below. The subject's treatment assignment was not to be unblinded in the event of such transition, except in the event of a medical emergency.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	One subject discontinued study drug due to an adverse event (in the sebelipase alfa group). No patients in the sebelipase alfa group were excluded from the FAS analysis. 2 patients were excluded from the PP analysis: 1 subject due to 'Deviation of time window between week 18 and week 20'; 1 subject due to 'Received less than 9 complete double-blind study drug infusions. No patients in the placebo group were excluded from the FAS analysis. One patient was excluded from PP analysis due to 'Deviation of time window between week 18 and week 20'
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	The Full Analysis Set (FAS) comprised subjects in the Consented Set who, in addition, were randomised and received at least 1 dose of sebelipase alfa or placebo. The FAS was a modified intention-to-treat (ITT) dataset. No imputation of missing data was performed for the efficacy parameters. If the rate of missing or incomplete data appeared to differ across treatment groups, sensitivity analyses may have been performed to assess various scenarios. Final decisions regarding preplanned sensitivity analyses were made during the blind data review meeting. Additional post-hoc sensitivity analyses may have been performed if unblinded results led to additional questions about analysis assumptions.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: LAL-CL03 (single arm trial)		
Study question	**Response** **yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	The target population for this study was subjects presenting with LAL Deficiency in infancy with evidence of rapidly progressive disease based on documented growth failure within the first 6 months of life. Patients were recruited according to pre-defined inclusion/exclusion criteria.

Was the exposure accurately measured to minimise bias?	Yes	All subjects who initiated treatment under the LAL-CL03 protocol received a starting dose of 0.35 mg/kg weekly and were escalated to a dose of 1 mg/kg every week once acceptable safety and tolerability had been demonstrated during at least 2 infusions at the dose of 0.35 mg/kg. All infusions of sebelipase alfa were administered under controlled conditions by qualified site personnel in accordance with the LAL-CL03 protocol and investigational medicinal product (IMP) Manual (or for infusions under Temporary Use Authorisation, in accordance with similar written guidance provided to the investigator upon shipment of study drug) and applicable institutional standards and local regulations. All IMP administration was documented in the electronic case report form, including reasons for any missed or incomplete infusions. The IMP accountability records maintained by the Investigator documented the IMP dispensed to each subject.
Was the outcome accurately measured to minimise bias?	Yes	The primary outcome of survival was not subject to biased reporting. Measures were taken to minimise potential confounding effects on the evaluation of survival. Haematopoietic stem cell transplant, while not proven to effectively treat clinical manifestations or impact survival, was an exclusion criterion for this study, as was the use of pre-conditioning regimens in preparation for HSCT. Supportive interventions were permitted, as these were medically necessary to ameliorate acute life-threatening complications in these often critically ill infants. Use of supportive interventions was carefully documented prior to and throughout the trial, and this enabled an evaluation of the impact of sebelipase alfa on the medical requirement for these interventions - particularly the need for nutritional support and blood transfusions, which are commonly applied in the management of affected infants after they are diagnosed.
Have the authors identified all important confounding factors?		The primary endpoint of survival to 12 months of age represents a clinically meaningful response to treatment in these patients. A placebo control was not considered appropriate for this study given the life-threatening complications of LAL Deficiency presenting in infants, the rapidity of disease progression, and the lack of potential for spontaneous improvement in the absence of disease-modifying treatment. A carefully selected historical cohort as a control group.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Objective criteria for growth failure within the first 6 months of life were used to ensure the historical cohort matched the LAL-CL03 population. Additional measures were taken to minimise potential confounding effects on the evaluation of survival. Haematopoietic stem cell transplant, while not proven to effectively treat clinical manifestations or impact survival, was an exclusion criterion for this study, as was the use of pre-conditioning regimens in preparation for HSCT. Supportive interventions were permitted, as these

		were medically necessary to ameliorate acute life-threatening complications in these often critically ill infants. Use of supportive interventions was carefully documented prior to and throughout the trial. During the conduct of this study, emerging clinical data indicated that some subjects in the study were developing antibodies to sebelipase alfa, and thus could be developing neutralising antibodies with the potential to impact efficacy. In response to observations in 1 subject, the protocol was amended to allow a further dose escalation to 5 mg/kg every week in the specific situation where a subject receiving a dose of 3 mg/kg every week met the protocol definition for suboptimal response, and this suboptimal response was observed in association with the presence of neutralising antibodies.
Was the follow-up of patients complete?	Yes	As of the data cut-off for this CSR (10 Jun 2014), 6 (67%) subjects had received treatment with sebelipase alfa through to at least 12 months of age and 3 (33%) subjects were considered early terminated due to death prior to 12 months of age. No subject discontinued from the study prior to 12 months of age for reasons other than death.
How precise (for example, in terms of confidence interval and p values) are the results?	NA	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Study name: LAL-01/04 (dose ranging trial and extension study)		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	This study recruited adult patients with liver dysfunction due to LAL Deficiency. Patients were recruited according to pre-defined inclusion/exclusion criteria. Sites pre-identified potentially eligible subjects, and the Sponsor approved these subjects to initiate screening. To minimize potential bias in this process, the Sponsor only had access to the subject's pre-screening identifier at the time of approving subjects for screening. A sequential enrolment number was assigned by the site after receiving Sponsor approval to initiate screening.
Was the exposure accurately measured to minimise bias?	Yes	Subjects received 4 IV infusions of sebelipase alfa, administered every week at a dose of 0.35 mg/kg (Cohort 1), 1 mg/kg (Cohort 2), or 3 mg/kg (Cohort 3). The 9 treated subjects each received 4 complete infusions of sebelipase alfa at their allocated dose. Minor deviations in the administration of IMP were reported for 3 subjects. All infusions of sebelipase alfa were administered

		under controlled conditions by qualified site personnel in accordance with the study protocol, IMP Instruction Manual, and applicable institutional standards and local regulations. Reasons for any missed or incomplete infusions were clearly documented in the electronic case report form. In addition, the Investigator or designee maintained accountability records for all IMP received, dispensed, returned, and/or destroyed. Therefore, no additional measures of treatment compliance were required.
Was the outcome accurately measured to minimise bias?	Yes	The main objective was to investigate the safety and tolerability of sebelipase alfa. Adverse events were obtained through spontaneous reporting or elicited by specific questioning or examination of the subject, and were recorded from the time of informed consent until completion of the last scheduled visit at approximately 30 days after the last infusion of IMP. In addition, any serious adverse event (SAE) occurring after completion of the last scheduled visit and considered to be at least possibly related to IMP was also recorded. Exploratory efficacy outcomes included changes in biochemical markers (serum transaminases and lipids) which were accurately measured at multiple pre-defined timepoints and as quantitative measures and less subject to bias. All laboratory data were standardized to SI units; serum lipids, serum ferritin, and high-sensitivity C-reactive protein (hsCRP) were also reported in conventional units.
Have the authors identified all important confounding factors?	Yes	The authors discuss the open-label nature, study size and dosing strategy in relation to the objectives of the study.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The planned enrolment was 9 subjects, with each dose cohort comprising 3 subjects who received up to 4 infusions of sebelipase alfa. This sample size and dosing strategy was chosen to provide a reasonable estimation of the safety and tolerability of sebelipase alfa while enabling the study to be recruited and completed within a reasonable timeframe given the low prevalence of late onset LAL Deficiency. Subjects were excluded from this study if they had clinically significant laboratory abnormalities (other than liver enzymes or lipids), a clinically significant concurrent disease, serious inter-current illness, or concomitant medications that might interfere with study participation or data interpretation.
Was the follow-up of patients complete?	Yes	Nine patients were recruited and completed study LAL-CL01 as planned. Eight patients from LAL-CL01 were recruited into the ongoing long term study LAL-CL04.
How precise (for example, in terms of confidence interval and p	NA	

values) are the results?		
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

Clinical Study Efficacy Endpoints

The primary efficacy endpoint in Study LAL-CL03 was the proportion of infants who survived to 12 months of age. Although the disease is rare, given the rapid progression and early mortality observed in this population, early death occurs predictably and survival is a readily assessed endpoint. Infants presenting with LAL Deficiency typically die within the first 6 months of life, and demonstrating a clear improvement in survival in these subjects provides strong evidence of the clinical benefit of ERT across the disease spectrum.

The primary objective in LAL-CL02 was to demonstrate the efficacy of sebelipase alfa, relative to placebo, based on normalisation of ALT. Unlike in infants, where a defined population with rapidly progressive disease and reliably poor clinical outcome (i.e., death) could be selected, the rate of disease progression in LAL Deficiency presenting in children and adults is more heterogeneous. This, combined with the rarity of the disease, precludes performing studies of the size and duration that would be required to directly assess the impact of ERT on clinical events associated with progressive liver disease (e.g., decompensated cirrhosis or liver-related mortality) or CVD (e.g., cardiac-related mortality) in this subset of subjects with LAL Deficiency.

In recognition of the multiple abnormalities resulting from the enzyme deficiency, including dyslipidaemia multiple secondary endpoints were evaluated sequentially for statistical significance using a hierarchical sequence testing approach.

LAL-CL01 was a dose-escalation study primarily to evaluate the safety and tolerability of sebelipase alfa. Exploratory outcomes investigating the effect on transaminases and dyslipidaemia and long-term data from LAL-CL04 provide supportive evidence for the key outcomes in LAL-CL02.

For further discussion on choice of endpoints see Section 9.9.2.

Data sets and statistical analysis

The definitions of datasets for analysis were consistent with those given in the ICH E9 Guideline on Statistical Consideration in the Design of Clinical trials (1998). Standard statistical methodology was used in both pivotal studies as outlined below.

Study LAL-CL03

The primary evaluation of efficacy in Study LAL-CL03 was based on the 'Primary Efficacy Analysis Set' (PES), defined as all subjects who received any amount of sebelipase alfa and who were ≤ 8 months of age at the time of their first infusion.

The primary efficacy endpoint, the proportion of subjects surviving to 12 months of age, was estimated along with an exact 95% CI based on the Clopper-Pearson method. In support of this analysis, Kaplan-Meier survival curves were generated from birth to 12 months of age and from first infusion of sebelipase alfa to 12 months of age, as well as an estimate of the median survival time and corresponding exact 95% CI after the first infusion of sebelipase alfa.

Study LAL-CL02

The primary analysis set for evaluation of efficacy in Study LAL-CL02 was the 'Full Analysis Set' (FAS), defined as randomised subjects who received any amount of sebelipase alfa or placebo.

The primary efficacy endpoint in Study LAL-CL02 was the proportion of subjects who achieved ALT normalisation at the end of the double-blind treatment period (last scheduled measurement at Week 20 or last available measurement for subjects who terminated double-blind treatment early). If the final assessment of ALT was < 10 weeks (70 days) after the first dose, the subject was considered a non-responder in the analysis. The comparison of sebelipase alfa to placebo was conducted using Fisher's exact test.

To provide strong control of the type I error rate for multiple key secondary endpoints, a fixed sequential testing approach was adopted. That is, if the analysis of the primary efficacy endpoint was statistically significant at the pre-specified nominal $\alpha = 0.05$ level, then statistical hypothesis tests of the secondary endpoints would be performed in a fixed sequence.

Phase 2/3 Study LAL-CL03: Results of Primary Efficacy Endpoint, Survival in Infants

Infants with rapidly progressive LAL Deficiency, as evidenced by failure to thrive within the first 6 months of life, who received treatment with sebelipase alfa, demonstrated prolonged survival compared with an untreated historical control group.

The efficacy of sebelipase alfa in infants was evaluated by comparing the proportion of sebelipase alfa-treated subjects in Study LAL-CL03 who survived beyond 12 months of age with the survival experience from a cohort of infants with LAL Deficiency from the natural history study LAL-1-NH01 who had similar demographic and disease characteristics. From the natural history study, a subpopulation of 21 infants with failure to thrive within the first 6 months of life, based on objective criteria similar to those used in Study LAL-CL03 and, like subjects in Study LAL-CL03, who had not received prior HSCT or liver transplant, was used for the primary comparison.

Survival curves from birth for all subjects in Study LAL-CL03 and for untreated patients with early failure to thrive in Study LAL-1 NH01 are displayed in Figure C9.3. In Study LAL-CL03, 6 of 9 sebelipase alfa-treated infants with LAL Deficiency and evidence of early failure to thrive survived beyond 12 months (67% survival; 95% CI: [redacted] (Data on file, CSR LAL-CL03). In contrast, none of the 21 infants in the natural history study with LAL Deficiency and evidence of early failure to thrive who were untreated survived to 12 months of age (0% survival; 95% CI: 0%, 16.11%) (Data on file, CSR LAL-CL03). These results demonstrate that treatment with sebelipase alfa provides a clinically meaningful improvement in survival in infants with rapidly progressive disease due to LAL Deficiency.

Figure C9.3: Kaplan-Meier Plot of Survival from Birth to 12 Months of Age for Sebelipase alfa-Treated Subjects in Study LAL-CL03 (PES) vs. Untreated Patients in Study LAL-1-NH01 (Patients with Early Failure to Thrive Only)

Source: Data on file, CSR LAL-CL03
Note: For Study LAL-1-NH01, patients were considered untreated if they had not received haematopoietic stem cell transplant, liver transplant, or enzyme replacement therapy.

[redacted]

The ages at their last available assessment of the 6 subjects who received sebelipase alfa and who were alive as of the data cut-off (10 Jun 2014), ranged from 12.0 to 42.2 months (Data on file, CSR LAL-CL03). Median age at death for the 3 infants who died prior to 12 months of age was 2.92 months (range: 2.8 to 4.3 months) (Data on file, CSR LAL-CL03 CSR); the Investigators assessed all 3 deaths as unrelated to study treatment. With continued treatment beyond 12 months of age, 1 additional subject died after the data cut-off at 15 months of age [redacted] Details on subject deaths are provided in Section 9.7.3

Evaluation of Improvement in Liver Pathology: Transaminase Levels, Liver Fat Content, Liver Volume, and Liver Histopathology

Improvement in Transaminase Levels

Sebelipase alfa addresses the root cause of LAL Deficiency as evidenced by reductions in liver injury as evidenced by improvements in serum transaminase levels, including normalisation. The effect was consistently maintained over long-term treatment.

Study LAL-CL02

Study LAL-CL02 met its primary efficacy endpoint: treatment with sebelipase alfa led to normalisation of ALT levels in a significantly greater proportion of subjects than placebo ($p = 0.0271$) (Table C9.11). At the end of the double-blind treatment period, 31% of subjects in the sebelipase alfa group compared with 7% of subjects in the placebo group achieved normalisation in ALT based on age- and gender-specific normal ranges provided by the central laboratory performing the assay[2] (Burton, 2015a). [redacted]

All sebelipase alfa-treated subjects had a reduction in ALT level following initiation of study treatment. Review of a waterfall plot showing change from Baseline to the last time point in the double-blind period in ALT on a per-subject basis clearly demonstrates the relative improvements in ALT for sebelipase alfa treated subjects compared with those who received placebo (Figure C9.4).

[2] Per the central laboratory, the normal ranges for ALT were 6 to 34 U/L for females aged 4 to 69 years and males aged 4 to 10 years and 6 to 43 U/L for males aged 10 to 69 years.

Table C9.11: Summary of Primary and Secondary Efficacy Endpoints, including Fixed Sequence Test Results (Study LAL-CL02, Full Analysis Set)

Endpoint, Statistic	Population	Sebelipase alfa (N = 36)	Placebo (N = 30)	Difference (p-value)[a]	Statistically significant per fixed sequence test[b]
PRIMARY ENDPOINT:					
Normalisation of ALT, % (n/N)[c]	All, N = 66	31% (11/36)	7% (2/30)	24% (0.0271)	Yes
SECONDARY ENDPOINTS:					
Relative reduction in LDL-c, Mean (SD)[d]	All, N = 66	-28% (22.3)	-6% (13.0)	-22% (<0.0001)	Yes
Relative reduction in Non-HDL-c , Mean (SD) [d]	All, N = 66	-28% (18.6)	-7% (10.9)	-21% (<0.0001)	Yes
Normalisation of AST, % (n/N)[e]	Abnormal at Baseline, N = 65	42% (15/36)	3% (1/29)	39% (0.0003)	Yes
Relative reduction in triglyceride, Mean (SD)[d]	All, N = 66	-25% (29.4)	-11% (28.8)	-14% (0.0375)	Yes
Relative increase in HDL-c, Mean (SD)[d]	All, N = 66	20% (16.8)	-0.3% (12.3)	20% (<0.0001)	Yes
Relative reduction in liver fat content, Mean (SD)[d]	MRI Eligible[f] (N = 57)	-32% (26.8)	-4% (15.6)	-28% (<0.0001)	Yes
Improvement in liver histopathology, % (n/N)[g]	Consent to Biopsy[h] (N = 26)	63% (10/16)	40% (4/10)	23% (0.4216)	No
Relative reduction in liver volume, Mean (SD)	MRI Eligible[f] (N = 60)	-10% (10.5)	-3% (10.1)	-8% (0.0068)	No

Source: Data on File, CSR LAL-CL02

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; MRI = magnetic resonance imaging; SD = standard deviation; ULN = upper limit of normal

[a] p-value for treatment differences (Fisher's exact test for normalisation and liver histology endpoints and Wilcoxon rank sum test for all other endpoints).

[b] Overall Type 1 error rate controlled by a fixed sequence test, in the order presented in the table, beginning with Normalisation of ALT.

[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.

[d] Presented as mean percentage change from Baseline.

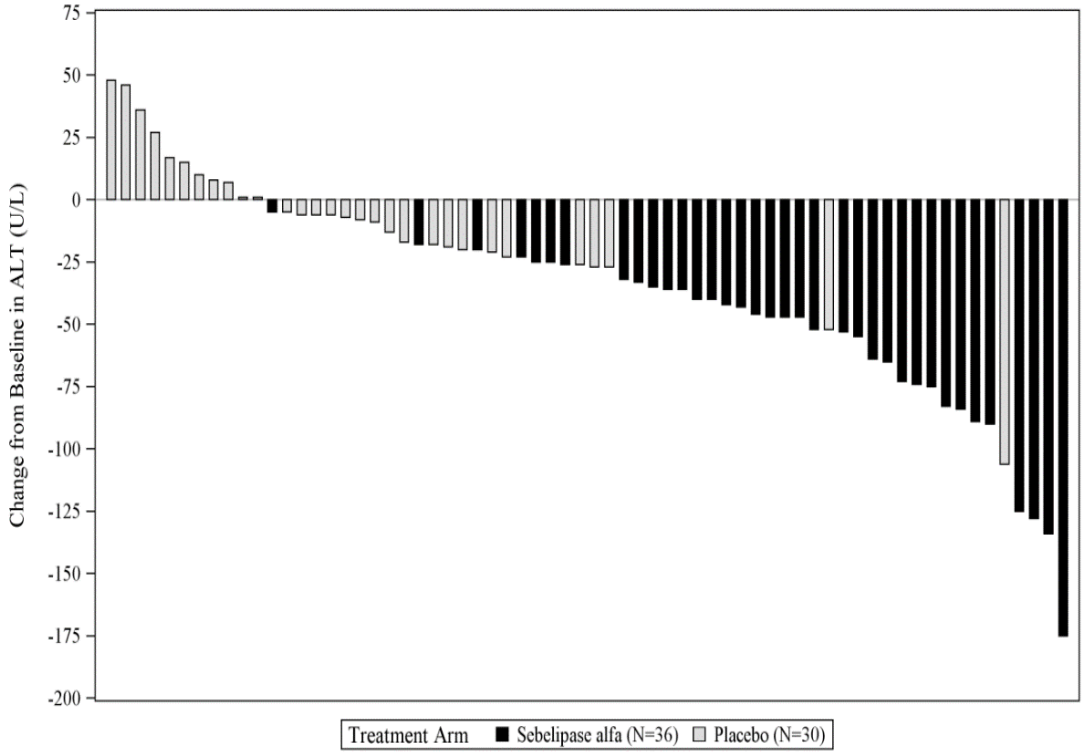
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).

[f] Abdominal MRI was required for all subjects except 1) those with internal or otherwise non-removable metal medical items and 2) children for whom sedation was required but medically contraindicated. Multi-echo gradient echo assessments of liver fat content were not required in children who could not hold their breath for 15-30 seconds.

[g] The primary disease-specific histopathological assessment was steatosis as measured by morphometry. Proportion of subjects with improvement of ≥ 5% in steatosis score over Baseline is presented.

[h] For subjects ≥ 18 years of age, biopsies were required unless medically contraindicated. Biopsies were optional for subjects < 18 years of age

Figure C9.4: Waterfall Plot of Change in ALT (U/L) from Baseline to the Last Time point in the Double-blind Treatment Period, by Subject (Study LAL-CL02, FAS)

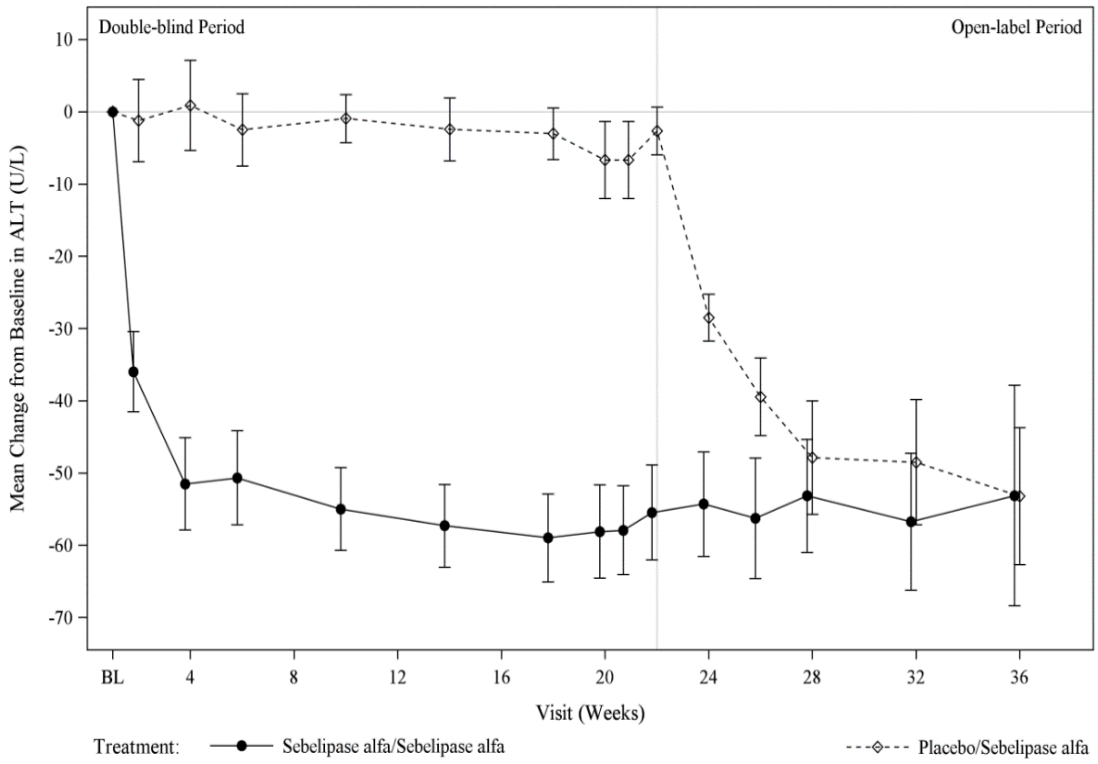


Source: Burton, 2015a
ALT = alanine aminotransferase

Following initiation of treatment with sebelipase alfa, improvements in ALT occurred rapidly with little or no improvement noted in subjects who were randomised to placebo (Figure C9.5). By Week 6, 34% (12 of 35 with data available) of sebelipase alfa treated subjects had normalisation of ALT levels with a similar proportion with normalisation in ALT at each week thereafter in the double-blind period (Data on file, CSR LAL-CL02).

Following transition from treatment with placebo to open-label treatment with sebelipase alfa, a similar rapid decline was observed in ALT levels (Figure C9.5). Importantly, among subjects randomised to sebelipase alfa, the treatment effect was maintained during long-term treatment with 1 mg/kg once every other week in the open-label extension period. [redacted]

Figure C9.5: Mean (±SE) Change from Baseline in ALT Values over Time (Study LAL-CL02, FAS, Double-blind Period and EAS, Open-label Period)



Source: Burton, 2015a
Sebelipase alfa/sebelipase alfa: subjects randomised to sebelipase alfa; Placebo/sebelipase alfa: subjects randomised to placebo who were crossed over to sebelipase alfa after the 20-week double-blind treatment period.
Note: Visits for a treatment sequence are presented if ≥ 5 subjects have data available.

Results for AST were similar to those for ALT. The percent of subjects with normalisation of AST levels was significantly higher in the sebelipase alfa group (42%) compared with placebo (3%) (p = 0.0003) (Table C9.11). As observed for ALT, AST normalisation was seen over a broad range of Baseline AST levels in the sebelipase alfa group (41 to 149 U/L), whereas AST normalisation in the placebo group was only seen in 1 subject with a low Baseline AST level (61 U/L). Similar to ALT, improvements in AST occurred rapidly following initiation of treatment with sebelipase alfa, with little or no improvement noted in the placebo group until subjects initiated treatment with sebelipase alfa after Week 20 (Data on file, CSR LAL-CL02).

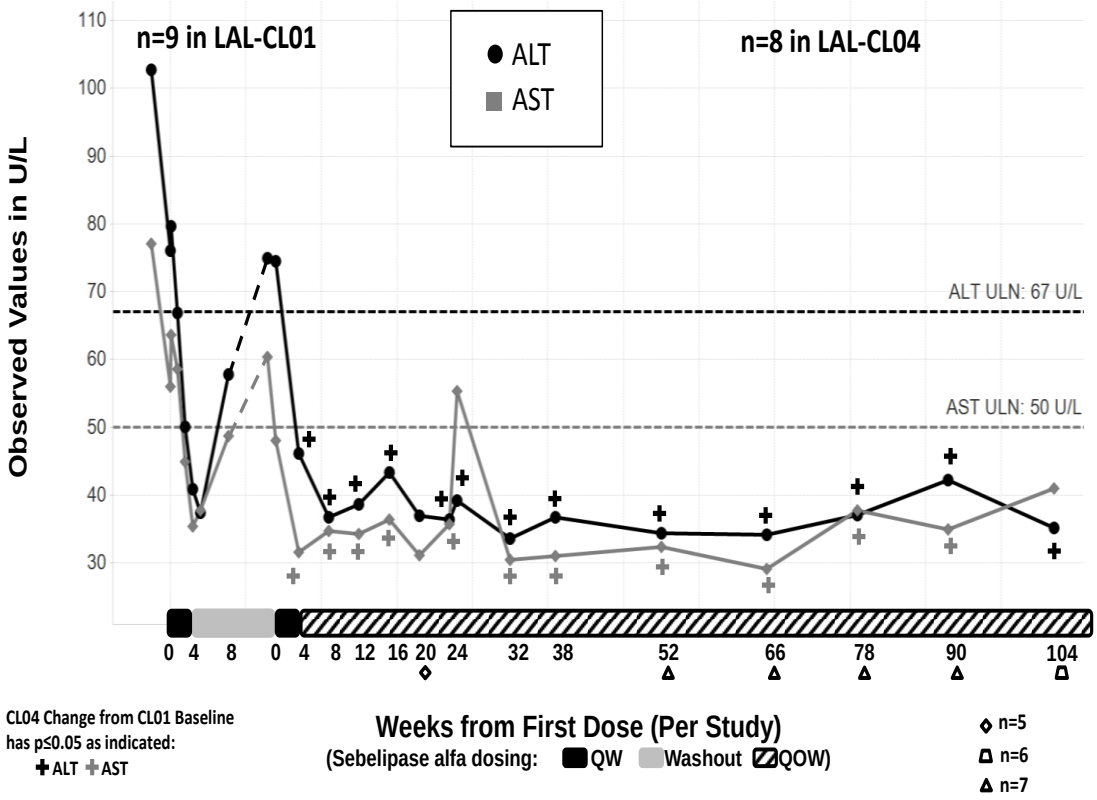
In addition to the improvements in serum transaminases, favourable effects of sebelipase alfa treatment were seen on other liver-related parameters, including GGT, ALP, and bilirubin (Data on file, CSR LAL-CL02).

Studies LAL-CL01 and LAL-CL04

Changes in serum transaminase levels observed in adults in Study LAL-CL01 were consistent with those reported in Study LAL-CL02 and were maintained over long-treatment during the extension study LAL-CL04.

Initiation of treatment with sebelipase alfa in Study LAL-CL01 produced a rapid decline in ALT and AST (Figure C9.6). When subjects went off treatment at the end of Study LAL-CL01 (interval between dosing of 9 to 28 weeks), both ALT and AST increased. This off-treatment increase supports the utility of these biochemical parameters in the monitoring of the clinical effects of sebelipase alfa and highlights the requirement for continuous treatment. Re-initiation of treatment in Study LAL-CL04 produced a similar rapid decline in ALT and AST and the improvements were maintained after the transition from once weekly to once every other week dosing. Note that the transient increase in mean AST at Week 25 was due to an isolated increase in a single subject, which resolved 2 weeks later.

Figure C9.6: Mean Hepatic Transaminases Over Time (Studies LAL-CL01 and LAL-CL04)



Source: Data on File, CSR LAL-CL04
Note: All 1-week-post-infusion laboratory data are presented 1 week after the Week 24 visit. Subjects were allowed to schedule this additional visit at Week 25, Week 27, or Week 29.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; qw = once weekly; qow = once every other week

Approximately 1 week after the fourth infusion in Study LAL-CL01, all 6 (100%) subjects with abnormal Baseline ALT had levels normalise (Data on File, CSR LAL-CL01). Normalisation of transaminase levels continued during long-term treatment (through Week 104) in the extension study LAL-CL04. At that time, all 5 subjects with abnormal ALT levels at Baseline for the extension study had ALT levels normalise (Data on file, CSR LAL-CL04). Results were similar for AST.

Study LAL-CL03

Consistent with results in children and adults, serum transaminase levels improved in infants enrolled in Study LAL-CL03 with rapidly progressive disease. This is in contrast to what was observed in untreated patients in Study LAL-1-NH01, where, in general, worsening of mean ALT and AST levels from diagnosis to death was observed (Data on file, CSR LAL-1-NH01).

In infants, ALT levels decreased rapidly following initiation of treatment with sebelipase alfa (Data on file, CSR LAL-CL03). [redacted] (Data on file, CSR LAL-CL03).

Similar results were observed in infants for changes in AST (Data on file, CSR LAL-CL03).

Liver Fat Content and Liver Volume

Children and adults randomised to sebelipase alfa experienced a significantly greater decrease from Baseline in hepatic fat content than those on placebo; a greater decrease in liver volume also was observed in the sebelipase alfa group compared to placebo. In infants, hepatomegaly/liver volume was shown to be reduced.

Study LAL-CL02

The percent reduction in hepatic fat content from Baseline to the end of the double-blind treatment period as assessed by MEGE-MRI was significantly greater for sebelipase alfa treated subjects (32%) compared with those who received placebo (4%) ($p < 0.0001$) (Table C9.11), indicating that treatment with sebelipase alfa was effective in reducing hepatic fat content consistent with expected effects on accumulated lysosomal lipids in these subjects. Consistent with these results, the percent reduction from Baseline in liver volume based on MRI also was greater in the sebelipase alfa group (10%) compared with placebo (3%) ($p = 0.0068$) (Table C9.11).

Study LAL-CL04

Reduction in hepatic fat and liver volume also was observed during long-term treatment with sebelipase alfa in Study LAL-CL04. Although data are limited, mean liver fat content at Baseline in Study LAL-CL04 was 9.16% (n = 5) with a mean reduction in fat fraction of 37% (n = 4) at Week 52 and 39% at Week 104 (n = 2). Mean Baseline liver volume was 1.05 multiples of normal (MN) (n = 8) with mean absolute decreases from Baseline of 0.10 (n = 7) and 0.18 (n = 5) at Weeks 52 and

104 respectively (Data on file, CSR LAL-CL04). Another useful PD metric confirming depletion of hepatic lipid accumulation is the degree of lipid mobilisation following infusion of sebelipase alfa. In contrast to the frequent increases in serum lipids above Baseline levels seen with initiation of dosing in Study LAL-CL04, increases in LDL-c above the Study LAL-CL04 Baseline were only seen in 1 similarly timed LDL-c sample taken after Week 24, and none of the subjects showed an increase in triglycerides > 50 mg/dL above the Study LAL-CL04 Baseline at this time point suggesting that much of the pathological accumulation of lipid had been successfully mobilised by this time point (Data on file, CSR LAL-CL04,).

Study LAL-CL03

Liver fat content was not assessed in infants in Study LAL-CL03 but liver volume was assessed by ultrasound and/or MRI (Data on file, CSR LAL-CL03). [redacted] (Data on file, CSR LAL-CL03).

Liver Histopathology

LAL-CL02

Analysis of the proportion of subjects with improvement versus worsening in microvesicular steatosis score suggested a potential favourable effect of sebelipase alfa on this parameter, although the difference versus placebo was not statistically significant. However, paired biopsies (Baseline and 20 weeks) were available in only a limited number of subjects and methodological issues had the potential to confound the interpretation of the biopsy results.

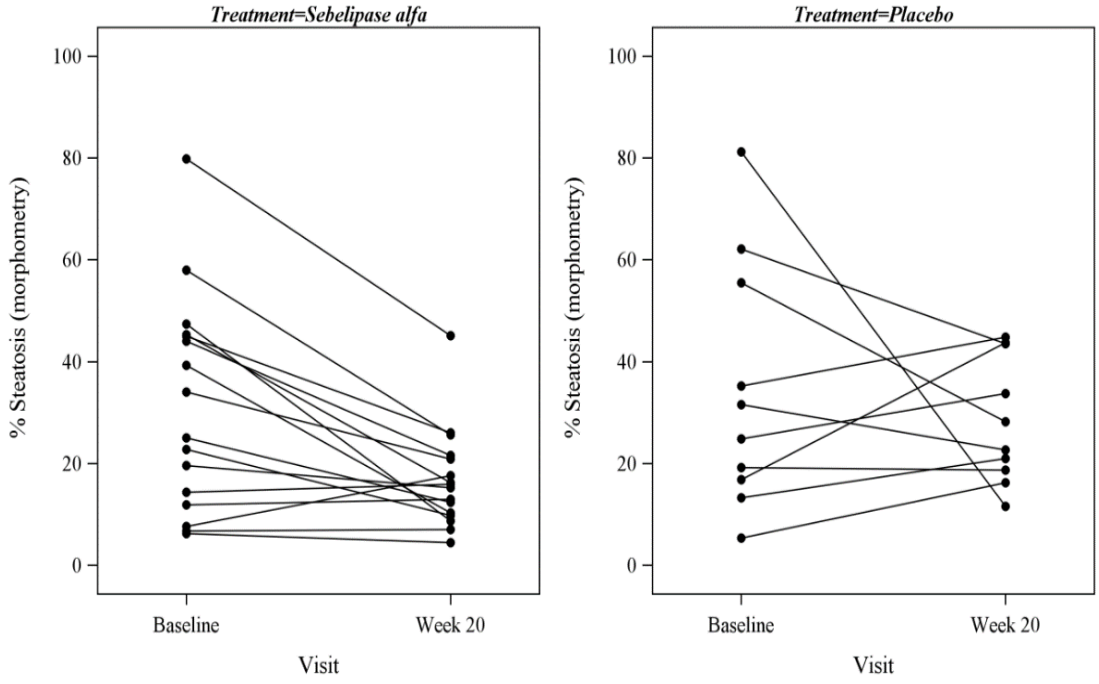
Baseline biopsies for evaluation of liver histopathology were obtained in 32 subjects in Study LAL-CL02; paired biopsies, including Baseline and on-treatment, were available in 27. Results for Baseline and the last time point in the double-blind treatment were assessed centrally by a blinded pathologist for these 27 subjects, including 17 in the sebelipase alfa group and 10 in the placebo group; 1 subject in the sebelipase alfa group was excluded from the analysis since the biopsy was performed after entry into the open-label portion of the study.

Improvement in liver histopathology (defined as a ≥ 5% decrease in hepatic steatosis score, as assessed by morphometry of H&E sections) from Baseline to the last time point in the double-blind period, as determined by central blinded read, was reported in a greater proportion of subjects in the sebelipase alfa group than in the placebo

group (10 of 16 subjects; 63% vs. 4 of 10 subjects; 40%, respectively; p = 0.4216) (Table C9.11).

In 15 (94%) of 16 subjects in the sebelipase alfa group, no change or an improvement from Baseline was reported in liver histopathology compared with 5 (50%) of 10 subjects in the placebo group (Figure C9.7) (Data on file, CSR LAL-CL02). In contrast, worsening from Baseline in liver histopathology was reported in a greater proportion of subjects in the placebo group (5 of 10 subjects; 50%) than in the sebelipase alfa group (1 of 16 subjects; 6%), [redacted]

Figure C9.7: Change from Baseline to the Last Time Point in the Double-blind Period in Morphometry Scores (Percent Steatosis), by Subject and Treatment Group



Source: Burton, 2015a

LAL-CL04/03

In Study LAL-CL04, pathology reports of post-treatment liver biopsies as well as historical pre-treatment biopsies were available from 2 subjects (Data on file, CSR LAL-CL04). In these cases, pathology reports suggested that histopathological improvements were observed following extended treatment with sebelipase alfa in steatosis and fibrosis, although biopsies were not evaluated in a central laboratory. In

1 of these cases, the pathologist's comments describe a reduction in steatosis based on visual assessment from ~80% to 20-30%, accompanied by an apparently significant improvement in fibrosis. However, note that the validity of percentage fat estimate by visual assessment described in local reports has not been established.

No liver biopsies were obtained in infants enrolled in Study LAL-CL03.

Evaluation of Improvement in Dyslipidaemia

Sebelipase alfa was significantly more effective than placebo in reducing LDL-c, non-HDL-c, and triglyceride levels and increasing HDL-c in children and adults and was also shown to impact dyslipidaemia favourably in infants. The effect was consistently maintained over long-term treatment.

It was hypothesized that initial dosing with sebelipase alfa might lead to breakdown and mobilisation of accumulated lysosomal cholesteryl ester and triglycerides with release of free cholesterol, free fatty acids, and glycerol. It was anticipated that in the short-term, these lipid breakdown products would be re-packaged and secreted from the liver before seeing improvements in LAL Deficiency-related dyslipidaemia once the pathological lipid accumulations had been fully mobilized. In children and adults with LAL Deficiency, this mobilisation was observed and was found to be transient, after which lipid parameters associated with dyslipidaemia improved from Baseline.

Study LAL-CL02

In Study LAL-CL02, following a transient increase in serum lipids similar to what had been observed in Studies LAL-CL01/LAL-CL04 (see below), treatment with sebelipase alfa led to a statistically significant greater mean percent change in LDL-c levels from Baseline to the end of the double-blind treatment period (-28%) compared with subjects who received placebo (-6%) ($p < 0.0001$) (Table C9.11; Figure C9.8). Results for non-HDL-c (-28% versus -7%, respectively; $p < 0.0001$) and triglycerides (-25% versus -11%, respectively; $p = 0.0375$) were similar. The marked decreases in LDL-c were associated with statistically significant increases in HDL-c levels in favour of sebelipase alfa (20% versus -0.3%; $p < 0.0001$) (Table C9.11).

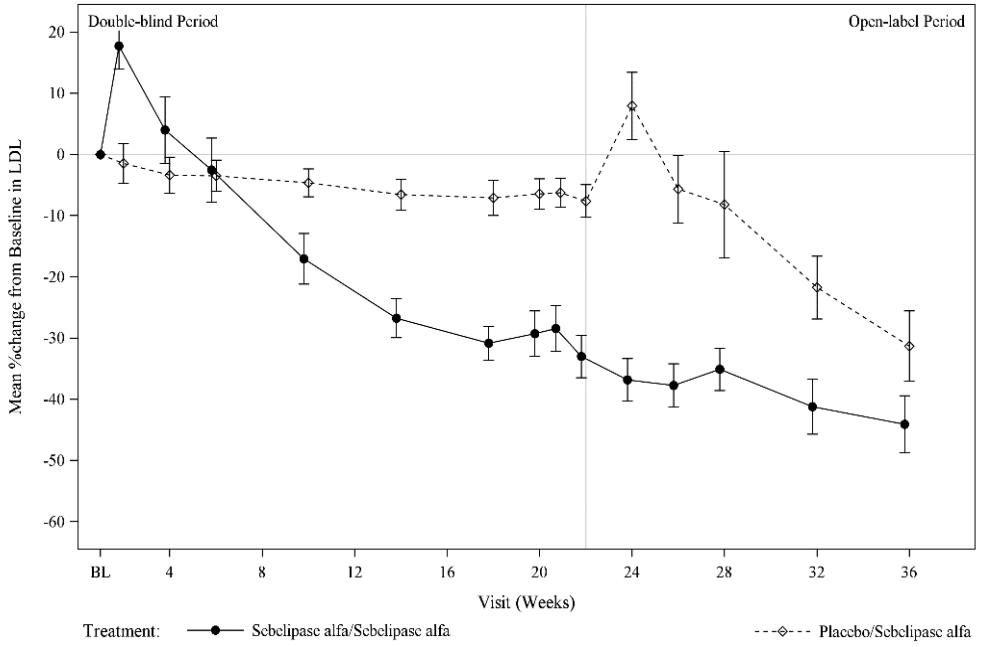
[redacted]

Following transition of placebo-treated subjects to open-label treatment with sebelipase alfa in the open-label extension (Figure C9.8), a similar transient increase with subsequent rapid decline in LDL-c was observed, as was an improvement in

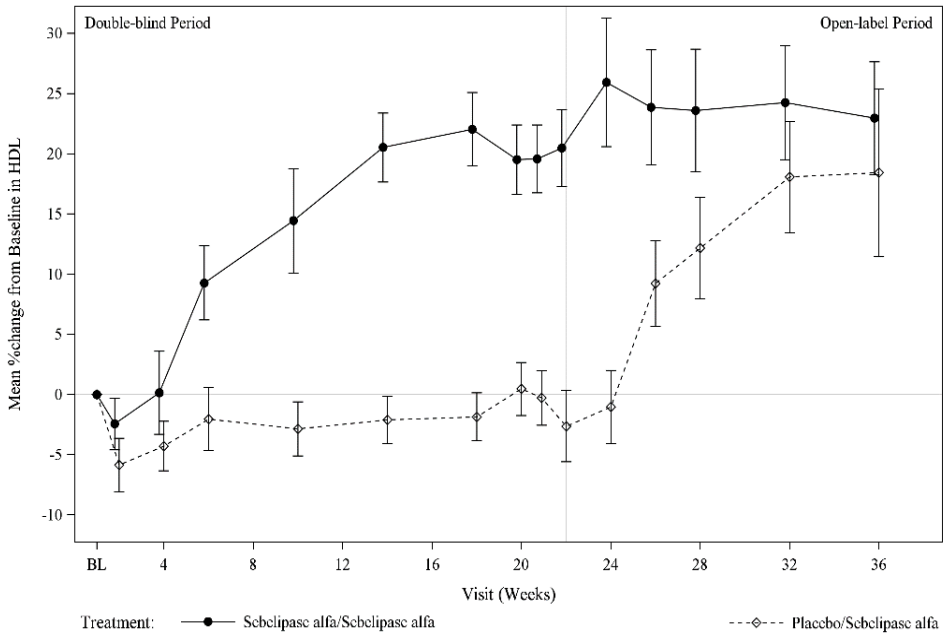
HDL-c. Importantly among the subjects randomised to sebelipase alfa, further reductions in LDL-c were observed during the open-label extension.

Figure C9.8: Mean Percent Change from Baseline in LDL-c and HDL-c over Time (Study LAL-CL02, FAS, Double-blind Period and EAS, Open-label Period)

LDL-c



HDL-c



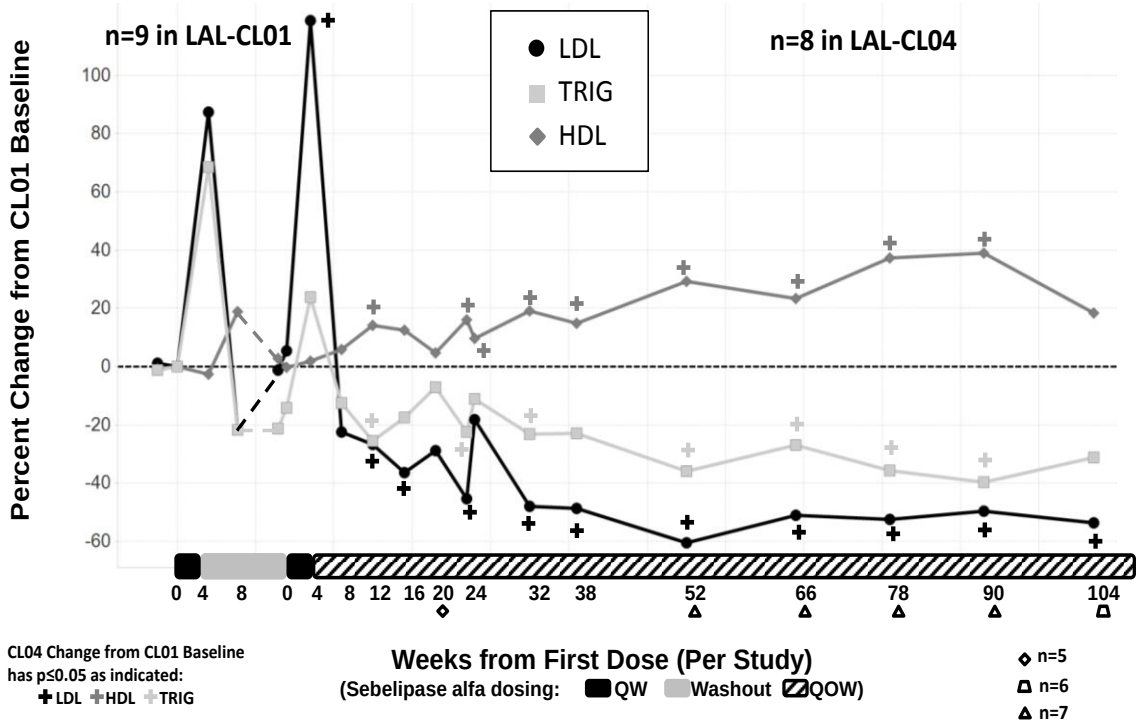
Source: Data on File, CSR LAL-CL02
Notes: LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol.
Sebelipase alfa/sebelipase alfa: subjects randomized to sebelipase alfa; Placebo/sebelipase alfa: subjects randomized to placebo who were crossed over to sebelipase alfa after the 20-week double-blind treatment period.
Visits for a treatment sequence are presented if ≥5 subjects have data available. As the Baseline value in this figure (Week 0) is 0%, the initial increase in LDL-c is demonstrated by the mean percent increase from Baseline of 18% in the sebelipase alfa group at Week 2 and of 16% in the placebo/sebelipase alfa group at Week 24.

Studies LAL-CL01/LAL-CL04

In adults in Study LAL-CL01, more substantial increases were noted for cholesterol and triglycerides during the initial 4-week treatment period (Figure C9.9). This was again observed following the initial 4 weekly infusions in Study LAL-CL04 (Data on file, CSR LAL-CL04) as subjects who entered the extension study had been off treatment with sebelipase alfa ranging from 9 to 28 weeks. These increases were likely higher in Studies LAL-CL01/LAL-CL04 than those observed in Study LAL-CL02 due either to the more frequent dosing interval or more frequent assessments conducted in the earlier studies. By Week 104, all 7 subjects in Study LAL-CL04 with data available at the time of the data cut-off showed decreases from their original Study LAL-CL01 Baseline values in LDL-c and most had increases in HDL-c and decreases in triglycerides (Data on file, CSR LAL-CL04).

Of note, as was observed with transaminase levels, when subjects went off treatment at the end of Study LAL-CL01 (interval between dosing of 9 to 28 weeks), LDL-c levels increased and HDL-c levels decreased from the lowest and highest levels, respectively, within 4 weeks after the last dose of sebelipase alfa in Study LAL-CL01 during the period between studies. These observations support the utility of these biochemical parameters in the monitoring of the clinical effects of sebelipase alfa and highlight the requirement for continuous treatment with sebelipase alfa.

Figure C9.9: Mean Percent Change from Baseline in Serum Lipids (Studies LAL-CL01 and LAL-CL04)



Source: Data on file, CSR LAL-CL04
HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; qw = once weekly; qow = once every other week; TRIG = triglycerides
Note: All 1-week-post-infusion laboratory data are presented 1 week after the Week 24 visit. Subjects were allowed to schedule this additional visit at Week 25, Week 27, or Week 29.

Study LAL-CL03

In the infants enrolled in Study LAL-CL03, lipid fluctuations were expected due to several factors, including dietary factors, blood samples that were not typically obtained in the fasting state, and changes in nutritional supplementation, most notably changes in total parenteral nutrition, which is known to cause elevations in triglycerides. In addition, interpretation of the impact of LAL enzyme deficiency on serum lipids in infants is complicated by the potential impact of intercurrent malabsorption resulting in malnutrition and inanition.

Even with all of these potential confounding factors, LDL-c levels were shown to [redacted]

Evaluation of Improvement in Growth and Weight Gain

Sebelipase alfa has been shown to improve growth in infants with LAL Deficiency. Onset of the favourable effects on weight was typically rapid, occurring within 4 weeks of initiation of therapy.

LAL-CL03

Growth deceleration from birth to the Baseline assessment in Study LAL-CL03 was observed for all [redacted]; at the time of entry into the study, [redacted](Data on file, CSR LAL-CL03). Marked and rapid improvements in WFA percentiles following initiation of sebelipase alfa treatment were observed [redacted] (Data on file, CSR LAL-CL03).

[redacted] (Data on file, CSR LAL-CL03).

These data contrast with what was observed in infants from the natural history study. In that study, rapid and marked decreases in WFA percentiles were observed over time in a majority of patients. Relative to the first chart record, WFA percentiles [redacted]

[redacted] (Data on file, CSR LAL-1-NH01).

LAL-CL02/LAL-CL01/LAL-CL04

Improvement in growth was not a secondary endpoint in the pivotal study in children and adults (LAL-CL02). A longer duration of follow-up is likely required to determine any effect of treatment on growth in children (≤ 18 years of age).

As studies LAL-CL01 and LAL-CL04 were conducted in adults, evaluations of growth and weight gain were not conducted.

Other Efficacy Measures

In addition to the above efficacy outcomes, the following evaluations also demonstrate the clinical benefits of treatment with sebelipase alfa (Data on file, CSR LAL-CL03):

- Improvements in haematological parameters were observed in infants with rapidly progressive disease:

  [redacted]

- Reduction in serum markers of inflammation, including ferritin and high sensitivity C-reactive protein (hs-CRP), were observed during treatment with sebelipase alfa:

  [redacted]

[redacted]

[redacted]

Quality of Life

A description and results of the HRQL measures can be found in Section 10.1.3.

Evaluation of the Efficacy of Sebelipase Alfa in Subgroups

Given the marked differences between LAL Deficiency presenting in infants compared with children and adults, subgroup efficacy analyses focused on data from children and adults. Primary and key secondary efficacy analyses were conducted on data from Study LAL-CL02 for subgroups based on age, gender, and race, Baseline indicators of liver function, Baseline serum lipids, and use of LLMs. The effects of genotype and the presence of cirrhosis on liver biopsy were also investigated.

Efficacy by Demographic and Baseline Characteristics

Analyses of the primary endpoint of ALT normalisation and secondary efficacy endpoints in LAL-CL02 demonstrate the effectiveness of sebelipase alfa across subgroups based on demographic and Baseline characteristics.

There were no clinically meaningful differences noted in the effectiveness of sebelipase alfa based on gender, race, ethnicity, or genetic mutation category. Analyses of the primary and secondary efficacy endpoints by age at randomisation demonstrate the effectiveness of sebelipase alfa relative to placebo in all age categories, with, in general, the effect of treatment being greater in subjects aged ≥ 12 years compared to those < 12 years. Clinical studies did not include subjects aged 65 years and older. It is not known whether they respond differently than younger subjects.

Although some differences were noted across subgroups by Baseline disease characteristic, review of the efficacy data in each of the subgroups, including ALT level, liver volume, presence of cirrhosis, LDL-c level, or use of LLMs, demonstrated

that treatment with sebelipase alfa was effective in improving a broad range of disease-related abnormalities across subgroups.

Efficacy by Dose and Regimen

Every other week dosing of sebelipase alfa is sufficient for a broad population but weekly dosing is required for patients who present with rapidly progressive disease during infancy.

The recommended dose of sebelipase alfa is 1 mg/kg administered as an IV infusion once every other week for children and adults. In patients presenting with rapidly progressive disease during infancy, the recommended starting dose is 1 mg/kg administered as an IV infusion once weekly. In clinical studies, subjects who presented with rapidly progressive disease in infancy were dose escalated to 3 mg/kg once weekly.

A discussion of the effect of dose and regimen on the efficacy of sebelipase alfa is provided below.

Effects of Dose and Regimen on Efficacy in Infants

In Study LAL-CL03, infants received sebelipase alfa at 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. Dose adjustment to 3 mg/kg once weekly based on clinical response occurred [redacted]

A formal analysis of dose-response relationship was not performed on the data from infants in Study LAL-CL03 as all but 1 subject was allocated to the same starting dose of 0.35 mg/kg once weekly, and subjects receiving more than 4 infusions of sebelipase alfa were sequentially dose escalated to 1 mg/kg and eventually 3 mg/kg. [redacted]

[redacted]

[redacted]

Based on these data a starting dose of 1 mg/kg sebelipase alfa administered once weekly is recommended in infants presenting with rapidly progressive LAL Deficiency with further escalation to 3 mg/kg once weekly as needed based on persistence of abnormalities associated with the disease.

Effects of Dose and Regimen on Efficacy in Children and Adults

In Study LAL-CL01, all 3 doses (0.35, 1, and 3 mg/kg) of sebelipase alfa administered once weekly for 4 weeks were shown to be biologically active, as evidenced by decreases in ALT and AST and initial increases in serum lipids followed by improvement in dyslipidaemia. The improvements in liver biochemical parameters and serum lipids were observed within 2 and 4 weeks, respectively, and were reversible following discontinuation of sebelipase alfa therapy (Figure C9.6 and C9.9). Following re-initiation of once weekly dosing in Study LAL-CL04, the improvements in serum biochemical markers observed in Study LAL-CL01 were replicated and were maintained following the switch from a once weekly to once every other week dosing regimen at doses of 1 and 3 mg/kg every other week and through to 104 weeks, providing the first long-term assessment of efficacy of sebelipase alfa.

In children and adults in Study LAL-CL02, sebelipase alfa was administered at 1 mg/kg every other week throughout treatment with no escalations to higher doses reported prior to the data cut-off for analysis. The 1 mg/kg every other week sebelipase alfa dose regimen was more effective than placebo in improving a broad range of disease-related abnormalities, including normalisation of serum transaminases, improvement in dyslipidaemia, and reduction in liver fat content. During the open-label treatment period, these improvements were maintained in the subjects treated with sebelipase alfa during the double-blind period, and a similar pattern of response was observed in subjects switched from placebo to 1 mg/kg qow sebelipase.

Based on these data, the 1 mg/kg every other week dosing regimen is recommended for children and adults with LAL Deficiency.

Efficacy by Anti-Drug Antibody Status

The overall rate of immunogenicity in studies with sebelipase alfa appears low relative to the experience with many other ERTs, although a higher incidence has been observed in infants than children and adults. Of the few subjects who did show apparent seroconversion, evidence of tolerisation has been observed, although this remains to be confirmed. There is no evidence of an impact of anti-drug antibody (ADA) status on efficacy parameters, although some reduction in efficacy was observed in 1 infant associated with the development of ADAs.

In Study LAL-CL03, 4 subjects were ADA positive during at least 1 assessment,. Most subjects who developed ADAs did so within the first 2 months of exposure (Data on file, CSR LAL-CL03).

In Study LAL-CL02, 35 of the 36 subjects who received sebelipase alfa in the double-blind period were evaluated for ADAs. Five (14%) subjects had at least 1 positive ADA test. Those subjects who developed ADAs did so within the first 3 months of exposure (Data on file, CSR LAL-CL02). None of the 5 subjects developed neutralizing antibodies at any time,

In Study LAL-CL01, all samples from the 9 subjects enrolled were negative for ADAs as were all samples from 7 of 8 subjects in Study LAL-CL04. [redacted]

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

The primary population for efficacy analyses in the randomised controlled study LAL-CL02, was the Full Analysis Set (FAS) which comprised randomised subjects who received at least 1 dose of sebelipase alfa or placebo. The FAS was a modified intention-to-treat (ITT) dataset. All 66 (100%) subjects enrolled, 36 in the sebelipase alfa group and 30 in the placebo group were included in the FAS.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The primary studies used to evaluate the safety of treatment with sebelipase alfa are the pivotal studies conducted in infants (LAL-CL03) and children and adults (LAL-CL02) and the Phase 1/2 study LAL-CL01 and its extension LAL-CL04. A tabular summary of these studies is provided in Table C9.3; critical study design features, including duration of therapy, dosing, and choice of control groups, are summarised in Section 9.5. In accordance with the requirements for an integrated safety analysis, a pooled safety assessment was conducted on the data from these 4 studies to determine if any safety signals would be revealed that were not otherwise evident in the individual studies.

The results are presented by study. A pooled analysis was undertaken (Pooled Safety Set), however given the differences in study design, the small number of subjects in pre-specified categories such as infants enrolled in Study LAL-CL03, and the differences in dose and regimen across the population, the most relevant interpretation of safety is available from the individual study results and in particular, from the randomised, placebo-controlled study in children and adults, Study LAL-CL02, which enrolled the majority of subjects (n = 66). This placebo-controlled study provides the most robust approach to assessing the relationship of administration of sebelipase alfa to treatment-emergent AEs (TEAEs) and other safety findings, including changes in laboratory parameters and vital signs.

In addition to the data from the 4 primary studies, safety data specific to deaths, serious adverse events (SAEs), and moderate or severe infusion-associated reaction (IARs) from Study LAL-CL06, Study LAL-CL08, and compassionate use subjects are summarised.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

Please see Section 9.7.3 for discussion of important adverse events. Common adverse event and common treatment-related adverse events observed in clinical studies LAL-CL03 and LAL-CL02 is shown in Tables C9.12 to C9.15 below.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Extent of Exposure

Among the 84 subjects included in the Pooled Safety Set, the majority (59 of 84, 70%) had received sebelipase alfa for ≥ 12 weeks at the time of the data cut-off, with 42% (35 of 84) having received treatment for ≥ 26 weeks (~6 months). A total of 15 subjects (18%) had received sebelipase alfa for ≥ 52 weeks (~1 year) with 9 (11%) having received ≥ 104 weeks (~2 years) of treatment as of the data cut-off.

Across these studies, sebelipase alfa was administered, weekly or every other week, as doses ranging from 0.35 mg/kg up to 5 mg/kg. Overall 1712 infusions of sebelipase alfa were administered in the 84 subjects, including 1250 infusions to 75 children and adults in Studies LAL-CL01/ LAL-CL04 and Study LAL-CL02 and 462 infusions to 9 infants in Study LAL-CL03. In children and adults, the majority of infusions (1009 of 1250, 81%), including all in the pivotal study LAL-CL02, were administered at the 1 mg/kg every other week dosing regimen. Among infants in Study LAL-CL03, most infusions (278 of 462, 60%) were administered at 3 mg/kg weekly with 141 infusions (31%) given at 1 mg/kg weekly. Exposure at the 5 mg/kg weekly regimen was limited to 8 infusions in 1 infant.

A small cohort of infants have received treatment with sebelipase alfa at a dose of 5mg/kg once weekly in clinical trials. This dose is not approved for use in the EU and data are evolving on this dosing strategy. Currently 3 children are receiving this dose in the UK clinical trial centre in Manchester.

Common Adverse Events

Across the clinical development programme in infants, children, and adults, a favourable safety profile has emerged for sebelipase alfa. The most common types of AEs were gastrointestinal disturbances, headache, pyrexia/body temperature increases and upper respiratory signs and symptoms. The majority of AEs were mild or moderate in severity and were assessed as unrelated to treatment with sebelipase alfa.

Common Adverse Events

Common Adverse Events in Infants

[redacted] enrolled in Study LAL-CL03 reported at least 1 TEAE. Table 9.12 presents the most commonly reported TEAEs during Study LAL-CL03, i.e., those events reported in 3 or more subjects. This cut point was chosen based on the small sample size for this study (N=9).

The most commonly reported TEAEs in Study LAL-CL03 were vomiting and diarrhoea (each 6 subjects, 67%); pyrexia/body temperature increased and rhinitis (each 5 subjects, 56%); anaemia (4 subjects, 44%); and cough, [redacted], nasopharyngitis, and urticaria (each 3 subjects, 33%).

[redacted] (Data on file, CSR LAL-CL03). [redacted]

Table C9.12: Summary of Treatment-emergent Adverse Events, Regardless of Causality, Occurring in 3 or More Subjects (Study LAL-CL03, Safety Population)

MedDRA System Organ Class Preferred Term	Subjects (N=9) n (%)
[redacted]	[redacted]
Gastrointestinal disorders	
Vomiting	6 (67)
Diarrhoea	6 (67)
[redacted] Urticaria	[redacted] 3 (33)
[redacted] Rhinitis	5 (56)
[redacted] Nasopharyngitis	[redacted] 3 (33)
[redacted]	[redacted]
[redacted] Anaemia	4 (44)
[redacted] Cough	3 (33)

Source: Data on file, CSR LAL-CL03
a Combined preferred terms; subjects who reported more than 1 event coded to these terms are counted only once.

Common Adverse Events in Children and Adults

In Study LAL-CL02, 86% (31 of 36) of subjects in the sebelipase alfa group and 93% (28 of 30) of subjects in the placebo group reported at least 1 TEAE during the double-blind period. The most common (≥10% incidence) TEAEs reported during the double-blind period in the sebelipase alfa group with corresponding incidence in the placebo group were headache (28% and 20%, respectively), pyrexia/body temperature increased (25% and 23%, respectively), upper respiratory infection (17% and 20%, respectively), diarrhoea (17% in each group), oropharyngeal pain (17% and 3%, respectively), epistaxis (11% and 20%, respectively), and nasopharyngitis (11% and 10%, respectively) (Table C9.13).

Headache and oropharyngeal pain were the only TEAEs reported at a higher (>5% difference) incidence in the sebelipase alfa group compared with placebo. Of note, all but 1 case of oropharyngeal pain occurred in subjects in the northern hemisphere between the months October and April. Sore throat is recognised commonly in children. When data from the open-label period of Study LAL-CL02 were considered,

the safety profile of sebelipase alfa was consistent with that seen during the double-blind period (Data on file, CSR LAL-CL02).

In Studies LAL-CL01/LAL-CL04 conducted in adults, a similar safety profile was observed as was seen in Study LAL-CL02, although in general the incidence of individual events was higher and pain-related events were reported more frequently. During this study, the most commonly reported TEAEs across the 9 subjects were diarrhoea, abdominal pain, and nasopharyngitis (each 5 subjects, 56%), nausea (4 subjects, 44%), and ear pain, upper abdominal pain, headache, back pain, and myalgia (each 3 subjects, 33%).

Table C9.13: Summary of Treatment-emergent Adverse Events, Regardless of Causality, Occurring in 3 or More Sebelipase Alfa-treated Subjects, by Treatment Group (Study LAL-CL02, FAS, Double-blind Treatment Period)

MedDRA System Organ Class Preferred Term	**Sebelipase Alfa (N = 36) n (%)**	**Placebo (N = 30) n (%)**
Any treatment-emergent adverse event	*31 (86)*	*28 (93)*
Nervous system disorders		
Headache	10 (28)	6 (20)
General disorders and administration site conditions		
Pyrexia/Body temperature increased[a]	9 (25)	7 (23)
Asthenia	3 (8)	1 (3)
Gastrointestinal disorders		
Diarrhoea	6 (17)	5 (17)
Abdominal pain, including upper and lower[a]	4 (11)	4 (13)
Constipation	3 (8)	1 (3)
Nausea	3 (8)	2 (7)
Vomiting	3 (8)	3 (10)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	6 (17)	1 (3)
Epistaxis	4 (11)	6 (20)
Cough	3 (8)	3 (10)
Infections and infestations		
Upper respiratory tract infection	6 (17)	6 (20)
Nasopharyngitis	4 (11)	3 (10)

Source: Data on file, CSR LAL-CL02

a Combined preferred terms; subjects who reported more than 1 event coded to these terms are counted only once.

[redacted]

[redacted] (Table C9.14).

Table C9.14: Summary of Treatment-related Adverse Events (Study LAL-CL03, Safety Population)

MedDRA System Organ Class Preferred Term	Subjects n (%)
[redacted]	[redacted]

Source: Data on File, Summary of Clinical Safety

[a] Based on the Sponsor's medical review, there is a lack of evidence to support that the TEAEs of extravasation and infusion site oedema were related to sebelipase alfa. Although the terms were assessed as related to study drug by the Investigator, Sponsor review determined that study drug effusion and subsequent local oedema, both reported in a single subject, were related to central line needle placement as confirmed by testing of venous access.

Additional TEAEs reported in infants that were not assessed as treatment-related by the Investigators [redacted]

Common Treatment-related Adverse Events in Children and Adults

In Study LAL-CL02, treatment-related AEs were reported in 5 subjects (14%) in the sebelipase alfa group and 6 subjects (20%) in the placebo group during the double-blind period (Table C9.15). All treatment-related TEAEs (by preferred term) in the sebelipase alfa group were reported in only 1 subject.

Table C9.15: Summary of Treatment-related Adverse Events (Study LAL-CL02, FAS, Double-blind Treatment Period)

MedDRA System Organ Class Preferred Term	Sebelipase Alfa (N = 36) n (%)	Placebo (N = 30) n (%)
Any treatment-related adverse event	*5 (14)*	*6 (20)*
General disorders and administration site conditions		
Chest discomfort	1 (3)	0
Oedema	1 (3)	0
Pyrexia	0	2 (7)
Fatigue	0	1 (3)
Gastrointestinal disorders		
Nausea	1 (3)	1 (3)
Abdominal distension	1 (3)	0
Abdominal pain	0	1 (3)
Diarrhoea	0	1 (3)
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea	1 (3)	1 (3)
Laryngeal oedema	1 (3)	0
Psychiatric disorders		
Anxiety	1 (3)	0
Insomnia	1 (3)	0
Injury, poisoning and procedural complications		
Infusion related reaction	1 (3)	0
Investigations		
Body temperature increased	1 (3)	1 (3)
Weight increased	0	1 (3)
Reproductive system and breast disorders		
Menorrhagia	1 (3)	0
Skin and subcutaneous tissue disorders		
Rash	1 (3)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	0	1 (3)

Source: Data on file, CSR LAL-CL02

The only treatment-related AEs reported during open-label extension of Study LAL-CL02 that were not reported during the double-blind period were infusion site induration, urinary tract infection, dizziness, pruritus, rash papular, and urticaria, each reported in 1 subject (Data on file, CSR LAL-CL02).

Other treatment-related AEs reported in Studies LAL-CL01/LAL-CL04 included abdominal pain (3 subjects, 33%) and fatigue, hypercholesterolemia, hypertriglyceridemia, and hyperemia (each 1 subject, 11%).

Additional TEAEs reported in children and adults that were not assessed as treatment-related by the Investigators [redacted]

Deaths and Other Serious Adverse Events

As described in Section 9.3, treatment with sebelipase alfa conferred a survival advantage for infants with failure to thrive and rapidly progressive LAL Deficiency relative to an historical control group of untreated subjects. During double-blind treatment in Study LAL-CL02, the incidence of SAEs was low and similar in the sebelipase alfa and placebo arms. In general, the SAEs reported across the clinical programme were related to the subjects' underlying conditions or concurrent procedures.

Deaths

Overall, 3 deaths were reported in the sebelipase alfa clinical programme as of the data cut-off across the 4 primary studies evaluating safety; all subjects who died were enrolled in Study LAL-CL03. All fatal events were assessed as unrelated to sebelipase alfa treatment by the Investigators. All died after receiving 4 or fewer doses of sebelipase alfa with a median age at death of 2.9 years. [redacted]

Since the conduct of the integrated analyses through the cut-off date for late-breaking safety information (08 Sep 2014), [redacted]

Serious Adverse Events

Serious AEs were reported in 12 (14.3%) of the 84 subjects in the Pooled Safety Set. Not unexpectedly, SAEs were more frequent among infants in Study LAL-CL03 with the most rapidly progressive form of LAL Deficiency (8 of 9 subjects, 89%) and were

relatively infrequent among children and adults (4 of 75 subjects, 5%). The most commonly reported types of SAEs were infections (5 of 84 subjects, 6%). These types of events, primarily catheter site or device-related infections, which were reported in 4 (44%) of the 9 infants, occurred early in treatment (within 8 months) likely due to the compromised state of these infants at study entry. All 4 of these subjects remained on treatment with no further reports of catheter/line infections. Only 1 subject in Study LAL-CL02 reported a serious infection (gastroenteritis). The only other SAE reported in more than 1 subject in the Pooled Safety Set was pyrexia, reported in 2 subjects in Study LAL-CL03.

The majority of SAEs were assessed by the Investigator as unrelated to study treatment; 2 of 84 subjects in the Pooled Safety set reported treatment-related SAEs, which were also considered potential hypersensitivity reactions, including 1 subject each in Studies LAL-CL02 and LAL-CL03; in addition, 2 subjects in Study LAL-CL08 had treatment-related SAEs which were also considered potential hypersensitivity reactions.

Other Significant Adverse Events

Discontinuations from treatment with sebelipase alfa and dose modifications due to adverse events were uncommon. The majority of adverse events were mild to moderate in severity.

Adverse Events Leading to Treatment Discontinuation or Dose Modification

One subject in Study LAL-CL02 was discontinued study drug during the double-blind period after experiencing IARs after the first and second infusions of sebelipase alfa; the event was reported as a treatment-related SAE. This patient has now restarted treatment with sebelipase alfa.

[redacted]

One subject in Study LAL-CL04 reported severe AEs that were classified as IARs and treatment was interrupted at Week 40 (1 mg/kg every other week). After an independent Safety Committee review concluded the subject did not present with classical symptoms of laryngeal edema, the subject was successfully rechallenged with sebelipase alfa, restarting at Week 90 at a reduced infusion rate and dose of 0.35 mg/kg including pretreatment (antihistamine and antipyretic). The dose was re-escalated to 1 mg/kg every other week at the original infusion rate (50 mL/hr) 8 weeks later. As of Week 116, the subject continues on study treatment and is no longer receiving premedication.

Adverse Events of Severe Intensity

The majority of TEAEs reported during the sebelipase alfa studies were mild to moderate in severity. Across all 84 subjects in the Pooled Analysis Set, the most commonly reported severe TEAEs were diarrhoea, anaemia and dyspnoea each reported in 2 (2%) of the 84 subjects. All other TEAEs of severe intensity were reported in 1 subject.

Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions have occurred during treatment with sebelipase alfa. The reactions were generally mild to moderate in severity. These reactions were more common in infants and have been managed acutely and on an ongoing basis by decreasing the infusion rate, temporarily stopping the infusion, or administering antihistamines and/or antipyretics.

In the sebelipase alfa clinical development programme, IARs were considered events of special interest due to historical experience with other therapeutic protein products, including ERTs. A total of 16 (19%) of the 84 subjects who received sebelipase alfa during Studies LAL-CL02, LAL-CL03 and LAL-CL01/LAL-CL04, including 5 (56%) of 9 infants and 11 (15%) of 75 children and adults, were reported to have experienced signs and symptoms either consistent with or potentially related to a hypersensitivity reaction. The majority of these hypersensitivity-type events were mild to moderate in severity and assessed as treatment-related.

The majority of these possible hypersensitivity reactions occurred during or within 4 hours of completion of the infusion and were reported by the Investigator as an IAR. Where action was required, the management of these reactions included temporary interruption of the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. No subject permanently discontinued sebelipase alfa treatment due to a hypersensitivity reaction.

Review of the AE data during the double-blind period of Study LAL-CL02, showed that

[redacted]

Further Observations Related to Safety

As with all therapeutic proteins, there is potential for the development of immunogenicity. Overall,

[redacted]

[redacted]

No safety signals were observed based on a thorough evaluation of clinical laboratory data. A thorough review of haematology, renal function, liver function, and electrolytes showed no deleterious effect of sebelipase alfa on any of these parameters. Initial treatment with sebelipase alfa is associated with a transient and reversible increase in blood cholesterol and triglycerides consistent with mobilisation of accumulated lysosomal lipid from the tissues as a result of correcting the pathophysiology of reduced lysosomal acid lipase activity. The increase in lipids was not associated with any clinical sequelae.

A thorough review of vital signs parameters, including systolic and diastolic blood pressure, heart rate, and respiratory rate, showed no consistent or clinically meaningful effect of sebelipase alfa on any of these parameters. A thorough review of ECG parameters over time on treatment across studies showed no clinically relevant effect of sebelipase alfa.

In general, the incidence of TEAEs, including SAEs, were relatively constant or decreased over time on treatment with sebelipase alfa; there was no evidence for cumulative toxicity over long term treatment.

There were no clinically meaningful differences noted in the safety profile of sebelipase alfa based on gender, race, or use of LLMs; differences noted across age group were related to the population under study (i.e., infants with the rapidly progressive form of LAL Deficiency compared with children and adults with LAL Deficiency).

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

Due to differences in study methodology and patient demographics, a meta-analysis was not considered to be appropriate. LAL-CL03 is a single arm study in which infants were treated with once weekly doses of sebelipase alfa (0.35 mg/kg escalating to 1mg/kg or 3mg/kg) in contrast to LAL-CL02 which is a randomised study that investigated sebelipase alfa administered at a dose of 1mg/kg every other week in paediatric and adult patients compared to placebo. An indirect comparison was not appropriate or possible since there are no other therapies available to treat LAL Deficiency.

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

Interpretation of the evidence

The pivotal development strategy included two studies focused on developing evidence of safety and efficacy. The first (LAL-CL03) was based on demonstrating a survival benefit in infants with the most rapidly progressive presentation of this disease where a placebo-controlled study would not be clinically or ethically acceptable. This was coupled with the second (LAL-CL02), a randomised, double-blind, placebo-controlled study evaluating improvements in multiple clinically important disease-related abnormalities in children and adults where the rate of disease progression is more variable.

In LAL-CL03, 67% of infants (n=9) survived to at least 12 months of age and continue on sebelipase alfa. At the last data cut-off the age range of surviving infants was 1 to 3.5 years. Based on insights from the natural history study LAL-1-NH01, 12-month survival represents more than a 3-fold increase in life expectancy beyond the median age at death for all infants with LAL Deficiency included in this study (3.71 months, N = 35) and for infants with failure to thrive due to LAL Deficiency (3.46 months, n = 26) (Data on file, CSR LAL-1-NH01). Twelve-month survival also represents a significant

improvement in survival for infants who received HSCT or liver transplant (median age at death of 8.6 months, n = 10) and infants with early failure to thrive who did not receive transplant, none of whom survived beyond 12 months (median age at death of 3.0 months, n = 21). The survival results demonstrate the clinical benefit of treatment with sebelipase alfa in a group of critically ill subjects with LAL Deficiency at high risk of early mortality who currently have no treatment options.

Initiation of treatment with sebelipase alfa produced a rapid decline in ALT and AST levels in the majority of people treated in all sebelipase alfa studies regardless of their baseline levels. In the pivotal study in children and adults, a significantly higher proportion of subjects with abnormal serum transaminase levels at Baseline who received sebelipase alfa had normalisation compared with subjects who received placebo, consistent with a reduction in liver cell injury. Where assessed in these studies, reductions in markers of liver injury were associated with changes in other biochemical markers of improved liver function (e.g., GGT). Importantly, improvement in liver function parameters was observed across the disease spectrum and the improvement was maintained over long-term treatment. The almost immediate response to therapy following transition to active treatment for those randomised to placebo in Study LAL-CL02, coupled with the observation of rapid reversal of response in subjects who were off treatment with sebelipase alfa after Study LAL-CL01, followed by rapid response again on treatment on Study LAL-CL04, provides confidence that the effects are indeed due to the therapeutic intervention of enzyme replacement. Consistent with results in children and adults, serum transaminase levels improved in infants enrolled in Study LAL-CL03 with rapidly progressive disease. This is in contrast to what was observed in untreated patients in Study LAL-1-NH01, where, in general, worsening of mean ALT and AST levels from diagnosis to death was observed (Data on file, CSR LAL-1-NH01).

Consistent with the expectation that enzyme replacement with sebelipase alfa is addressing the underlying cause of LAL Deficiency, treatment was associated with substantial improvement in dyslipidaemia. In children and adults, significant reductions were observed in LDL-c, as well as non-HDL-c and triglycerides, with increases noted in HDL-c. These improvements in the lipid profile observed in children and adults would be anticipated to lead to a reduction in cardiovascular risk across the disease spectrum (see *Section 9.9.3*). The similar response to therapy following transition of subjects randomised to placebo to active treatment in Study LAL-CL02 provides further evidence that the effects are indeed due to the therapeutic intervention of enzyme replacement. Importantly, the treatment effect on LDL-c and HDL-c was not only maintained, but levels continued to improve during the open-label extension period in subjects who initially received sebelipase alfa during the double-blind period. These results are consistent with findings from Study LAL-CL04, where further time-dependent improvements were seen in LDL-c and HDL-c levels in addition to evidence of long-term sustainability of the effect of sebelipase alfa over a longer duration of treatment. In infants, although the data are

limited, improvements in dyslipidaemia were observed based on a reduction in triglycerides and increases in HDL-c.

ERT with sebelipase alfa reduces the accumulation of lipid in the liver as evidenced by reduced hepatic fat content compared with placebo. A concordant decrease was observed in liver volume in children and adults treated with sebelipase alfa that was not observed with placebo. Further, reductions in liver volume were noted in infants who received sebelipase alfa.

Although the treatment group difference for improvement in liver histopathology in Study LAL-CL02 was not statistically significant, the results were in favour of sebelipase alfa. Despite challenges in the analysis (*see Section 9.9.2*), review of the totality of the data, including the histopathology results and results based on MEGE-MRI for hepatic fat content, which assesses a larger volume of liver tissue relative to biopsy, support the conclusion that sebelipase alfa leads to a reduction in hepatic fat content.

The safety and tolerability profile of sebelipase alfa is considered to be favourable when administered at the recommended doses of 1 mg/kg every other week in children and adults and 1 to 3 mg/kg once weekly in infants. 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. Review of the safety data across subgroups based on demographic and Baseline characteristics did not reveal any group for which the risk of treatment would outweigh the benefits. The use of LLMs by subjects receiving sebelipase alfa does not appear to impact the safety profile of sebelipase alfa.

The safety profile in infants with the most rapidly progressive form of LAL Deficiency was consistent with their more severe underlying condition and comorbidities. Not unexpectedly, [redacted] and were relatively infrequent among children and adults (4 of 75 subjects, 5%). The most common types of SAEs were infections, primarily catheter site or device-related infections in infants; [redacted]

Infusion-associated reactions are relatively common for medicinal products that contain proteins and are administered parenterally. Overall, 19% of subjects treated with sebelipase alfa were determined to have experienced signs and symptoms that could be consistent with or related to hypersensitivity reactions. [redacted]The majority of the events occurred during or

within 4 hours of the completion of the infusion and were mild in severity. Although a small number of subjects experienced severe reactions, no subject has permanently discontinued treatment with sebelipase alfa due to a possible hypersensitivity reaction. Hypersensitivity reactions, including anaphylaxis, have been observed with other ERTs, including those used to treat Gaucher disease and mucopolysaccharidoses.

The proposed prescribing information for sebelipase alfa includes appropriate warnings and precautions for hypersensitivity reactions, including anaphylaxis, specifically to stop the infusion and initiate appropriate medical treatment if a severe reaction is observed. Management options provided in the proposed prescribing information are based on the successful management of these events during clinical studies and include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. Pretreatment with antipyretics and/or antihistamines may prevent subsequent reactions in those cases where symptomatic treatment is required.

As with all therapeutic proteins, there is potential for immunogenicity. Overall, a low proportion of children and adults (3 of 58, 5%) were positive for sebelipase alfa antibodies at more than 1 time point compared with 3 (42%) of 7 infants. There is no evidence of an impact of antibodies on efficacy parameters. Based on review of AEs for subjects who did and did not develop ADAs, no clear relationship between the presence of ADAs and IARs or the overall TEAE profile was apparent.

There were no safety signals for sebelipase alfa treatment based on review of haematology, clinical chemistry, vital signs, or ECG parameters.

The Number Needed to Treat (NNT) was calculated based on key endpoints in studies LAL-CL03 and LAL-CL02. For infants treated in study LAL-CL03 the calculated NNT was 1.5 to avoid death before 12 months (compared to the historical control). For patients treated in study LAL-CL02 the NNT to achieve ALT normalisation is 4.2 (compared to the placebo arm).

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths and Limitations

Size and breadth of the clinical dataset

The Alexion-sponsored studies comprise the largest dataset ever of patients with LAL Deficiency. The efficacy and safety of sebelipase alfa has been assessed across a wide range of endpoints relevant to outcomes in patients with LAL Deficiency. In two pivotal clinical studies (LAL-CL02 and LAL-CL03) treatment with sebelipase alfa resulted in significant improvements in serum transaminases, disease-related lipid abnormalities, and liver fat fraction in children and adults and improvements in

survival and growth in infants. These marked improvements in transaminases and other hepatic disease markers reduce the risk of progression to fibrosis, cirrhosis, liver transplant, and death.

The clinical development programme for sebelipase alfa was designed to provide evidence of safety and efficacy across the full spectrum of patients with LAL Deficiency. In Study LAL-CL02, a broad population of paediatric and adult subjects with LAL Deficiency was eligible (≥4 years of age). A critical component of the rationale for the lower age limit of 4 years was the concern that subjects younger than this may present with potential differences in some disease manifestations and/or in the rate of disease progression. Thus, inclusion of such subjects could potentially create practical and ethical challenges in a placebo-controlled study and may have complicated interpretation of the study results. These challenges included, but were not limited to, the potential for Institutional Review Board or Ethics Committee concerns regarding enrolment of these very young children in a placebo-controlled study and the feasibility of MRI assessments in this population. Alexion has initiated an open-label study, LAL-CL06, which permits enrolment of subjects > 8 months of age, thus bridging this age gap.

Use of a historical control in Study LAL-CL03

Regulatory and scientific advice was sought for the clinical development programme. There has been general agreement regarding the approach to the demonstration of clinical benefit in infants presenting with rapidly progressive disease, which included use of a historical control given the reliably poor outcome in these patients. The presentation of LAL Deficiency in infants meets the conditions for use of an external or historical control, as defined under ICH E10, Choice of Control Group and Related Issues in Clinical Trials. To define a scientifically rigorous historical control group, the Sponsor conducted a separate retrospective natural history study of patients who presented with LAL Deficiency in infancy (LAL-1-NH01). A primary historical control group was identified from this study comprised of the subset of patients who were untreated (i.e., no HSCT or liver transplant) and had confirmed failure to thrive prior to 6 months of age. Study LAL-1-NH01 demonstrated that survival was predictably poor in infants presenting with LAL Deficiency but particularly so in infants with confirmed failure to thrive prior to 6 months of age. To ensure comparability of the populations and support comparisons between this primary historical control group and the subjects treated in Study LAL-CL03, identical criteria were used to identify infants with early failure to thrive.

Choice of endpoints in Study LAL-CL02

In children and adults, as previously noted, the rate of disease progression in LAL Deficiency is heterogeneous. This precluded designing or conducting a study of the size and duration that would be required to directly assess the impact of ERT on clinical events associated with progressive liver disease (e.g., decompensated cirrhosis or liver-related mortality) or CVD (e.g., cardiac-related mortality) particularly

in the context of the rarity of this disease. Thus, the design of the pivotal study in children and adults was based on evaluation of multiple endpoints, which, particularly when taken together, demonstrate the efficacy of ERT across multiple clinically important disease abnormalities. While it is recognised that these are surrogate endpoints, some of these assessments are used in clinical practice to monitor liver injury and the effectiveness of therapies in reducing cardiovascular risk.

Primary endpoint

The rationale for selection of ALT normalisation as the primary endpoint in Study LAL-CL02 included the following considerations:

- ALT is a well-accepted biomarker of liver injury, in particular, persistent elevation of serum transaminases is clinically significant in the context of known causes of chronic liver disease and/or drug-induced liver injury.
- Data from a highly relevant nonclinical model of LAL Deficiency show a strong concordance of elevated transaminases with progressive liver disease and development of fibrosis in untreated animals and importantly, a concordance of transaminase reduction with subsequent improvement in liver histology and improved survival in response to treatment with sebelipase alfa;
- There are historical precedents for use of ALT normalisation as a relevant endpoint in other chronic liver disease settings (e.g. in combination with virological endpoints in viral hepatitis (Tyzeka, telbivudine in hepatitis B; Hepsera, adefovir dipivoxil in paediatric patients with hepatitis B); and
- The endpoint could be measured reliably in all subjects enrolled in the study, an important consideration in a disease that primarily impacts a paediatric population where invasive procedures, such as liver biopsy, are challenging, particularly in the context of a double-blind, placebo-controlled study.

Further, published literature (Bernstein, 2013) and results from the natural history study in infants (LAL-1-NH01) and the observational study in children and adults (LAL-2-NH01) show that persistently elevated transaminases are an almost universal finding in patients with this disease. Of note, where data were available in the observational study LAL-2-NH01, there was a rapid decrease in ALT levels following liver transplantation correlating the relationship between serum transaminase levels and liver pathology. Additionally, at the time Study LAL-CL02 was initiated, improvements in several liver disease-related parameters, including serum transaminase levels, had been observed in adults treated with sebelipase alfa in Studies LAL-CL01/LAL-CL04 and in infants treated with sebelipase alfa in Study LAL-CL03.

Considerations regarding potential limitations of this endpoint were raised during key regulatory interactions during development. A principal concern was whether inherent variability and spontaneous changes in ALT levels of subjects with LAL deficiency would preclude the ability to reliably assess whether improvement in ALT is due to

the therapeutic intervention. The randomised placebo-controlled design of Study LAL-CL02 allows for a longitudinal confirmation of persistence of ALT elevation in subjects on the control arm for 20 weeks. The almost immediate response to therapy following transition of these subjects to active treatment, coupled with the observation of rapid reversal of response in subjects who were off treatment followed by rapid response again on treatment observed in subjects between Study LAL-CL01 and Study LAL-CL04, provides confidence that the effects are indeed due to the therapeutic intervention of enzyme replacement. Importantly, treatment of infants with rapidly progressive disease, who frequently die due to complications of liver failure, also resulted in rapid improvement in ALT and other clinically important liver parameters. Finally, to be clinically meaningful, it was important to demonstrate in this and in the other clinical studies with sebelipase alfa that reduction and normalisation of ALT are sustained with treatment.

Secondary outcomes

Clinically important secondary endpoints were also evaluated in Study LAL-CL02 to provide a totality of evidence supporting clinical benefit in this rare multisystem disease and confirming that effective enzyme replacement is addressing the root cause of disease pathogenesis. Key secondary endpoints focused on the importance of restoring normal homeostasis to lipid metabolism as evidenced by the correction of dyslipidaemia and demonstrating improvements in liver volume, fat content, and histopathology. A fixed sequence of key secondary endpoints was defined and a hierarchical statistical testing approach was employed to evaluate these clinically relevant disease abnormalities.

Correction of dyslipidaemia, including reduction in LDL-c, triglycerides, and non-HDL-c with improvement in HDL-c levels, was a key secondary objective designed to: 1) demonstrate restoration of normal lipid metabolism and 2) support clinical benefit based on a reduction in CVD risk. Circulating LDL-c levels have a well-documented positive association with CVD risk, and extensive data from randomized controlled clinical studies indicate that reductions in LDL-c are associated with reductions in that risk (Grundy, 2004; Baigent, 2005; Baigent, 2010) demonstrating the causal nature of LDL-c in CVD. Recently reported evidence also supports the importance of reduction in triglycerides in improving cardiovascular risk (Do, 2013; Jorgensen, 2014; Crosby, 2014). The same reduction in risk of cardiovascular complications with reduction in LDL-c and triglycerides, particularly with concomitant increases in HDL-c, should translate to patients with LAL Deficiency.

LAL Deficiency-related increase in lysosomal lipid substrate, which is caused by the enzyme deficiency (i.e., the root cause of the disease), is characterized by increases in hepatic fat content. Thus, improvement in hepatic fat content was assessed in Study LAL-CL02 by abdominal imaging using multi-echo gradient echo (MEGE) MRI. Liver volume also was assessed as a separate measure of substrate reduction. To ensure consistency across subjects and study centres, MRIs were read centrally.

Despite the paucity of historical information related to histopathology in LAL Deficiency, it was considered important to evaluate the potential for histopathological changes associated with treatment with sebelipase alfa. However, unlike other chronic liver diseases, there is no established histopathological scoring system, and it was recognized that there would be challenges in the ability to obtain biopsies in a global study evaluating paediatric subjects who may be randomized to a placebo arm. In contrast to other efficacy assessments, comparison of the effects of sebelipase alfa and placebo on liver histology was only possible in a subset of the trial population. In addition, post hoc unblinded evaluation of biopsy slides suggested that the morphometry results for steatosis in selected biopsies may have been influenced by variability in H&E staining, which had the potential to confound the interpretation of some biopsies.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The clinical development programme for sebelipase alfa was designed to provide evidence of safety and efficacy across the full spectrum of patients with LAL Deficiency and is representative of the patients expected to be treated in clinical practice in England. Approximately 18% of patients included in sebelipase alfa studies (including the natural history cohort study LAL-1-NH01) were from the UK (Table C9.16).

Table C9.16: Number of UK patients enrolled in the sebelipase alfa clinical development programme

Study Identifier	UK	Total
LAL-1-NH01	12	40
LAL-CL01 & LAL-CL04	3*	9
LAL-CL02	4	66
LAL-CL03	3	9
Total	22	124

*One patient did not enter LAL-CL04

As discussed in Section 9.4.3, a placebo-controlled study design was employed in Study LAL-CL02. This is appropriate and in line with the scope of this submission since no alternative effective treatments exist. Patients in LAL-CL02 could continue other medical management for LAL Deficiency at a stable dose (prior to and for at least the first 32 weeks of treatment) while participating in this study.

A retrospective natural history study was undertaken to provide a historical control for Study LAL-CL03. The efficacy of sebelipase alfa in infants was evaluated by

comparing the proportion of sebelipase alfa-treated subjects in Study LAL-CL03 who survived beyond 12 months of age with the survival experience from a cohort of infants with LAL Deficiency from the natural history study LAL-1-NH01 who had similar demographic and disease characteristics. From the natural history study, a subpopulation of 21 infants with growth failure within the first 6 months of life based on objective criteria similar to those used in Study LAL-CL03 and, like subjects in Study LAL-CL03, who had not received prior HSCT or liver transplant, was used for the primary comparison. As discussed in Section 9.9.1, comparison can also be made with the wider LAL-1-NH01 population, which included infants who had received HSCT or a liver transplant and therefore may be considered representative of best supportive care.

The outcomes relative to the scope have been addressed by the clinical evidence presented (Sections 9.6 and 9.9.1) as follows:

Survival

LAL Deficiency is a progressive multisystem disease, which frequently manifests at a young age leading to serious complications. In infants, these complications include failure to thrive with progressive liver injury, hepatocellular failure, rapid development of liver fibrosis, and death typically within the first 6 months of life. Sebelipase alfa extended survival in infants with LAL Deficiency, a group of critically ill subjects at high risk of early mortality who currently have no treatment options.

The mortality benefit observed in infants can be extrapolated to the broader population since many clinically relevant disease manifestations are common across the disease spectrum and ERT with sebelipase alfa results in common beneficial effects, particularly with respect to liver disease parameters. The consistent and substantial effects across multiple clinically important disease abnormalities predict with a reasonable degree of confidence that children and adults treated with sebelipase alfa will be at reduced risk of important clinical events associated with disease progression that would occur in the absence of effective intervention. These benefits are particularly important given the early age at which many patients present with significant liver damage as evidenced by the level of fibrosis and cirrhosis observed in Study LAL-CL02 liver biopsies.

Transaminase level

Sebelipase alfa treatment resulted in reductions in liver injury as evidenced by improvements in serum transaminase levels, including normalisation. In the prevalent population of children and adults chronic liver injury leads to liver fibrosis and cirrhosis and complications associated with advanced liver disease such as portal hypertension, bleeding varices, hepatic encephalopathy, and requirement for liver transplant. Therefore although not directly measured in LAL-CL02, it would be expected that sebelipase alfa treatment would prevent or reduce fibrosis and cirrhosis and long-term liver complications.

Liver fat content

LAL Deficiency-related increase in lysosomal lipid substrate, which is caused by the enzyme deficiency (i.e., the root cause of the disease), is characterised by increases in hepatic fat content. Thus, improvement in hepatic fat content was assessed in Study LAL-CL02 by abdominal imaging using MEGE-MRI.

Lipids and cardiovascular risk

Sebelipase alfa was significantly more effective than placebo in reducing LDL-c, non-HDL-c, and triglyceride levels and increasing HDL-c in children and adults and was [redacted] The effect was consistently maintained over long-term treatment and therefore sebelipase alfa is expected to reduce the inherent risks associated with dyslipidaemia.

LAL Deficiency leads to marked disturbances of lipid metabolism resulting in severe dyslipidaemia affecting multiple lipid parameters (including elevated LDL-c and triglycerides and low HDL-c), all of which are associated with increased cardiovascular risk. In addition LAL Deficiency may play a more direct role in atherosclerosis risk based on an important role for LAL in cholesterol efflux from macrophage foam cells (Ouimet, 2011; Ouimet, 2012). LAL administration has also been shown to reduce atherosclerotic plaques in an LDL receptor-deficient mouse model (Du, 2004).

As discussed above, reductions in circulating LDL-c levels and triglycerides is associated with reductions in cardiovascular risk (Grundy, 2004; Baigent, 2005; Baigent, 2010; Do, 2013; Jorgensen, 2014; Crosby, 2014). The same reduction in risk of cardiovascular complications with reduction in LDL-c and triglycerides, particularly with concomitant increases in HDL-c, should translate to patients with LAL Deficiency.

Liver synthetic function, liver disease progression, liver transplant and cardiovascular events were not assessed in the sebelipase alfa clinical studies.

Health-related quality of life

The quality of life of patients was assessed in LAL-CL02. Quality of life of carers was not assessed in clinical studies but has been assessed in an independent survey (Section 7.1).

[redacted] (see Section 10). As discussed in Section 7 and 10, quality of life is expected to be markedly reduced in LAL Deficiency patients who have suffered decompensated cirrhosis, liver transplant, and/or a serious cardiovascular event. LAL-CL02 excluded the following patient types, many of whom could be expected to have much lower HRQL:

- Patients who had very severe hepatic dysfunction (Child-Pugh Class C).
- Patients who had other medical conditions or comorbidities that, in the opinion of the Investigator, would have interfered with study compliance or data interpretation, including but not restricted to severe intercurrent illness,

known causes of active liver disease other than LAL Deficiency (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease, or physician concerns about excess alcohol consumption), human immunodeficiency virus (HIV), poorly-controlled diabetes, or cancers other than non-melanoma skin cancer.

- Patients who had previous haematopoietic or liver transplant procedure.

[redacted] Severe reductions in HRQL occur later. Subsequent trials, such as CL06, will examine the effect of sebelipase alfa on patients with more severe disease and presumably lower HRQL (e.g., post-transplant patients).

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

It should be noted that no patients aged between 6 months and 4 years of age have been included in studies reported to date, however ongoing studies LAL-CL06 and LAL-CL08 will provide data on the clinical impact of sebelipase alfa in these patients. Sebelipase alfa is indicated for the treatment of patients of all ages with LAL Deficiency, therefore given the serious nature of the disease there is no reason to deny treatment to any patient based on age.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

No criteria would be required in clinical practice to select suitable patients.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

There are limited data relating to the impact of disease manifestations on the quality of life of patients with LAL Deficiency, however much can be learned from examining the natural history and outcomes of this severe condition combined with insights from conditions of a similar nature.

Although the population in the EU LAL-D Survey (described in Section 7.1) may not be fully representative of the wider untreated population, it provides useful insights into the symptoms that are most burdensome for patients.

Gastrointestinal (GI) manifestations:

LAL Deficiency involves massive accumulation of cholesteryl esters (CE) in the intestinal tract, and especially in the intestinal villi. This accumulation accounts for many of the GI symptoms in patients with LAL Deficiency. Infants and children can present with severe vomiting, malabsorption, diarrhoea, steatorrhea, and failure to thrive. It has been estimated that approximately one-third of children with LAL Deficiency present with severe GI symptoms (Reiner, 2014).

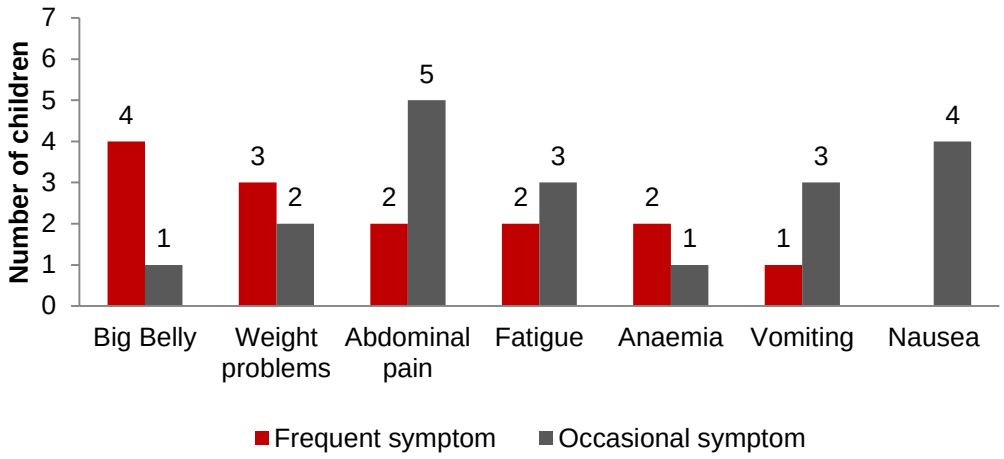
These symptoms are known to have a negative impact on HRQL in patients with functional gastrointestinal disorders (Koloski, 2000), and would be expected to very significantly impact the HRQL of patients with LAL Deficiency which is a progressive disease and can be expected to be more severe than functional GI disorders. Indeed, the results of the EU LAL-D Survey showed that abdominal pain, diarrhoea, nausea and loss of appetite were reported as frequent symptoms and that these symptoms could be very burdensome, considerably affecting patient's lives.

Hepatobiliary manifestations:

In the liver, LAL Deficiency leads to massive accumulation of CE in hepatocytes, Kuppfer cells and macrophages (Bernstein, 2013; Reiner, 2014); this results in hepatomegaly in almost every LAL Deficiency patient, and splenomegaly in an overwhelming majority.

In the EU LAL-D Survey, the majority of patients (73%) reported an enlarged liver (eight out of eleven patients, of which, seven were children). These patients mentioned suffering from frequent abdominal pain, fatigue, swollen abdomen and weight problems (Figure C10.1). Patients suffering from hepatomegaly had a higher number of symptoms occurring frequently in comparison to patients not suffering from hepatomegaly. The only adult who suffered from hepatomegaly and splenomegaly reported that he frequently suffered from abdominal pain, nausea, vomiting and fatigue.

Figure C10.1: Frequency of symptoms among children with LAL Deficiency suffering from hepatomegaly (n=7)



The underlying pathology in the liver involves progression of the liver disease to fibrosis and micronodular cirrhosis, which are usually associated with only minor HRQL implications. However, the disease progresses to portal hypertension resulting in decompensated cirrhosis and liver failure. Additional manifestations of liver disease progression include ascites; esophageal varices with the high potential for rupture and bleeding; coagulopathy with increased bleeding risk; jaundice; and the need for liver transplantation. Patients with liver disease from LAL Deficiency are also at risk of progressing to liver cancer. Ultimately these patients can suffer premature deaths from either liver failure or liver cancer (Bernstein, 2013).

In addition to the hepatic complications, these patients can also suffer from gallbladder dysfunction including cholestasis, which is associated with the jaundice seen in these patients.

The presence of jaundice, and the severe symptoms associated with liver disease progression and liver transplantation have been strongly documented to have very deleterious HRQL impact in patients with other liver diseases. In patients with nonalcoholic steatohepatitis (NASH), the health utility was 0.82 with compensated cirrhosis; 0.60 for decompensated cirrhosis; and 0.69 in the first year of liver transplant (Mahady, 2012). The rapid drop-off in HRQL between compensated and decompensated cirrhosis was quite stark.

The HRQL decrement associated with these same complications in LAL Deficiency patients is expected to be as severe as in patients with other reasons for their liver disease. In addition, the reported mean age of onset of LAL Deficiency is usually decades earlier than age of onset of other forms of liver disease. In the largest report of LAL Deficiency patients currently reported in the literature (N=135), the median age of onset was 5 years (83% of all patients had onset of disease before age 13) (Bernstein, 2013). In contrast, children chronically infected with hepatitis B usually perinatally or as infants, take several decades before manifesting any liver disease

(Chen, 2009; Lorio, 2007). Though NAFLD/NASH can occur in childhood, the highest prevalence of advanced liver disease occurs in adults; with patients >50 years experiencing more advanced liver disease than those <50 years old (Vernon, 2011).

Given that patients with LAL Deficiency end up with significant liver complications usually at a younger age than the patients with other types of liver diseases; the gains in life expectancy and quality adjusted life years from preventing end stage liver disease in LAL Deficiency patients is likely to vastly surpass that from preventing end stage liver disease in patients with viral hepatitis, alcoholic hepatitis or NAFLD/NASH.

Cardiovascular manifestations:

LAL Deficiency is associated with severe dyslipidaemia leading to premature atherosclerosis (Bernstein, 2013; Reiner, 2014). The link between dyslipidaemia and major cardiovascular disease (CVD) is well established. LAL Deficiency patients are at a much higher risk of CVD events than unaffected persons of similar age and gender, as shown in an analysis of the baseline data from the ARISE study (Shah, 2015). In this analysis, baseline data from LAL Deficiency patients showed a 54% relative increase in CVD risk compared to unaffected patients of similar age and gender. Evidence of actual cases of CVD resulting in death or major cardiovascular surgery can be found in three case reports in the literature (Elleder, 2000; Elleder, 1990; Gasche, 1997). The implications of this include a high risk for premature cerebrovascular and coronary artery disease (CAD); both of which negatively impact HRQL. The impact of CAD on HRQL is well established and HRQL in CAD patients is also correlated very strongly with mortality risk (Abdallah, 2013). There is also evidence that younger patients (<65 years old) with CAD have a lower HRQL than older patients (Kim, 2003); this is understandable given that younger patients, such as those with LAL Deficiency, may have higher expectations of health given their age.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

LAL Deficiency is a heterogeneous disease and the quality of life of affected patients is expected to vary depending on the symptoms they experience and the severity of symptoms.

From early on in the disease course, many patients will suffer from gastrointestinal complaints (infants and children can present with severe vomiting, malabsorption, diarrhoea, steatorrhea, and failure to thrive). In the patient survey detailed in Section 7.1, swollen abdomen, weight problems and itchy skin were symptoms experienced mainly by children (with average age 5.6 years). Children reported swollen abdomen and anaemia as mainly very burdensome symptoms, while adults mainly indicated

nausea as a very burdensome symptom. Abdominal pain was a frequent complaint in both adults and children.

LAL Deficiency is a progressive condition, resulting in accelerated atherosclerosis, deterioration of liver function and systemic complications. It is expected that HRQL would decrease with disease severity and with the onset of liver and cardiovascular complications as described above. In a subset from an observational study in LAL-deficient children and adults, it is estimated that approximately 50% of children and adults with LAL Deficiency progressed to fibrosis, cirrhosis, and liver transplant within 3 years of initial clinical manifestation (Data on file: CSR LAL-2-NH01). Considering the paediatric nature of disease the decrement in quality of life associated with the serious complications of LAL Deficiency are likely to occur at an early age in many patients.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-consequence analysis.
- Results with confidence intervals.

The objective of measuring HRQL in the sebelipase alfa clinical program

A primary objective of measuring HRQL changes in any clinical trial is to ensure that new technologies do not negatively impact the patients HRQL even as clinical efficacy and safety are assessed. A second objective is often to assess any positive impact of treatment on HRQL. Though no disease specific HRQL measures exist, HRQL was assessed (as an exploratory endpoint) in the sebelipase alfa clinical trial program. Though a beneficial effect was hoped for, given the sample size, it was clear the study was not powered to detect any such beneficial HRQL effect of treatment. It was however also important to ensure no negative impact from the use of the drug; this was critically important given that the early stages of LAL Deficiency may be clinically silent even in the presence of significant liver damage.

Given the inclusion/exclusion criteria, the LAL-CL02 trial excluded the following patient types, many of whom could be expected to have much lower HRQL:

- Those with very severe hepatic dysfunction (Child-Pugh Class C).
- Those who had a previous haematopoietic or liver transplant procedure.

The enrolled population therefore included patients with substantial pathological liver damage at baseline, but not severe enough to report significant decrements in HRQL at study entry when compared to the general population. Consistent with other chronic liver diseases, the significant impact on HRQL comes with progression to more severe liver disease states such as decompensated cirrhosis/liver failure, liver cancer and liver transplantation.

There is no literature yet on HRQL of LAL Deficiency patients who have suffered decompensated cirrhosis, liver transplant, and/or a serious cardiovascular event. However, expert opinion and the literature suggest that LAL Deficiency patients who have suffered these serious events will have markedly reduced HRQL, as one would expect given the experience of unaffected persons with similar health conditions.

Subsequent trials, such as LAL-CL06, will examine the effect of sebelipase alfa on patients with more severe disease and presumably lower HRQL (e.g., post-transplant patients).

Summary of the instruments used in measuring HRQL in LAL-CL02

In LAL-CL02 (ARISE), HRQL was measured using three instruments: the Chronic Liver Disease Questionnaire (CLDQ), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), and the Pediatric Quality of Life Inventory (PedsQL™) questionnaire. Each was administered at baseline and at the end of the double blind period (approximately 20 weeks). Given that none of these were developed nor validated in patients with LAL Deficiency, the behavioural characteristics of these instruments in LAL Deficiency patients were uncertain.

CLDQ

The CLDQ is a disease-specific instrument designed to assess health-related HRQL in subjects with chronic liver disease (Younoussi, 1999). In LAL-CL02, the CLDQ was self -administered to all subjects who were ≥17 years of age on the date of informed consent. The CLDQ has 29 items with a range of scores from 1 (worst possible function) to 7 (best possible function); higher values indicate better HRQL.

FACIT Fatigue

The 13-item FACIT-Fatigue scale was developed to measure levels of fatigue in people living with a chronic disease. In this study, the FACIT-Fatigue scale version 4 was self-administered by all subjects who were ≥17 years of age at date of informed consent. The FACIT-Fatigue total score ranges from 0 to 52. A score of <30 indicates severe fatigue. A higher value indicates a better HRQL. The FACIT-Fatigue total

score could only be calculated if more than 50% of the items were answered (a minimum of 7 of 13 items) (Cella, 2002).

PedsQL

The PedsQL is composed of generic core scales and disease-specific modules. The 23 item PedsQL 4.0 Generic Core Scales was designed to measure the core dimensions of health, as delineated by the World Health Organization (WHO), as well as role (school) functioning in healthy children and those with acute or chronic health conditions. The PedsQL Generic Core Scales includes 4 multidimensional scales of physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). In addition to the total scale score (all 23 items), 2 summary scores, the Physical Health Summary (8 items) and Psychosocial Health Summary (15 items), were also reported. In this study, the PedsQL 4.0 Generic Core Scales were self-administered by subjects who were 5 to <18 years of age on the date of informed consent, using one of the 3 self-report forms (ages 5-7, 8 12, or 13-18), as appropriate to the subject's age (Varni, 2009). Parent proxy reports were not used in this study. The minimal clinically important difference is 4.4 (Varni, 2007).

Results

The analyses of the HRQL included evaluation of change from baseline within each group as well as assessment of any differences between the sebelipase alfa and placebo groups.

Any interpretation of these HRQL data has to take into consideration the fact that not the entire study population (N= 36 sebelipase alfa and 30 placebo) was eligible to complete the various questionnaires. This is a result of the age groups for which these instruments have been validated. For the CLDQ and FACIT fatigue, only subjects 17 or older at enrolment could participate (N= 13 sebelipase alfa and 7 placebo); for PedsQL, only subjects 5 to ≤18 at enrolment could participate (N= 25 sebelipase alfa and 23 placebo). These very small sample sizes mean that strong inferences cannot be drawn about any between group differences.

Overall, and as expected given the inclusion/exclusion criteria, subjects enrolled in LAL-CL02 reported HRQL at baseline that suggested [redacted]

CLDQ

[redacted]

[redacted]

FACIT Fatigue

[redacted]

PedsQL

[redacted]

Conclusion of the HRQL analysis for sebelipase alfa

The evaluation of HRQL shows the following:

[redacted]

- These patients do not reflect the spectrum of disease complications such as DCC/liver failure, liver cancer, coronary artery disease, or liver transplant, during which HRQL would be severely impacted.
- Treatment with sebelipase alfa does not negatively impact the HRQL of these patients and hence the efficacy results observed are not associated with a HRQL penalty.
- For a variety of reasons (lack of statistical power, baseline HRQL scores with high risk of ceiling effect, lack of disease specific instruments), this study did not show any difference between sebelipase alfa and placebo as expected, as it was never designed to test that hypothesis.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was used to transform quality of life data in the clinical trials.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systemic search for quality of life in LAL Deficiency was conducted as part of the economic search. Please see Section 11.

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.

- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

No studies other than the clinical trial reported were found to have reported quality of life in LAL Deficiency patients.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No studies other than the clinical trial reported were found to have reported quality of life in LAL Deficiency patients so a comparison is not possible.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

Treatment with sebelipase alfa (or placebo) did not negatively impact the HRQL of patients in LAL-CL02 and hence the efficacy results observed are not associated with a HRQL penalty. Thus, adverse events are not expected to impact on HRQL and were therefore not included in the cost-consequence analysis. Infusion reactions were seen in some patients but these were manageable using standard supportive measures.

Quality-of-life data used in cost-consequences analysis

10.1.9 Please summarise the values you have chosen for your cost-consequence analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

The quality of life data from the clinical trial (see section 10.1.3) shows the following:

- The quality of life of the patients enrolled in LAL-CL02 is sufficiently maintained that at baseline
- The quality of life of the patients enrolled in LAL-CL02 is similar to that of unaffected individuals as a result of the study inclusion/exclusion criteria.

- The patients included in LAL-CL02 do not reflect the spectrum of disease complications such as DCC/liver failure, liver cancer, coronary artery disease, or liver transplant, during which quality of life would be severely impacted.
- Treatment with sebelipase alfa does not negatively impact the HRQL of patients and hence the efficacy results observed are not associated with a HRQL penalty.

For a variety of reasons (lack of statistical power, baseline HRQL scores with high risk of ceiling effect, lack of disease specific instruments), LAL-CL02 did not show any difference between sebelipase alfa and placebo, but was never designed to test that hypothesis.

Consequently, quality of life data used in the cost-consequence model was derived from the literature, rather than the trial data.

As part of a NIHR-funded evaluation of 'cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease' a systematic review of quality of life in NAFLD was conducted by Crossan et al (Crossan, 2015). Three studies reported quality of life values for NAFLD patients:

- Mahady et al (2012) used utilities from studies based on other causes of liver disease (Chong, 2003; Younossi, 2001; Ratcliffe, 2002; Siebert, 2003; McLernon, 2008) and assumed that cirrhosis, decompensated cirrhosis and HCC represent a common pathway for liver disease and that the decrement in quality of life associated with these conditions is similar irrespective of the initial cause.
- David et al. (2009) assessed HRQL of patients with diagnosed NAFLD and NASH. Using the SF-36, they found that patients with NALFD had lower reported scores and greater degrees of physical limitations than patients with HBV or HCV. They noted that the physical component summary score was similar to that of patients with HBV in a DCC health state. HRQL was lower in the respondents with NASH and the authors also found that scores were worse for persons with CC than without CC. The authors reported the median SF-36 physical component score by fibrosis level, but insufficient information was provided for the other components required to enable mapping to the preference-based SF-6D in order to calculate QALYs.
- Donnan et al. (2009) reported HRQL data for liver disease health states for all aetiologies including NASH. However, this was based on clinical opinion rather than empirical data reported by patients. The authors surveyed 18 general practitioners (GPs) and 12 hepatologists in Scotland and England using a questionnaire and a Delphi approach. In addition, this report did not detail on what scale the values were estimated, and so it was not possible to interpret the reported estimates.

In light of the methods used and data reported by David et al. (2009) and Donnan et al. (2009), utilities reported by Mahady et al (2012) were deemed the most appropriate to use in the cost-consequence analysis.

Infant patient health utilities do not exist in the public domain. It is assumed that infants with LAL Deficiency that die within the first year of life have a low utility of 0.25 as they are permanently hospitalised. Given infants that die within the first year of life live for 3.45 months, the utility applied to infants that die is 0.07 ((3.45/12)*0.25). Infants that survive beyond the first year are assumed to have a utility of 0.5 as they are also hospitalised for a significant time so would have a relatively low quality of life. Clinical expert opinion is that some babies could be discharged from hospital within 1 month of receiving sebelipase alfa thus a utility of 0.5 is likely to be a conservative estimate.

The utilities used in the cost-consequence model are detailed in Table C10.1.

Table C10.1: Summary of quality-of-life values for cost-consequence analysis

State	Utility value	95% confidence interval	Reference	Justification
LAL Deficiency without CC, DCC or HCC	0.92	0.65 – 0.95	Mahady et al (2012)	'Well with F3/F4 fibrosis' state from Mahady et al (2012) is comparable to 'LAL Deficiency without CC, DCC or HCC' state
CC	0.82	0.65 – 0.89		Best available source
DCC	0.60	0.46 – 0.81		
HCC	0.73	0.50 – 0.80		
Liver transplant	0.69	0.62 – 0.86		
Infants dying	0.07	0 – 0.14	Assumption	No published data on quality of life of infants with severe growth failure due to LAL Deficiency
Infants surviving	0.50	0.25 – 1.00		

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

An advisory board was conducted to ratify all elements of the cost-consequence model, including the chosen utility values. Please see section 12.2.5 for details.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Quality of life dramatically deteriorates as patients' liver disease progresses. In the early stages of the disease, illustrated by relatively high utilities for the 'LAL Deficiency without CC, DCC or HCC' and CC states, there is a relatively minor impact on the patients' quality of life and does not drastically impact daily lives, as evidenced the quality of life data collected in LAL-CL02. Patients' quality of life dramatically decreases when patients progress to DCC or HCC. There is some scope of variance of HRQL within health states; however, fundamentally, the HRQL is assumed to stay constant within individual health state.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects identified in the literature or clinical trials were deliberately excluded from the analysis. As discussed in section 10.1.1, cardiovascular and gastrointestinal manifestations are also associated with detriments in quality of life. However, due to lack of data, the heterogeneous nature of LAL Deficiency and the chosen model structure – which focuses on the primary manifestation of the disease – no quality of life values for cardiovascular or gastrointestinal manifestations were included in the analysis.

Furthermore, due to lack of available data on the health effects of caregivers by disease states, caregiver disutilities were not included in the analysis. Infant hospitalisation places a significant burden on caregivers and the burden continues after hospitalisation (Tomlinson, 1995). Empiric estimates of burden of illness on caregivers are sparse and measurement methodologies are unproven (Wittenberg, 2013). It is therefore difficult to quantify the impact that LAL Deficiency has on health effects beyond patients, although qualitative data suggests it is substantial. A systematic review of caregiver and family disutilities found the disutility for childhood diseases ranges between 0.1 (congenital anomalies), 0.092 (rotavirus-associated gastroenteritis), 0.08 (activity limitations) and 0.04 (spina bifida). Given this data were excluded, the incremental QALYs gained for sebelipase alfa are likely to be underestimated in this analysis.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not appropriate. The baseline quality of life values correspond to the initial distribution of patients at baseline over the health states as observed from LAL-CL02.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Quality of life is constant within a given health state. A patient's health utility changes over time based on the transitions that patient makes between health states.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

The utility estimates derived from the published study have not been amended.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy

alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Sebelipase alfa is indicated for long-term enzyme replacement therapy in patients with LAL Deficiency. Natural history data indicates that without treatment, LAL Deficiency patients with infant-onset die within the first 6 months of life and patients with paediatric or adult onset have significant morbidity and reduced life expectancy.

LAL Deficiency is a genetic disease and not curable with enzyme replacement therapy; sebelipase alfa treatment is intended to improve survival and health outcomes in patients, but the underlying disease remains. Evidence from the sebelipase alfa clinical trials indicate that patients continue to benefit from on-going enzyme replacement therapy. Specifically, as illustrated by the spikes in Figure C9.6, when subjects went off treatment at the end of Study LAL-CL01 (interval between dosing of 9 to 28 weeks), both ALT and AST increased. This dramatic and immediate off-treatment increase in ALT and AST supports the requirement for continuous treatment.

At present, there is no evidence to guide the development of treatment continuation rules for sebelipase alfa; hence Alexion has not developed any. As with most drugs developed for ultra-rare diseases, Alexion plans to continue to study the impact of sebelipase alfa in all LAL Deficiency patients, by enrolling patients into the LAL Deficiency registry.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

A search of the Cochrane database of systematic reviews yielded no existing published literature reviews of economic data for LAL Deficiency patients. Consequently, a systematic search of the literature was conducted on 1st June 2015 with the aim of identifying all economic studies for LAL Deficiency that could be used to inform the design of the economic model or provide utilities, resource use or cost data for the economic model. Table D11.1 details the databases that were searched in the review.

Table D11.1: Databases searched

Database	Year	Platform
EMBASE	1974 to 2015 Week 19	Ovid
Cochrane Central Register of Controlled Trials	Up to April 2015	Ovid
Cochrane Database of Abstracts of Reviews of Effects	Up to 2nd Quarter 2015	Ovid
Health Technology Assessment	Up to 2nd Quarter 2015	Ovid
NHS Economic Evaluation Database	Up to 2nd Quarter 2015	Ovid
Medline (R)	1946 to May Week 2 2015	Ovid
Medline complete	1865 to current	EBSCO
EconLit	All available	EBSCO

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature.

Using the inclusion and exclusion criteria defined in Table D11.2, two reviewers assessed the publication title and abstracts resulting from the searches detailed in Appendix 3, followed by review of the full text articles (where available). A third reviewer resolved contradictory decisions.

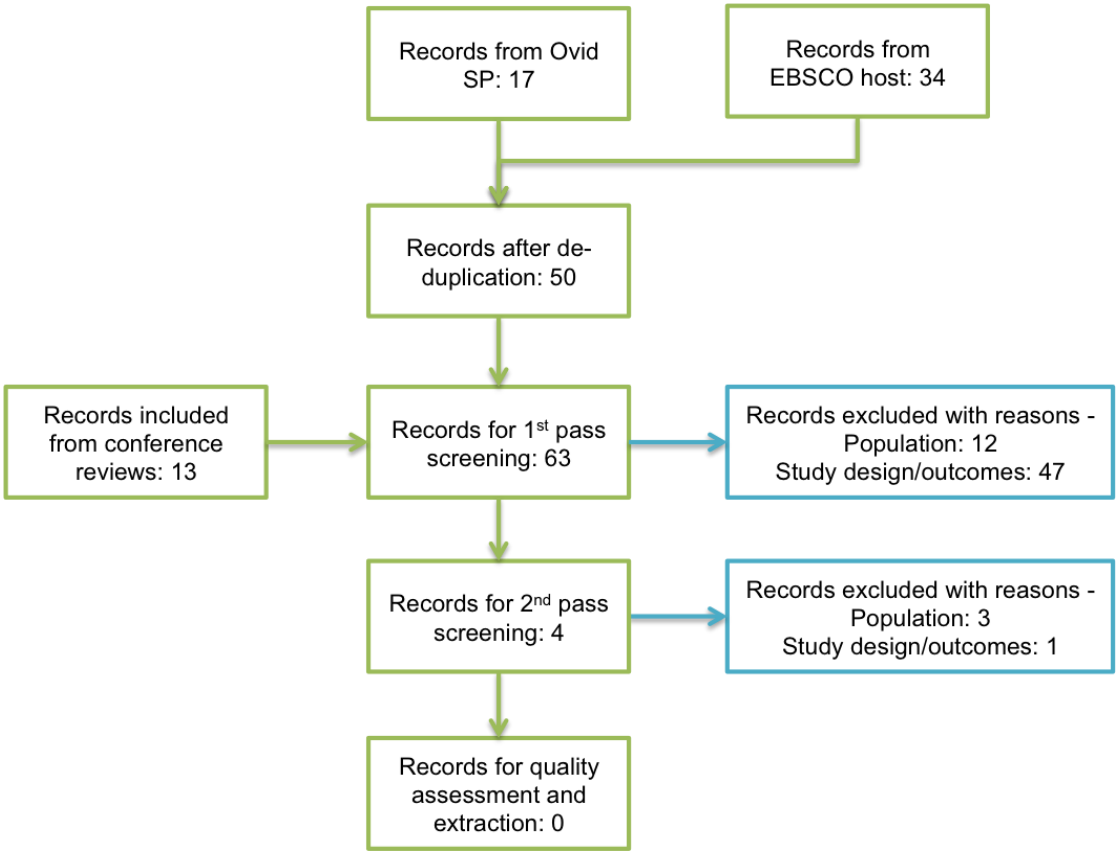
Table D11.2: Selection criteria used for health economic studies

Inclusion criteria	
Population	Lysosomal Acid Lipase Deficiency Wolman's disease Cholesteryl Ester Storage disease
Interventions	Any
Outcomes	Quality of life Costs Resource use Cost-effectiveness data
Study design	Observational studies Economic evaluations
Language restrictions	None
Exclusion criteria	
Population	Liposomal Acid Lipase Deficiency Cholesterol ester storage disease
Interventions	None applied
Outcomes	None applied
Study design	Animal Individual case study reports Letters Comment articles
Language restrictions	None applied

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

A PRIMSA diagram outlining the search results at each stage of the review is provided in Figure D11.1. No results were found.

Figure D11.1: PRISMA diagram for economic literature search



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

Not applicable; no economic studies of LAL Deficiency were found.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Not applicable; no economic studies of LAL Deficiency were found.

12 De novo cost-consequence analysis

Section 12 requires the sponsor to provide information on the de novo cost-consequence analysis.

The de novo cost-consequence analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-consequence analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-consequence analysis?

Sebelipase alfa is indicated for long-term enzyme replacement therapy in patients of all ages with LAL Deficiency; this is the patient population reflected in the economic model.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-consequence analysis is different from the scope.

Prior to approval of sebelipase alfa, there were no safe and effective, regulatory-approved therapies available to treat patients with LAL Deficiency. Sebelipase alfa is therefore compared to best supportive care (BSC), which includes lipid-lowering therapies, vitamin E, haematopoietic stem cells and liver transplantation.

BSC is only supportive in nature and does not address the underlying defect in LAL Deficiency. Rather, the main objective is to lessen the burden of LAL deficiency related complications. Although some temporary stabilisation of the clinical condition has been described, these interventions do not appear to substantially modify the outcome in affected patients (Hoeg, 1984; Meyers, 1985).

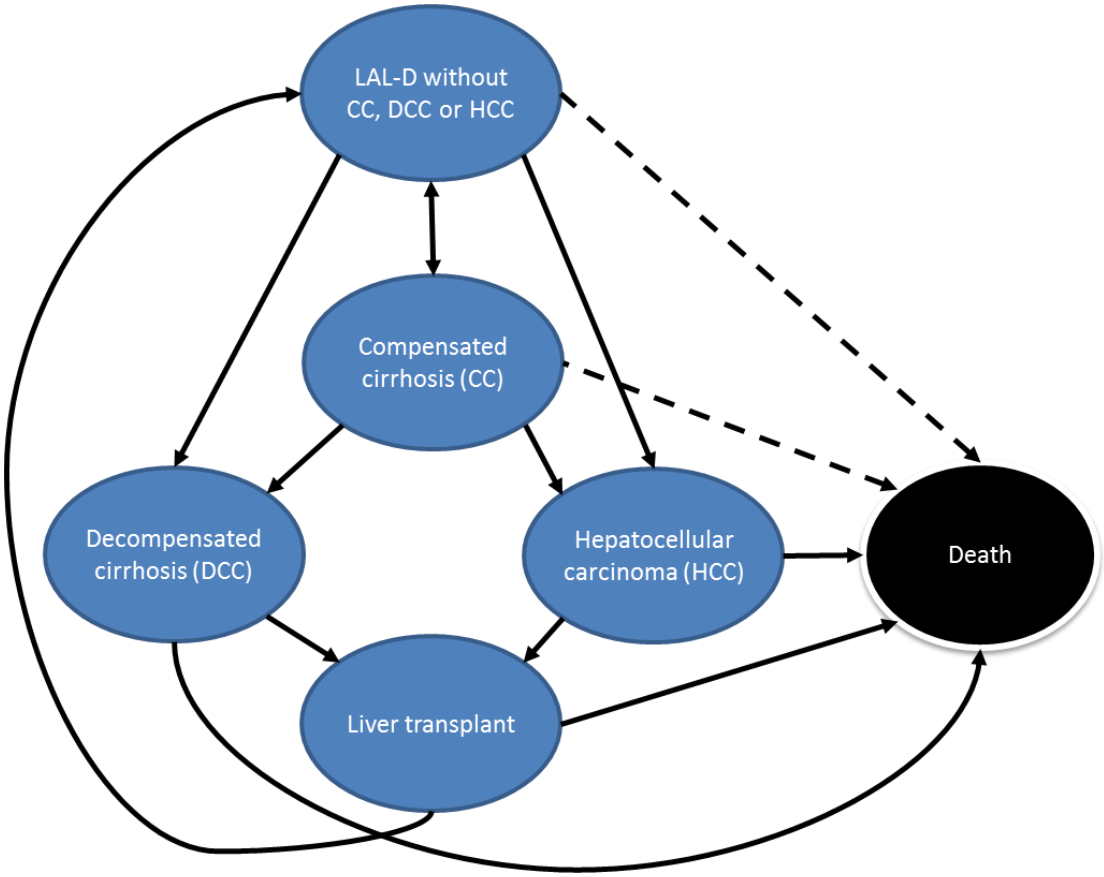
Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

The model is a 6-state Markov model, as detailed in Figure D12.1. The dashed arrows are only possible for patients who are up to one year old and reflect potential for death within first year of diagnosis in patients with infant-onset disease (Jones, 2015a). Patients can receive a liver transplant either from the decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC) states. Once patients have received a liver transplant, they are assumed to return to the baseline state.

Please also see Appendix 6 for a copy of the cost-consequence model itself.

Figure D12.1: Cost-consequence model schematic



12.1.4 Justify the chosen structure in line with the clinical pathway of care.

As detailed in Section 11, there are no published economic studies of LAL Deficiency. To date, there have also been no direct observational studies characterising the long-term clinical progression or costs related to LAL Deficiency published. LAL Deficiency particularly affects the liver, leading to fibrosis, compensated cirrhosis (CC), DCC, HCC and liver transplantation. Although patients with LAL Deficiency have cardiovascular, gastrointestinal and other manifestations, liver disease progression is often the most prominent manifestation and is likely more

aggressive than other more common liver diseases. Additionally, since LAL Deficiency is a genetic disease, in contrast to many other liver diseases, liver disease and symptoms are present from very early in life where many clinical manifestations are often first noted in childhood. The median age of clinical onset is 5 years of age (Bernstein, 2013). Consequently, the model was based on patient progression through liver disease.

According to clinical experts, NAFLD (and its progressive form, NASH) is the best model analogue for LAL Deficiency. NAFLD and NASH have been frequently studied with published long-term outcomes data. These diseases provide insights into prediction of liver disease progression in LAL Deficiency as there are some commonalities in the progression from fibrosis to CC to HCC or liver transplant. Preliminary analysis indicates that LAL Deficient patients may progress more rapidly than patients with other liver diseases (Alkhouri, 2013; Angulo, 1999).

Crossan et al. (2015) performed a systematic literature review of NAFLD/NASH health-related quality of life (HRQL) studies and treatments. The authors identified one economic model of the disease, namely Mahady et al. (2012), where a cost utility analysis was conducted using a deterministic Markov model, to assess treatment strategies from a third-party payer perspective in Australia. Mahady et al. (2012) assumed an annual cycle length over a lifetime horizon. Progression rate estimates were derived from a published systematic review and other published literature, and supplemented with data from an international database of NAFLD patients (Bhala, 2011).

The economic evaluation published by Mahady et al. (2012) was adapted to evaluate sebelipase alfa for the treatment of LAL Deficiency. The structure of the model is consistent with that of other liver disease progression models in the literature. Models published by Tsochatzis et al. (2014), Hartwell et al. (2011); Shepherd et al. (2007); Wright et al. (2006) and Saab et al. (2014) all include the same disease progression that includes fibrosis, CC and DCC, HCC, and liver transplant.

The model is based on the structure in Mahady et al. (2012) with a few exceptions:

1. The initial state in the model for sebelipase alfa is labelled as ‘LAL Deficiency without CC, DCC or HCC’, whereas Mahady et al. (2012) termed it “well”, “fibrosis” or alternatively “advanced fibrosis”.
2. Mahady et al. (2012) included additional HCC treatment-related states related to resection, locoregional treatment, treatment with sorafenib and palliation. The model for sebelipase alfa excludes these states that are a function of treatment decisions and patient access that may not apply to LAL Deficiency patients. Exclusion of these states is consistent with other liver disease models including most HCV models, for example Hartwell et al. (2011).
3. The model for sebelipase alfa assumes that following a successful liver transplant, patients transition back to the ‘LAL Deficiency without CC, DCC or HCC’ health state. This assumption is based on the fact that the LAL

Deficiency patients' underlying disease is not cured, and progression is important to consider given the young starting age of the patients involved. In other words, a post-liver transplant state is excluded. Post-transplant costs are not tracked in the model.

4. The model for sebelipase alfa assumes a patient can die directly from the 'LAL Deficiency without CC, DCC or HCC' state only if that patient is under age 1. The historical control infant study (LAL-1-NH01) clearly demonstrated that death within a year is the expected outcome of infants who are treated with BSC.

Importantly, the model excludes important aspects of LAL Deficiency and the therapeutic effect of sebelipase alfa owing to small sample sizes and a lack of information on the natural history of the disease. In particular, the reduction in severely elevated LDL-c is a primary benefit of sebelipase alfa (Burton, 2015a). LDL-c reductions have been strongly associated with reductions in the risk of cardiovascular events (D'Agostino, 2008). Estimating the benefit from LDL-c reduction in paediatric populations is difficult because accepted population-based cardiovascular risk equations are derived from samples of older patients at risk for cardiovascular events. For instance, when applying the Framingham risk equation to an LAL Deficiency patient who is age 15 at baseline, the coefficient on age reduces the background risk to almost zero based on the risk profile of a non LAL Deficiency patient population. However, we know that LAL Deficiency patients can experience cardiovascular events before age 18, indicating that population-based models underestimate cardiovascular risk among patients with LAL Deficiency (Cagle, 1986). Accordingly, these risk equations, which are the primary means of including cardiovascular events into a health state transition model, are not included in the current model.

Other important outcomes such as marked failure to thrive (growth failure), severe malabsorption, other gastrointestinal symptoms, pulmonary hypertension associated with intimal lipid deposition in pulmonary arteries, severe hypersplenism, mesenteric lipodystrophy, anaemia, and thrombocytopenia are excluded from the model owing to lack of data and the complexity of how these models would need to be parameterized (Bernstein, 2013). Nevertheless, patients with LAL Deficiency face damage and complications related to involvement of multiple vital organs including the intestines, spleen, and heart. It is estimated that 87% of LAL Deficiency patients experience manifestations in more than one organ (Bernstein, 2013).

By excluding these other severe disease manifestations associated with LAL Deficiency, it is likely that this model underestimates the value of sebelipase alfa in the treatment of LAL Deficiency.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Considering minimal data availability, the limited patient numbers, and lack of economic data related to LAL Deficiency, several assumptions were made in the model (Table D12.1).

Table D12.1: Assumptions made in the cost-consequence model

Assumption	Justification
The model is based on liver disease progression.	This is the primary manifestation of disease in LAL Deficiency patients.
NAFLD/NASH is the closest disease analogue to LAL Deficiency.	This is based on clinical opinion.
Base case state transition probabilities for the natural (untreated) course of LAL Deficiency are partly based on a patient population of biopsy-proven NASH (Mahady, 2012).	This patient population and corresponding Markov model is the closest population predicting progressive liver disease for LAL Deficiency patients. The justification for these transition probabilities is provided in section 12.2.
The HCC mortality rate from Hartwell et al. (2011), which is an HCV study, is the same for LAL Deficiency patients with HCC.	There are no published studies of the long-term outcomes of LAL Deficiency patients thus the best available analogue data has been used.
Progression over time for patients treated with sebelipase alfa is derived from the trial data using FIB-4 liver scores.	Estimates of progression transition probabilities from non-cirrhotic to cirrhotic use FIB-4 scores that are generated using a published mapping from Alanine transaminase (ALT), aspartate aminotransferase (AST) and platelet test (PLT) (Sterling, 2006). This approach was used given that this was the most valid source of data for the entire ARISE trial sample.
The 20-week data observed in the LAL-CL02 study provides a reasonable indication of how patients' clinical status will progress over time.	Data from a small number of patients in the LAL-CL04 study showed stabilisation of transaminases up to week 104 supporting the long-term effect of sebelipase alfa. Furthermore, given sebelipase alfa directly addresses the underlying cause of disease by replacement of the missing or deficient enzyme, there is no reason why the treatment effect of sebelipase alfa would not continue.
There is no excess risk of death due to liver causes for LAL Deficiency patients in the 'LAL Deficiency without CC, DCC or HCC' state.	Patients in the 'LAL Deficiency without CC, DCC or HCC' state are only at risk of death related to causes other than liver disease. The risk of death from the fibrosis state in Mahady et al (2012) was 0.4% but this was labelled as all-cause death. There is very little risk of patients dying due to liver causes if patients only have fibrosis; progression to CC, DCC or HCC is associated with increased risk of death (Mahady, 2012). Note – there is excess risk of death for LAL Deficiency patients who have not progressed to compensated cirrhosis from non-liver related causes such as cardiovascular disease. As stated in section 12.1.4, these non-liver aspects are excluded from the model owing to a lack of data.

12.1.6 Define what the model's health states are intended to capture.

The model's health states are intended to capture the lifelong costs and quality-adjusted life years (QALYs) incurred by LAL Deficiency patients and how treatment with sebelipase alfa impacts these outcomes. Note that the states are limited to the liver pathology aspect of LAL Deficiency. As stated in section 12.1.4, non-liver aspects are clinically important but are excluded from the model owing to a lack of data.

12.1.7 Describe any key features of the model not previously reported.

Table D12.2: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime	LAL Deficiency is a chronic condition that drastically impacts patients' life expectancy. In line with the NICE reference case, a lifetime horizon is used to reflect all-important differences in costs, life years and QALYs between sebelipase alfa and best supportive care.	NICE, 2013
Discount rate on costs and outcomes	1.5%	Patients treated with sebelipase alfa will have a much longer life expectancy than patients treated with best supportive care. In line with NICE guidelines for when non-reference case discount rate of 1.5% can be used.	NICE, 2013
Perspective	NHS and PSS (National Health Service and Personal Social Services)	In line with the NICE reference case.	NICE, 2013
Cycle length	1 year	That this aligns with published liver pathology models.	Mahady et al., 2012 Hartwell et al., 2011
Half-cycle correction	N/A	The model employs a half-cycle correction for all costs and utilities in the first and last model cycles.	N/A

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-consequence analysis.

Best supportive care transition probabilities

A 100% transition probability to the death state is used patients treated with BSC who are under age 1, reflecting that 21 of 21 infants in the natural history study of untreated infants with early growth failure (LAL-1-NH01) died within 12 months (Jones, 2015a). Thus, patients only transition between the 'LAL Deficiency without CC, DCC or HCC' state and death states so transitions to and from the CC, DCC, HCC and liver transplants states are not required for infants.

For all other ages in the model, transitional probabilities for best supportive care were based on Mahady et al. (Table D12.3).

Table D12.3: Transition probabilities for NASH patients used by Mahady et al. (2012)

	Fibrosis	CC	DCC	Hepatoma	Liver transplant	Death	Total
Fibrosis	0.91	0.04	0.013	0.004	0	0.004	0.971
CC	0	0.82	0.06	0.03	0	0.04	0.95
DCC	0	0	0.76	0.03	0.05	0.16	1.00
Hepatoma	0	0	0	0.37	0.2	0.43	1.00
Liver transplant	0.88	0	0	0	0	0.12	1.00

Transitional probabilities for best supportive care patients above the age of 1 were obtained directly from Mahady et al. with four exceptions:

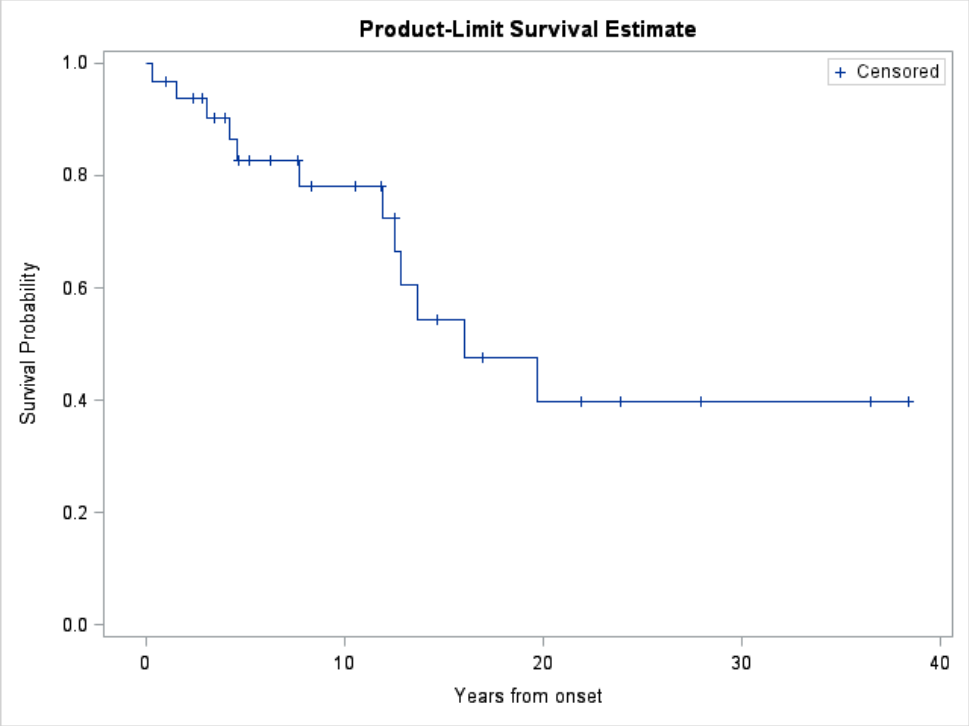
1. The transitional probabilities from the fibrosis and CC states in Mahady et al. (2012) do not sum to 100%. It is therefore assumed that the remainder (0.029 for the fibrosis state and 0.05 for the CC state) would be proportionally allocated across all the other states. For example, the probability of remaining in the CC state is divided by the sum of the total transitional probabilities (i.e. 0.82/0.95) to yield 0.863.
2. Unlike Mahady et al. (2012), it is assumed that there is no excess mortality rate from the 'LAL Deficiency without CC, DCC or HCC' state due to liver-related causes. Note that in reality, owing to the other manifestations of LAL Deficiency aside from liver pathology, there is an excess mortality rate for 'LAL Deficiency without CC, DCC or HCC' patients.
3. Additional HCC treatment states (resection, locoregional treatment, treatment with sorafenib, and palliation) in Mahady et al. were excluded from the model structure, as detailed in section 12.1.4. Consequently, transition probabilities published by Hartwell et al. (Table 38, page 66 of publication) were used for transitions to death from the HCC state (by assuming that costs, health utility and outcome for HCC is the same in LAL Deficiency as HCV) (Hartwell,

2011). The assumption about liver transplant is retained from Mahady et al., and it is assumed that the remainder of the probability is the likelihood of patients remaining in HCC.

4. Mahady et al. uses transition probabilities for the “fibrosis” state to refer to those with advanced liver fibrosis in a patient population with NAFLD/NASH. Preliminary analyses indicate that LAL Deficiency patients progress faster than patients with other liver diseases (Alkhouri, 2013; Angulo, 1999). To evaluate sebelipase alfa in LAL Deficiency, transition probabilities for patients with LAL Deficiency who have any fibrosis stage is required. Unfortunately, there are no publications in the public domain on this progression rate to CC for LAL Deficiency patients so trial data has been analysed to estimate this probability, as detailed below.

Survival analysis was conducted to approximate the rate of transitioning from fibrosis to CC using the LAL-CL02 trial data. Specifically, LAL-CL02 patients with a known baseline Ishak score (N=32) were analysed. An accelerated failure time (AFT) survival model was estimated assuming a constant hazard. The failure event was defined as the earliest mention (either a pre-baseline medical record or at baseline of the LAL-CL02 trial) of a confirmed case of CC (N=12). Study time was defined to begin on the date of a patient’s first record of LAL Deficiency symptom onset, and to end on the earlier of the date of the baseline biopsy or first record of cirrhosis in medical history. Note that two patients in the pre-trials data had medical records of CC, but subsequently were deemed pre-cirrhotic based on baseline biopsy. The results are that the hazard rate for starting fibrosis and becoming CC is 0.0325, which translates to an annual transition probability of 3.2% (standard error 0.0313 thus 95% CI 0% - 9%). The Kaplan Meier curve related to this analysis is shown in Figure D12.2.

Figure D12.2: Time to compensated cirrhosis state in LAL-CL02 patients



Notes: Subjects were included if they had an Ishak score at baseline and were included in the analysis set. Date of LAL Deficiency symptom onset was defined based on the earliest medical history of a LAL Deficiency symptom. Medical history date of cirrhosis was based on the earliest medical history of cirrhosis. If missing in either of these dates, the month of symptom onset was assumed to be January and the day of diagnosis was assumed to be the 1st. Cirrhosis defined as an Ishak score of 5 or 6 at baseline, or a medical history of cirrhosis of the liver or cirrhosis related to LAL Deficiency.

This estimate for the rate of transitioning from 'LAL Deficiency without CC, DCC or HCC' to CC is conservative: the failure data for 8 patients of the 12 CC patients was assumed to be the on the date of the patient's trial baseline biopsy. However, the actual first date on which these patients became CC was almost certainly earlier. If this were true, the transitional probability estimate used in the model is biased down, which underestimates the modelled value of sebelipase alfa.

The final resulting transition probabilities used for LAL Deficiency patients that receive best supportive care are given in Table D12.4.

Table D12.4: Transition probabilities for best supportive care LAL Deficiency patients over the age of 1

Time point n+1 / Time point n	LAL Deficiency without CC, DCC or HCC	CC	DCC	HCC	Liver transplant	Death	Source
LAL Deficiency without CC, DCC or HCC	96%*	3%**	1%**	0%**	0%**	0%***	*LAL-CL02 **Mahady 2012 ***Assumption
CC	0%	86%	6%	3%	0%	4%	Mahady 2012
DCC	0%	0%	76%	3%	5%	16%	Mahady 2012
HCC	0%	0%	0%	37%*	20%**	43%***	*Assumption **Mahady 2012 ***Hartwell 2011
Liver transplant	88%	0%	0%	0%	0%	12%	Mahady 2012

In addition to the probabilities of LAL Deficiency liver pathology-related death detailed in Table D12.4, age-gender specific all-cause mortality rates from the general population of England were also applied (ONS, 2015a).

Sebelipase alfa transition probabilities

The pivotal Phase 2/3 study in infants, of the 9 infants that received sebelipase alfa, 6 survived beyond 12 months, thus the mortality rate for the year was 33% (Jones, 2015b). The transition probability from the 'LAL Deficiency without CC, DCC or HCC' states to death applied in the model in the first year of infant's life is therefore 33%. This is in comparison to the 0% survival rate at 12 months of age for patients treated with best supportive care.

In addition to this infant transition probability, patients treated with sebelipase alfa are assumed to have the following transition probabilities different to patients treated with BSC:

- Transitions between the 'LAL deficiency without CC, DCC, HCC' and CC states
- Transitions from the 'LAL deficiency without CC, DCC, HCC' and CC states to the HCC and DCC states

<u>Transitions between the 'LAL Deficiency without CC, DCC, HCC' and CC states</u>

Clinical trial data was used to parameterise the transitions between the 'LAL Deficiency without CC, DCC and HCC' and CC states.

The epidemiologic gold standard for staging liver fibrosis is biopsy, but due to small numbers of patients, it is not possible to estimate transition probabilities from biopsy data. In infants, biopsy is not performed owing to risk to the infant's tenuous health status. In LAL-CL02, biopsies were collected in fewer than half of the patients. Biopsy required consent for paediatric patients, thus the sample in which biopsies are available is non-random. Furthermore, repeat biopsies are required to assess progress or regress. This resulted in a potentially unrepresentative set of only 10 placebo patients and 16 sebelipase alfa patients with repeat biopsies in the double-blind phase of LAL-CL02.

In the absence of comprehensive data, liver scoring algorithms were used to estimate levels of fibrosis based on laboratory data. Liver scoring algorithms specifically estimate risk of fibrosis progression at different thresholds and approximate CC; they are not exact measures. Using the laboratory data collected in LAL-CL02 at baseline and 20 weeks, we are able to estimate three scores:

1. Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) based on the Upper Limit of Normal (ULN) of AST and platelet test (PLT) results (Lin, 2011; Loaeza-del-Castillo, 2007):

   *APRI = {[AST / ULN of AST (40)] / PLT}*100*

2. Forns Index based on age, cholesterol (TCHOL), PLT, gamma-glutamyl transpeptidase (GGT) (Forns, 2002):

   *Forns Index = 7.811 – (3.131*ln(PLT)) + (0.781*ln(GGT)) + (3.467*ln(age)) – (0.014*TCHOL))*

3. FIB-4 based on Alanine transaminase (ALT), AST, PLT (Sterling, 2006):

   *FIB-4 = (age*AST) / ((PLT)*(ALT)^0.5)*

The Forns Index was developed and calibrated for use in adults with scores >1. This is problematic as children often have a negative score, which is outside the mathematical prediction space, due to their young age. The Forns Index is also less sensitive at modelling the transition from fibrosis to CC.

The APRI score is less informative as it utilizes a smaller subset of laboratory data than the other scores.

FIB-4, by contrast, incorporates ALT, the primary endpoint of the trial; it also includes AST, a secondary endpoint of the analysis. Furthermore, FIB-4 has been shown to provide excellent discrimination (the area under the receiving operating characteristic curve, c = 0.81) in paediatric patients with NAFLD (similar to the LAL Deficiency paediatric patients), superior to that of the Forns Index (c = 0.73) and APRI (c = 0.70)

(Yang, 2012). Consequently, in the base case analysis, the FIB-4 score is used as it is superior to Forns and APRI.

FIB-4 scores and component data are presented in Table D12.5 for the sebelipase alfa and placebo patients at baseline and week 20 in which complete data were available. In placebo patients the FIB-4 score increased by 0.07 from baseline, indicating worsening liver function, whilst in the sebelipase alfa group, FIB-4 scores decreased by 0.23, indicating improving liver function.

Table D12.5: Analysis of FIB-4 scores and components, baseline and week 20, in LAL-CL02

	Sebelipase alfa	Placebo
Baseline		
N	33	29
FIB-4, mean	0.83	0.61
% moderate / advanced fibrosis (>0.60[1])	39%	17%
% moderate / advanced fibrosis (≥1.00[1])	27%	17%
% potentially cirrhotic (>1.45[1])	15%	14%
% potentially cirrhotic (≥3.25[1])	3%	0%
Age (years), mean	17.4	15.1
Platelets (10^9/L), mean	226.8	242.9
ALT (U/L), mean	107.2	98.7
AST (U/L), mean	88.2	79.1
Week 20		
N	30	30
FIB-4, mean	0.60	0.67
% moderate / advanced fibrosis (>0.60[1])	30%	23%
% moderate / advanced fibrosis (≥1.00[1])	13%	17%
% potentially cirrhotic (>1.45[1])	10%	10%
% potentially cirrhotic (≥3.25[1])	0%	0%
Age (years), mean	17.4	15.6
Platelets (10^9/L), mean	245.7	244.5
ALT (U/L), mean	44.7	92.4
AST (U/L), mean	43.9	71.9
Change from baseline		
FIB-4 mean change from baseline	-0.23	0.07
Platelets (10^9/L), mean	15.0	-0.7
ALT (U/L), mean	-58.5	-6.7
AST (U/L), mean	-42.4	-6.3

[1] *Threshold values for moderate/advanced fibrosis and potentially cirrhotic were taken from Sterling et al. (2006).*

FIB-4 scoring was used to assess whether each patient made a transition, either from the FIB-4-predicted 'LAL Deficiency without CC, DCC or HCC' state to the FIB-4-predicted CC state, or vice versa.

FIB-4 scoring may use several different thresholds to define the difference between levels of fibrosis or cirrhosis, including the most sensitive (i.e. lowest threshold) definitions of FIB-4>0.6 or FIB-4≥1.0, which proxy for mild to moderate/advanced fibrosis, and the less sensitive definitions of FIB-4>1.45 or FIB-4≥3.25, which proxy for transitions from non-cirrhotic to potentially cirrhotic (Sterling, 2006).

For the base case, the FIB-4>1.45 threshold is used (Table D12.6). The justification for the FIB-4>1.45 threshold is that it is one of the two thresholds of FIB-4 scores that predict transitions from non-cirrhotic to potentially cirrhotic (as opposed to mild to moderate/advanced fibrosis). Of these two thresholds, the FIB-4 is better aligned at estimating the number of patients with CC at baseline. At baseline, the FIB-4>1.45 predicts that there are 25 non-cirrhotic and 4 potentially cirrhotic patients in both the sebelipase alfa and placebo groups. Trial biopsy data at baseline showed there were 5 cirrhotic patients in the sebelipase alfa and placebo groups (Data on file, CSR LAL-CL02) thus the FIB-4>1.45 is comparable to the trial evidence. The interpretation of Table D12.6 is that the 25 sebelipase alfa patients that were non-cirrhotic at baseline have a 100% probability of remaining in the non-cirrhotic state at the FIB-4>1.45 threshold. Also, one of the four patients that started in the potentially cirrhotic state at baseline in the sebelipase alfa group transitioned to the non-cirrhotic state at week 20. In other words, none of the non-cirrhotic sebelipase alfa patients progressed, and 25% of the cirrhotic sebelipase alfa patients improved.

Only patients with scores at baseline and at week 20 are included in the analysis. It is assumed that the transition probabilities values using baseline to week 20 data represent transitional probabilities over one year. Converting the 20-week transitions to annual rates would result in even faster transitions. However, owing to the values indicating fibrosis regression rather than progression for sebelipase alfa-treated patients, this is considered a conservative assumption.

Interestingly, the same pattern of transitional probabilities was observed for placebo-treated patients when using the FIB-4>1.45 threshold (Table D12.6). However, across the other FIB-4 thresholds and liver scores, placebo-treated patients tended to perform worse, as indicated by the lower values in the green cells of Table D12.7. Based on the natural history progression of LAL Deficiency patients and even NASH/NAFLD patients, it was deemed that the transition probabilities to the cirrhosis state from Mahady et al. (2012) were more representative of best supportive care over the long term than derived transitions from the 20 week placebo data.

Sensitivity analysis is conducted using the placebo liver scores for BSC from Table D12.6. Sensitivity analysis is also conducted on the threshold for FIB-4 scores (BSC at FIB-4>0.6; sebelipase alfa at FIB-4>0.6 and FIB-4≥3.25 as these represent the outer bounds of the potential analyses) and the use of APRI and Forns Index scores.

Table D12.6: Transition probabilities between 'LAL deficiency without CC, DCC or HCC' and CC states, calculated using FIB-4 scores with threshold of >1.45

		Sebelipase alfa Week 20			*Placebo Week 20*	
		Non-cirrhotic	Potentially cirrhotic		Non-cirrhotic	Potentially cirrhotic
Baseline	Non-cirrhotic (n=25)	100%	0%	Non-cirrhotic (n=25)	100%	0%
	Potentially cirrhotic (n=4)	25%	75%	Potentially cirrhotic (n=4)	25%	75%

Note: Table 12.5 presents average statistics at baseline and week 20 for patients with complete data at either baseline or week 20 (i.e., patients with complete data at baseline are included in the baseline calculation and patients with complete data at week 20 are included in the week 20 calculation). To be included in Table 12.6, which presents transitions from baseline to week 20, patients are required to have complete data at baseline and week 20, so that a transition could be observed.

Table D12.7: Transition probabilities between 'LAL deficiency without CC, DCC or HCC' and CC states, calculated using FIB-4 scores with alternative thresholds and Forns Index and APRI scores

Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)

		Sebelipase alfa Week 20			*Placebo at Week 20*	
		Mild	Mod/Adv		Mild	Mod/Adv
Baseline	Mild (n=17)	94%	6%	Mild (n=24)	92%	8%
	Mod/Adv (n=12)	33%	67%	Mod/Adv (n=5)	0%	100%

Mild to Moderate/Advanced Fibrosis (FIB-4>1.0)

		Sebelipase alfa Week 20			*Placebo at Week 20*	
		Mild	Mod/Adv		Mild	Mod/Adv
Baseline	Mild (n=21)	100%	0%	Mild (n=24)	100%	0%
	Mod/Adv (n=8)	50%	50%	Mod/Adv (n=5)	0%	100%

Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)

		Sebelipase alfa Week 20			*Placebo at Week 20*	
		Non-cirrhotic	Potentially cirrhotic		Non-cirrhotic	Potentially cirrhotic
Baseline	Non-cirrhotic (n=28)	100%	0%	Non-cirrhotic (n=29)	100%	0%
	Potentially cirrhotic (n=1)	100%	0%	Potentially cirrhotic (n=0)	25%	75%

Potentially Significant Fibrosis (Forns>4.2)

	Sebelipase alfa Week 20			*Placebo at Week 20*	
	No	Yes		No	Yes

Baseline	No (n=26)	100%	0%	No (n=27)	96%	4%
	Yes (n=4)	0%	100%	Yes (n=2)	0%	100%

Potentially Significant Fibrosis (APRI>1.5)

		Sebelipase alfa Week 20			*Placebo at Week 20*	
		No	Yes		No	Yes
Baseline	No (n=22)	100%	0%	No (n=26)	96%	4%
	Yes (n=7)	86%	14%	Yes (n=3)	33%	67%

Transitions from the 'LAL deficiency without CC, DCC, HCC' and CC states to the HCC and DCC states

In the clinical trials for sebelipase alfa, which included 2,691 weeks of treatment (Table D12.8), there were no observed instances of patients on sebelipase alfa transitioning to DCC or HCC and no deaths (aside from the deaths in the LAL-CL03 infant trial which applies only to those under the age of 1). Consequently, a 0% transition probability to HCC or DCC is assumed for sebelipase alfa. Sebelipase alfa restores normal lipid metabolism, so it is expected that liver progression to these states will be suspended. This is also consistent with the liver score data that indicate that liver disease is on balance regressing and not progressing for patients on sebelipase alfa.

Table D12.8: Observable weeks on sebelipase alfa by trial and overall

Trial	Subjects	Mean weeks	Standard deviation	Median	Min	Max	Sum (weeks)
LAL-CL02	66	20.56	15.04	22.14	0.14	68.14	1357.00
LAL-CL03	9	53.11	53.99	60.29	0.14	164.71	478.00
LAL-CL01/CL04	9	95.06	34.96	107.86	3.14	114.14	855.57
LAL-CL01	9	3.16	0.11	3.14	3.00	3.43	28.43
LAL-CL04	8	103.39	6.23	104.86	89.14	111.00	827.14
Overall	84	32.03	34.05	22.43	0.14	164.71	2690.57

Note: These durations are calculated based on time from first to last sebelipase alfa exposure, which can differ slightly from the time from baseline to last measure.

Final transition matrices for sebelipase alfa treated patients

The final resulting transition probabilities used for LAL Deficiency patients that receive sebelipase alfa are given in Table D12.9.

Table D12.9: Base case transition probabilities for patients with LAL Deficiency treated with sebelipase alfa

Time point n / Time point n+1	LAL Deficiency without CC, DCC or HCC	CC	DCC	HCC	Liver transplant	Death	Source
LAL Deficiency without CC, DCC or HCC	100%*	0%*	0%**	0%**	0%**	0%**	*LAL-CL02 **Assumption
CC	25%*	75%*	0%**	0%**	0%**	0%**	*LAL-CL02 **Assumption
DCC	0%	0%	76%	3%	5%	16%	Mahady 2012
HCC	0%	0%	0%	37%*	20%**	43%***	*Assumption **Mahady 2012 ***Hartwell 2011
Liver transplant	88%	0%	0%	0%	0%	12%	Mahady 2012

As per transition probabilities for best supportive care patients, in addition the probabilities of death detailed in Table D12.9, age-gender specific all-cause mortality rates from the general population of England were also applied (ONS, 2015a).

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

In the cost-consequence analysis, it is assumed that the treatment effect of sebelipase alfa observed in the 20 week study persists over a lifetime i.e. patients treated with sebelipase alfa do not experience any progression in liver disease.

Sebelipase alfa directly address the underlying cause of disease by replacement of the missing or deficient enzyme, resulting in reduction of the accumulated substrates and restoration of normal lipid metabolism. Improvements in transaminase levels (ALT and AST) and lipids (LDL, HDL and triglycerides) were maintained in the long term, with no evidence for a diminished treatment effect in open-label clinical studies over 2-years of follow-up. Due to the mechanism of action, the effect of sebelipase alfa is expected to continue over a lifetime.

This assumptions is also consistent with the Markovian structure of the model i.e. probabilities of transitioning between states is independent of time. Clinical experts validated this assumption at an advisory board (section 12.2.5).

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The transition probabilities for sebelipase alfa were derived by estimating FIB-4 scores using Alanine transaminase (ALT), aspartate aminotransferase (AST) and platelet test (PLT) results from LAL-CL02, using the relationship published by Sterling et al. (2006). Different thresholds are used to define the difference between levels of fibrosis (non-cirrhotic) or cirrhosis. The base case analysis uses a threshold of FIB-4>1.45 (Sterling, 2006) to estimate transition probabilities between the 'LAL Deficiency without CC, DCC or HCC' state and the CC state. See section 12.2.1 for further details.

12.2.4 Were adverse events included in the cost-consequence analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events (AEs) are not included in the cost-consequence study. Sebelipase alfa is generally well tolerated. Adverse reactions in LAL-CL02 were mostly mild to moderate in severity. The most serious adverse reactions experienced by 3% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria. See section 9.7 for further detail of adverse events.

No long-term studies of BSC-treated patients have been conducted, so AEs related to its use are unknown. The open label trials have informed the AE profile of sebelipase alfa with longer-term treatment.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

An advisory board was conducted in October 2014 with four clinical experts in hepatology or rare disease and two health economists to review sebelipase alfa

clinical data and discuss the health economic analysis. Four European markets were represented: UK, Spain, Germany and Italy.

Meeting participants:

- Professor Sandro Muntoni, MD. Director, Centre for Metabolic Diseases and Atherosclerosis, University of Caligari, Italy.
- Carmen Ribes-Koninckx, MD PhD. President of SEGHNP (Spanish Society for Paediatric Gastroenterology Hepatology and Nutrition) Head of the Paediatric Gastrohepatology Unit at LA FE Hospital, Valencia, Spain.
- Monica Lopez Rodriguez, MD. Assistant Physician in Internal Medicine in IMSALUD, the Community of Madrid, Spain.
- Emmanuel Tsochatzis, MD. Senior Lecturer and Honorary Consultant, UCL Institute for Liver and Digestive Health, Royal Free London NHS Foundation Trust, UK.
- Stefan Willich, MD. Professor, Institute for Social Medicine, Epidemiology and Health Economics, Charite University Medical Center, Germany.
- Pippa Anderson, BSc, MSc. Director, Swansea Centre for Health Economics, Wales.

The participants discussed the health economic model framework and assumptions with emphasis on identifying the correct disease states, transition probabilities, health utilities and medical resource utilisation parameters. Important feedback on the clinical parameters used in the model:

- Dr. Tsochatzis suggested that the NASH population is the right population to use, and that Mahady et al. (2012) is the only cost-effectiveness publication in this area.
- Dr. Tsochatzis mentioned that NAFLD probabilities likely underestimate mortality rates and that these transition probabilities would be higher in a LAL Deficiency population since LAL Deficiency patients are dying due to several different disease manifestations.
- Dr. Tsochatzis stated transition probabilities up to the point of cirrhosis are likely different in LAL Deficiency patients because of the lag in diagnosis. From the point of cirrhosis onwards, they likely would be fairly similar.
- Dr. Tsochatzis also mentioned the potential for cirrhosis to regress (along with all associated risks) as evidenced by Marcellin et al. (2013).

In summary, the approach taken to modelling the clinical progression of LAL Deficiency patients was deemed appropriate by hepatologists.

In addition to the advisory board, review of the final model was also conducted with Dr Simon Jones, Consultant Metabolic Paediatrician at Manchester Children's Hospital.

12.2.6 Summarise all the variables included in the cost-consequence analysis. Provide cross-references to other parts of the submission.

Age, weight and gender were included to calculate treatment costs and all-cause mortality rates. The age at baseline in the base case analysis was the average age of the LAL-CL02, LAL-CL03 and LAL-1-NH01 cohorts (Table D12.10).

All variables included in the cost-consequence model are detailed in Table D12.11.

Table D12.10: Baseline characteristics (age, health state distribution) in model

Scenario (source)	N	Average Age	Modelled Age	Percentage at Baseline	
				LAL Deficiency without CC, DCC or HCC	CC
Base case (LAL-CL02, LAL-CL03 and LAL-1-NH01)	96	11.46	11	84%	16%
Infants (LAL-CL03 and LAL-1-NH01)	30	0.08	0	100%	0%
Children and adults (LAL-CL02)	66	16.63	17	69%	31%

Notes

Age is calculated as age at treatment initiation in LAL-CL02 and LAL-CL03 but at the earliest chart review in LAL-1-NH01. Age is calculated among all patients, but severity distribution just among patients with baseline biopsies.

All infants are assumed to be in fibrosis. Only untreated patients with early growth failure are included from LAL-1-NH01, which is the sample used in the survival comparison to the treated infant study.

Table D12.11: Summary of variables applied in the cost-consequence model

Variable	Value	Range	Distribution	Source
Baseline characteristics				
Age	11	0 to 17	Gamma	LAL-CL02, LAL-CL03 and LAL-1-NH01
Weight	42.2 kg	7.68 to 68.25	N/A	RCPCH, 2015
Proportion male	50%	N/A	N/A	LAL-CL02
Percentage with LAL Deficiency without CC, DCC, or HCC at baseline	84%	69% to 100%	Dirichlet	LAL-CL02 and assumption
Percentage with CC at baseline	16%	0% to 31%	Dirichlet	LAL-CL02 and assumption
Best supportive care transition probabilities				
'LAL Deficiency without CC, DCC, or HCC' to CC	3.2%	0% to 9%	Beta	Analysis of pre-baseline LAL-CL02 data
CC to 'LAL Deficiency without CC, DCC, or HCC'	0%	0% to 4%	Beta	Analysis of pre-baseline LAL-CL02 data
'LAL Deficiency without CC, DCC, or HCC' or CC to death (under age 1)	100.0%	N/A	N/A	LAL-1-NH01
Natural history transition probabilities for best supportive care and sebelipase alfa				
'LAL Deficiency without CC, DCC, or HCC' to DCC	1.0%	1.0% to 8.8%	Beta	Mahady, 2012 adjusted
'LAL Deficiency without CC, DCC, or HCC' to HCC	0.3%	0.3% to 1.6%	Beta	Mahady, 2012 adjusted
'LAL Deficiency without CC, DCC, or HCC' to death (over age 1)	0%	N/A	N/A	Assumption
CC to DCC	6.3%	4.2% to 16.8%	Beta	Mahady, 2012 adjusted
CC to HCC	3.2%	0.7% to 5.3%	Beta	Mahady, 2012 adjusted
CC to death (over age 1)	4.2%	2.1% to 4.2%	Beta	Mahady, 2012 adjusted
CC to death (under age 1)	100.0%	N/A	N/A	LAL-1-NH01
DCC to HCC	3.0%	0.7% to 5%	Beta	Mahady, 2012 adjusted
DCC to liver transplant	5.0%	5% to 25%	Beta	Mahady, 2012 adjusted
DCC to death	16.0%	15% to 38%	Beta	Mahady, 2012 adjusted
HCC to liver transplant	20.0%	10% to 30%	Beta	Mahady, 2012 adjusted

HCC to death	43.0%	37% to 49%	Beta	Hartwell, 2011 adjusted
Liver transplant to death	12.0%	1% to 22%	Beta	Mahady, 2012 adjusted
Sebelipase alfa transition probabilities				
'LAL Deficiency without CC, DCC, or HCC' to CC	0%	0% to 4%	Beta	LAL-CL02
'LAL Deficiency without CC, DCC, or HCC' or CC to DCC or HCC	0%	N/A	N/A	Assumption based on LAL-CL02
'LAL Deficiency without CC, DCC, or HCC' to death (under age 1)	33.0%	N/A	N/A	LAL-CL03
'LAL Deficiency without CC, DCC, or HCC' to death (over age 1)	0%	N/A	N/A	Assumption
CC to 'LAL Deficiency without CC, DCC, or HCC'	25%	0% to 50%	Beta	LAL-CL02
Costs				
Cost of sebelipase alfa 20mg vial	£6,286	N/A	N/A	Department of Health approved list price
Administration cost per infusion	£165	N/A	N/A	NHS reference costs 2013-14
Annual hospitalisation cost for infants surviving	£90,090	£620 - £72,027	Gamma	NHS reference costs 2013-14, LAL-CL03
Annual hospitalisation cost for infants dying	£103,604	£962 - £108,108	Gamma	NHS reference costs 2013-14
'LAL Deficiency without CC, DCC, or HCC' health state (annually)	£620	£496 - £744	Gamma	Backx, 2014
CC health state (annually)	£962	£770 - £1,155	Gamma	Backx, 2014
DCC health state (annually)	£13,390	£10,712 - £16,068	Gamma	Hartwell, 2011
HCC health state (annually)	£11,932	£9,546 - £14,318	Gamma	Hartwell, 2011
Liver transplant health state (annually)	£54,011	£43,209 - £64,813	Gamma	Hartwell, 2011
Utilities				
Health utility for infants surviving	0.5	0.25 – 1.00	Beta	Assumption
Health utility for infants dying	0.07	0 – 0.14	Beta	Assumption
'LAL Deficiency without CC, DCC, or HCC' health state	0.92	0.74 – 1.00	Beta	Mahady, 2012
CC health state	0.82	0.66 – 0.98	Beta	Mahady, 2012

DCC health state	0.60	0.48 – 0.72	Beta	Mahady, 2012
HCC health state	0.73	0.58 – 0.88	Beta	Mahady, 2012
Liver transplant health state	0.69	0.55 – 0.83	Beta	Mahady, 2012
Other				
Cost discount rate	1.5%	0% - 6%	N/A	NICE, 2013
Outcomes discount rate	1.5%	0% - 6%	N/A	NICE, 2013

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The ICD10 code for LAL Deficiency is E75.5. The HRG codes on the PbR tariff that map from ICD10 code E75.5 are:

- Paediatric: PA25A or PA25B – Major gastrointestinal or metabolic disorders
- Adult: AA25A or AA25B – Cerebral Degenerations or Miscellaneous Disorders of Nervous System

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic search for resource data was conducted as part of a wider economic search. Please see section 11 for details. No resource identification, measurement or valuation studies for patients with LAL Deficiency were found.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[4].

Clinical advisers assessed the applicability of the costs included in the cost-consequence model as part of a full review of the model. Please see section 12.2.5 for details.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price for sebelipase alfa is £314.30 per mg or £6,286 per 20mg vial. Alexion are in the process of making sebelipase alfa available in 5mg vials, which will be costed at an equivalent price per mg (subject to approval from Department of Health), equating to a cost of £1,572 per 5mg vial. The 5mg vials will be available from January 2017 so 20mg vials are used during the first year of the cost-consequence analysis and 5mg vials thereafter.

12.3.5 If the list price is not used in the de novo cost-consequence model, provide the alternative price and a justification.

The list price of sebelipase alfa is used in the cost-consequence model. It was assumed that the cost of sebelipase alfa would reduce by 30% after 10 years due to the influence of generic pricing following patent expiration. This is consistent with price erosion observed when biologics face biosimilar competition in the United States (Mulcahy, 2014).

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost consequence model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

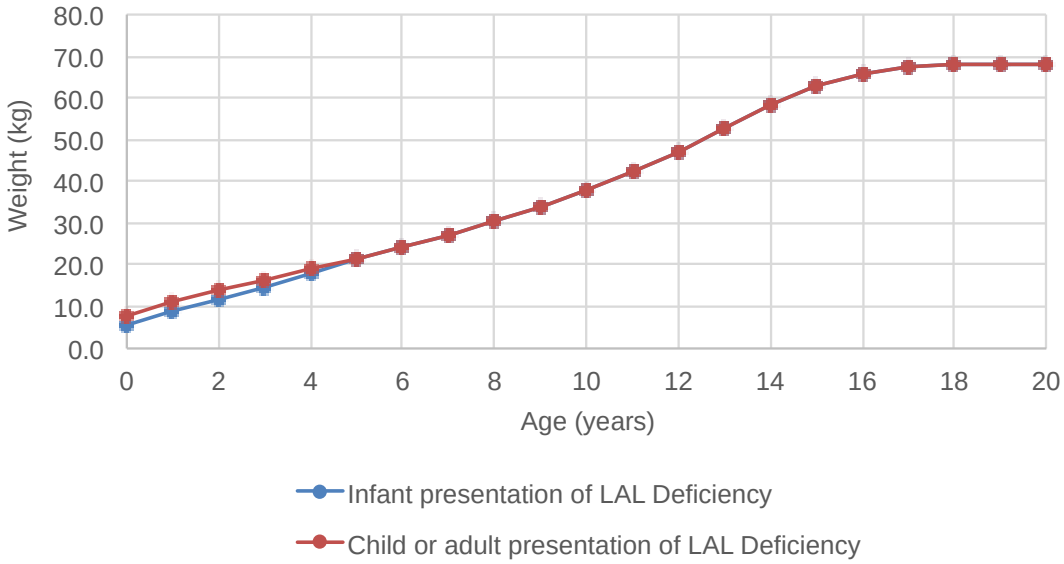
Dosing of sebelipase alfa is weight-based, and is maintained throughout the modelled patient's lifetime. The recommended dose for sebelipase alfa is as follows:

- Patients with paediatric or adult presentation of LAL Deficiency receive 1 mg/kg every other week.
- Patients with presentation of LAL Deficiency in infancy receive 3mg/kg every week.

Note that in LAL-CL03, infants with rapidly progressive LAL Deficiency were dose escalated from 1 mg/kg to 3 mg/kg once weekly within the first year of their lives, and no reversion from 3 mg/kg to 1 mg/kg was observed after escalation. Therefore, applying an infant dose of 3 mg/kg from baseline is likely to overestimate the cost for some infants and is therefore a conservative dosing assumption.

As patients age throughout the model, they are assumed to gain weight. UK growth charts from the Royal College of Paediatrics and Child Health (RCPCH) were used to estimate the weight of patients given their age (RCPCH, 2015). Gender-specific weight estimates are averaged based on the gender balance observed in LAL-CL02: 50% of patients were female in both arms (18/36 for sebelipase alfa, 15/30 for placebo). Weight gain for patients with presentation of LAL Deficiency in infancy differs from that for patients with paediatric or adult presentation in that treatment is assumed to raise weight from the 2nd percentile in the first year of life to the 75th percentile by age 5 and above. Patients with paediatric or adult presentation of LAL Deficiency are assigned the 75th percentile of weight throughout the modelled time horizon. The modelled weight for age curves are presented in Figure D12.3.

Figure D12.3: Weight for age curve derived from RCPCH growth charts



Sebelipase alfa is infused over 1 to 2 hours, depending on patient tolerability. It may be administered in an outpatient setting or at home. Administration costs for treatment in the outpatient setting were used in the base case analysis and were sourced from NHS reference costs 2013-14 (NHS, 2015). The non-consultant led outpatient cost of £68.66 was used per infusion.

Sebelipase alfa is not expected to require any specific additional monitoring or training.

Table D12.12: Costs per treatment/patient associated with the technology in the cost-consequence model

Items	Value	Source
Price of the technology per treatment/patient in the first 10 years at the baseline age of 11 years with 20mg vials	£6,286 per 20mg vial £18,858 per infusion £491,992 per year	UK list price Weight based on Royal College of Paediatrics and Child Health (RCPCH, 2015)
Price of the technology per treatment/patient after the first 10 years, corresponding to an age of 21, with 5mg vials	£1,100 per 5mg vial £15,401 per infusion £400,418 per year	Assumed UK list price after patent expiration Weight based on Royal College of Paediatrics and Child Health (RCPCH, 2015)
Price of the technology per treatment/patient in the first 10 years at the age of 1 year with 5mg vials	£1,572 per vial £3,143 per infusion £163,436 per year	Assumed UK list price for 5mg vials. Adult weight based on Royal College of Paediatrics and Child Health (RCPCH, 2015)
Administration cost for LAL Deficiency onset in children and adults	£68.66 per infusion £1,785 per year	NHS reference costs 2013-14, non-consultant-led outpatient cost (NHS, 2015)

Health-state costs

12.3.7 If the cost-consequence model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost-consequence model.

A systematic search of the literature yielded no costs specific to LAL Deficiency. Consequently, health state costs were sourced from the literature on patients with progressive liver disease.

Management costs for non-infant patients were based on a UK cost study and economic evaluation of hepatitis C virus (HCV) (Backx, 2014; Shepherd, 2007).

The aim of the HCV UK cost study was to compare disease progression, use of health services and costs to the UK (NHS) between patients with HCV genotype 1 infection who achieved a sustained viral response (SVR) following pegylated interferon and ribavirin therapy versus those who did not, using real-world data representative of routine NHS practice in the UK (Backx, 2014). A retrospective chart review of 193 patients with HCV genotype 1 infection was conducted. Health resource use was documented for each patient in each disease state and unit costs were from the NHS Payment by Results database. The resulting annual cost estimate for non-SVR patients in the chronic hepatitis state (mean £589, 95% CI £417-£833, n=54, 197 years follow up) was used for the 'LAL Deficiency without CC, DCC or HCC' state. The resulting annual cost for non-SVR patients in the cirrhosis state (mean £914, 95% CI £560-£1491, n=27, 103 years follow up) was used for the CC state. Following communication with the authors to confirm that the 2011-12 price year had been used, the costs were inflated from 2012 to 2014 values using Office for National Statistics Consumer Price Indices for Health (ONS, 2015b).

The aim of the economic evaluation was to assess the cost-effectiveness of interferon alfa and ribavirin for the treatment of mild chronic HCV (Shepherd, 2007). In the study, health state costs for DCC and HCC were taken from the observational study conducted during a UK mild HCV trial (Wright, 2006). Costs for liver transplantation were taken from a Department of Health funded study of the costs of liver transplantation. We assume patients who had a liver transplant do not have on-going costs related to post-transplant care. The costs were inflated from 2003-04 to 2014 values using Office for National Statistics Consumer Price Indices for Health (ONS, 2015b).

Costs used in the model for each of the liver disease health states are detailed in Table D12.13. We assume that the costs of the HCV patients are likely similar to NAFLD/NASH. We believe that these costs are likely lower than would be the case with a LAL Deficiency patient sample, given that the LAL Deficiency patients would tend to include children who will require speciality care, and the fact that the LAL

Deficiency can affect other disease systems aside from the liver. In this way, we consider the cost estimates to be conservative.

Given the lack of published data to enable the calculation of infant patient costs, costs were generated from LAL-1-NH01, NHS reference costs and assumptions. The mean survival time of untreated LAL Deficiency infants in LAL-1-NH01 was 3.45 months so we assumed the annual cost for infants that died was for 3.45 months of hospitalisation. Infant patients that survive following treatment with sebelipase alfa will still require a significant proportion of time in hospital from birth so we assumed 3 months of hospitalisation would be required.

The cost per day of hospitalisation was sourced as £1,001 from NHS reference costs 2013-14 "Paediatric Critical Care, Basic Critical Care" [XB07Z] (NHS, 2015). This equated to a total cost of £103,604 for infant patients dying from LAL Deficiency and a cost of £90,090 for surviving infants.

Table D12.13: Health state costs

Health state	Mean cost (£)	Variation	Source
LAL Deficiency without CC, DCC or HCC	620	439 - 877	Backx, 2014; ONS, 2015b
Compensated Cirrhosis	962	590 – 1,570	Backx, 2014; ONS, 2015b
Decompensated Cirrhosis	12,523	Not reported	Shepherd, 2007; ONS, 2015b
HCC	11,159	Not reported	Shepherd, 2007; ONS, 2015b
Liver Transplant	50,515	Not reported	Shepherd, 2007; ONS, 2015b
1st year cost for dying infants	103,604	Not available	Jones, 2015a; NHS, 2015
1st year cost for surviving infants	90,090	Not available	NHS, 2015 and assumption

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost-consequence model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

As detailed in section 12.2.4, adverse events were not included in the cost-consequence analysis.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Due to lack of data, no additional cost savings have been incorporated. See section 12.3.10 for further information.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Diseases affecting infants and children are associated with high burden on parents are informal carers and thus have a high indirect costs as parents are required to take leave from work to care for children and babies. Furthermore, adults with progressive liver disease are likely to have a reduced income due to the inability to work. However, no published UK costs from productivity losses are published so no indirect costs are included in the cost-consequence model. One Italian study has estimated that indirect costs account for 60% of the total costs of liver disease (Marcellusi et al, 2015). Since the analysis does not account for the high indirect costs and sebelipase alfa prevents patients from reaching severe disease states, the incremental costs of sebelipase alfa are likely underestimated in this analysis.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-consequence analysis.

The following scenario analyses have been conducted:

- Using a FIB-4 threshold of 0.6 and 3.25 to generate sebelipase alfa transition probabilities between the 'LAL Deficiency without CC, DCC or HCC' and CC states
- Using Forns and APRI scores to generate sebelipase alfa transition probabilities between the 'LAL Deficiency without CC, DCC or HCC' and CC states
- Using placebo data from the LAL-CL02 study to generate best supportive care transition probabilities between the 'LAL Deficiency without CC, DCC or HCC' and CC states
- Modelling the effect of sebelipase alfa on a cohort of only patients with infant-onset LAL Deficiency (and therefore 100% in the 'LAL Deficiency without CC, DCC or HCC' state at baseline)
- Modelling the effect of sebelipase alfa on a cohort of only patients with paediatric- or adult-onset LAL Deficiency (the LAL-CL02 cohort) (and therefore 69% in the 'LAL Deficiency without CC, DCC or HCC' state at baseline and the remainder in the CC state at baseline)

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic sensitivity analysis was conducted in the form of scenario analysis (see section 12.4.1) and one-way sensitivity analysis. Probabilistic sensitivity analysis (PSA) was also conducted.

In the one-way sensitivity analysis, parameters were varied either by the range reported (minimum and maximum) or the 95% confidence interval where available.

Where only a 95% confidence interval or range was reported, the standard error was approximated as being 2 standard deviations from the mean for the PSA. A gamma

distribution was used for all costs in the PSA, a dirichlet for the cohort distribution over health states at baseline and a beta distribution for all remaining parameters.

The PSA was conducted as a Monte Carlo simulation analysis with five hundred simulations. The health utility draws were constrained so that HCC and DCC health utility could not be greater than CC health utility, which could not be greater than LAL Deficiency without CC, DCC, or HCC health utility.

12.4.3 Complete tables as appropriate to summarise the variables used in the sensitivity analysis.

Table D12.14: Variables used in one-way deterministic sensitivity analysis

Variable	Base-case value	Minimum value	Maximum value	Rationale
Utilities				
'LAL Deficiency without CC, DCC or HCC' utility	0.92	0.65	0.95	Range reported by Mahady et al (2012)
Compensated Cirrhosis utility	0.82	0.65	0.89	
Decompensated Cirrhosis utility	0.6	0.46	0.81	
HCC utility	0.73	0.50	0.80	
Liver transplant (1st year) utility	0.69	0.62	0.86	
1st year utility for surviving infants	0.50	0.25	1.00	Arbitrary variation
1st year utility for dying patients	0.07	0	0.14	Arbitrary variation
Costs				
LAL Deficiency without CC, DCC or HCC	620	439	877	95% confidence interval reported in Backx, 2014
Compensated Cirrhosis	962	590	1,570	
Decompensated Cirrhosis	12,523	10,018	15,028	Arbitrary 20% variation as no range, standard error or confidence interval reported
HCC	11,159	8,927	13,391	
Liver Transplant	50,515	40,412	60,618	
1st year cost for dying infants	103,604	82,883	124,324	Arbitrary 20% variation
Best supportive care transition probabilities				
'LAL Deficiency without CC, DCC, or HCC' to CC	3.2%	0%	9%	Analysis of pre-baseline LAL-CL02 data

Variable	Base-case value	Minimum value	Maximum value	Rationale
CC to 'LAL Deficiency without CC, DCC, or HCC'	0%	0%	4%	Analysis of pre-baseline LAL-CL02 data
Natural history transition probabilities for best supportive care and sebelipase alfa				
'LAL Deficiency without CC, DCC, or HCC' to DCC	1.0%	1.0%	8.8%	Range from Mahady, 2012 adjusted
'LAL Deficiency without CC, DCC, or HCC' to HCC	0.3%	0.3%	1.6%	Range from Mahady, 2012 adjusted
CC to DCC	6.3%	4.2%	16.8%	Range from Mahady, 2012 adjusted
CC to HCC	3.2%	0.7%	5.3%	Range from Mahady, 2012 adjusted
CC to death (over age 1)	4.2%	2.1%	4.2%	Range from Mahady, 2012 adjusted
DCC to HCC	3.0%	0.7%	5%	Range from Mahady, 2012 adjusted
DCC to liver transplant	5.0%	5%	25%	Range from Mahady, 2012 adjusted
DCC to death	16.0%	15%	38%	Range from Mahady, 2012 adjusted
HCC to liver transplant	20.0%	10%	30%	Range from Mahady, 2012 adjusted
HCC to death	43.0%	37%	49%	Range from Mahady, 2012 adjusted
Liver transplant to death	12.0%	1%	22%	Range from Mahady, 2012 adjusted
Sebelipase alfa transition probabilities				
'LAL Deficiency without CC, DCC, or HCC' to CC	0%	0%	4%	LAL-CL02
CC to 'LAL Deficiency without CC, DCC, or HCC'	25%	0%	50%	LAL-CL02
Other parameters				
Discount rate	1.5%	0.0%	3.5%	NICE, 2013

Table D12.15: Variables used in multi-way scenario-based sensitivity analysis of patient scenarios

Scenario	N	Average Age	Modelled Age	Percentage at Baseline			
				LAL Deficiency without CC, DCC or HCC	CC	DCC	HCC
Base case	96	11.46	11	84%	16%	0%	0%
Infants (LAL-L03 and LAL-1-NH01)	30	0.08	0	100%	0%	0%	0%
LAL-CL02 cohort	66	16.63	17	69%	31%	0%	0%

Table D12.16: Variables used in multi-way scenario-based sensitivity analysis of transition probabilities

Scenario	Source of transition probabilities	Remaining in 'LAL Deficiency without CC, DCC, or HCC'	'LAL Deficiency without CC, DCC, or HCC' to CC	CC to 'LAL Deficiency without CC, DCC, or HCC'	Remaining in CC
Sebelipase alfa					
Base case	FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4>1.45)	100%	0%	25%	75%
1	FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)	94%	6%	33%	67%
2	FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)	100%	0%	100%	0%
3	Potentially Significant Fibrosis (Forns>4.2)	100%	0%	0%	100%
4	Potentially Significant Fibrosis (APRI>1.5)	100%	0%	86%	14%
Best supportive care					
Base case	Based on Mahady et al., adjusted	97%	3.2%	0%	100%
1	FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4>1.45)	100%	0%	25%	75%
2	FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)	92%	8%	0%	100%
3	Potentially Significant Fibrosis (Forns>4.2)	96%	4%	0%	100%
4	Potentially Significant Fibrosis (APRI>1.5)	96%	4%	33%	67%

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Treatment costs are excluded from the sensitivity analysis as the list price for sebelipase alfa is fixed.

12.5 Results of de novo cost-consequence analysis

Section 12.5 requires the sponsor to report the de novo cost-consequence analysis results. These should include the following:

- benefits
- costs
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean results (costs, QALYs)
- results of the sensitivity analysis.

Clinical outcomes from the model

12.5.1 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over).

Opportunity for model validation is limited. For infants, the model matches on survival at age 1. For the modelled LAL-CL02 cohort, the ALT and AST scores used in the model match those in the trials (Burton, 2015a).

12.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces for the sebelipase alfa and BSC groups are provided for the base case analysis in Figure D12.4 and D12.5. The sebelipase alfa treated patients are expected to spend the majority of their time alive in the LAL Deficiency without CC, DCC or HCC state; the BSC-treated patients are expected to spend the majority of their time in the death state.

Figure D12.4: Markov trace for best supportive care

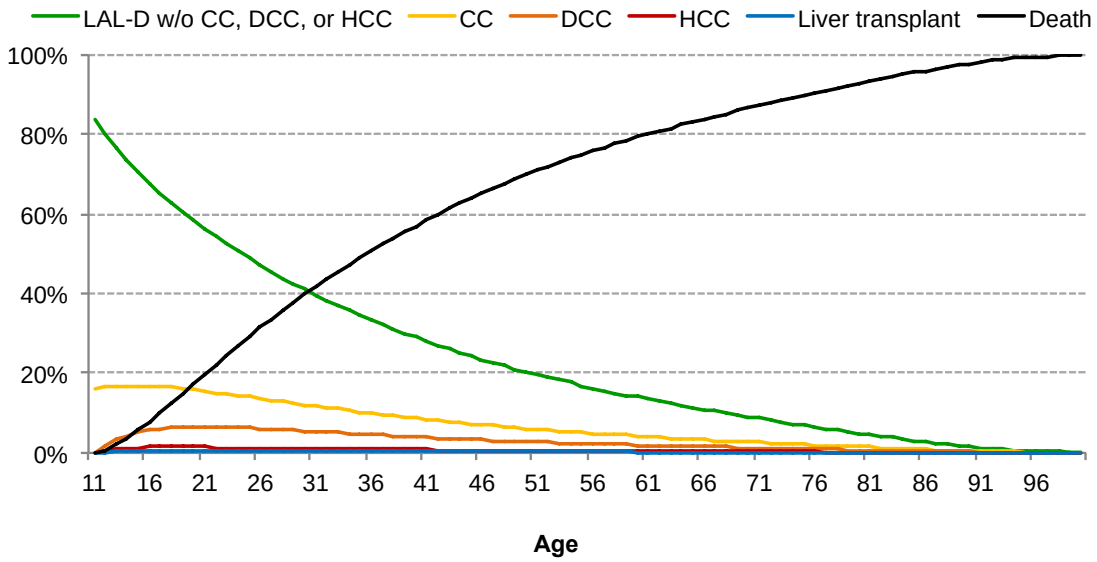
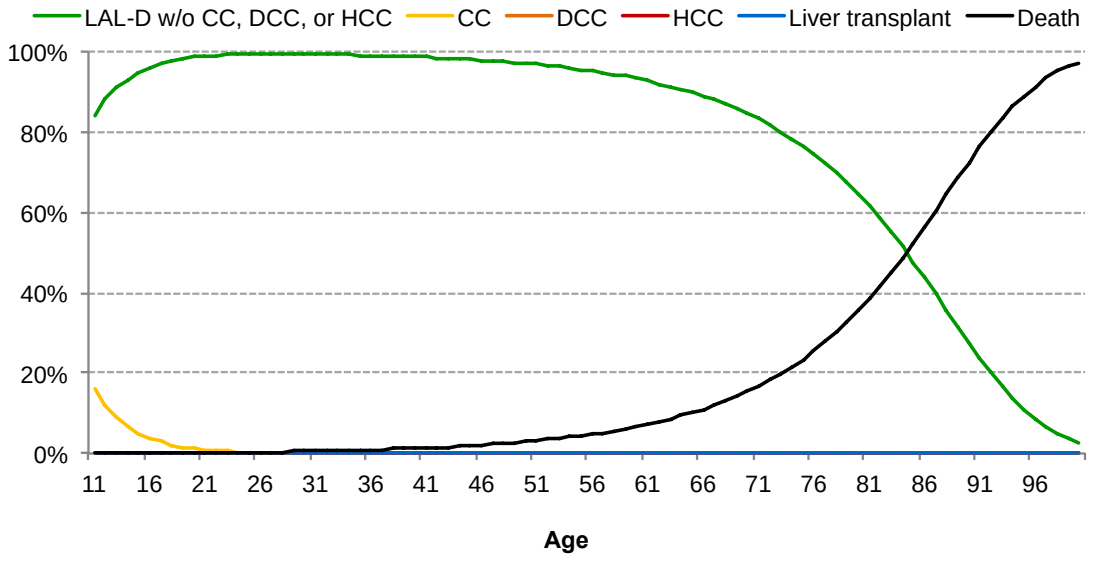


Figure D12.5: Markov trace for sebelipase alfa



12.5.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure D12.6: Accumulation of QALYs over time for best supportive care

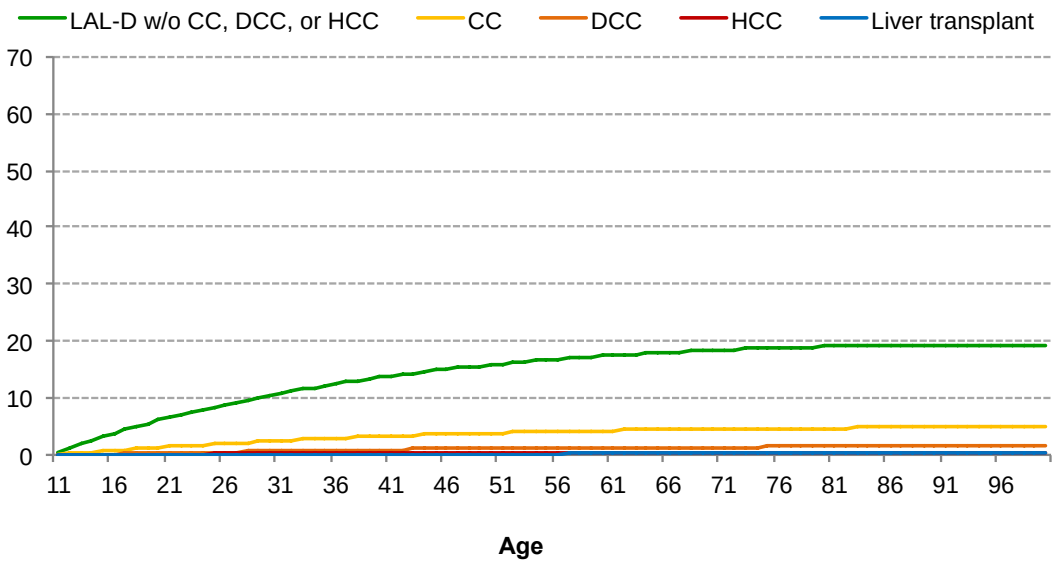
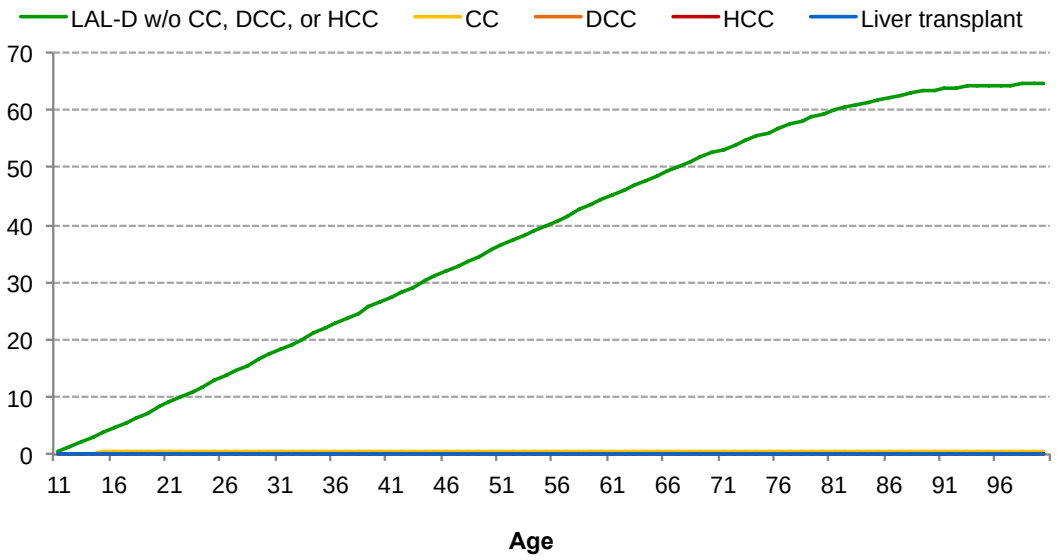
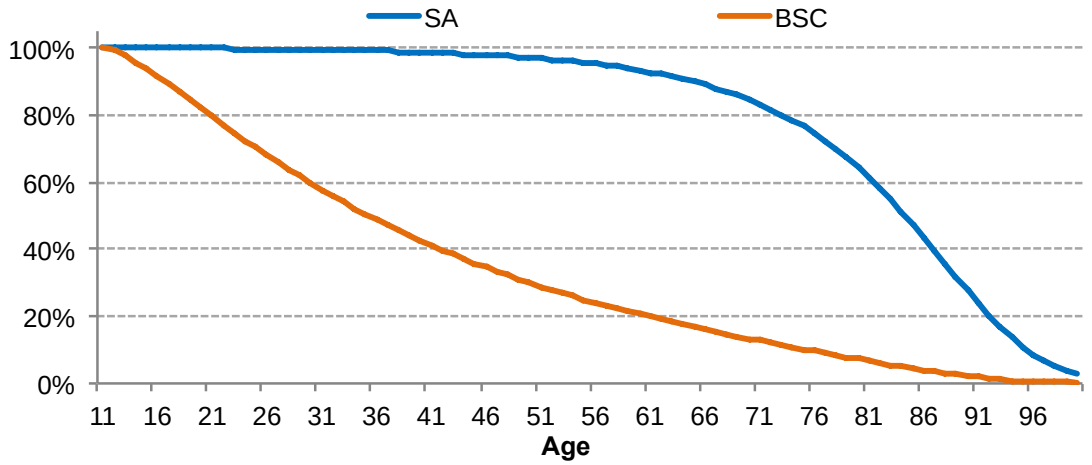


Figure D12.7: Accumulation of QALYs over time for sebelipase alfa



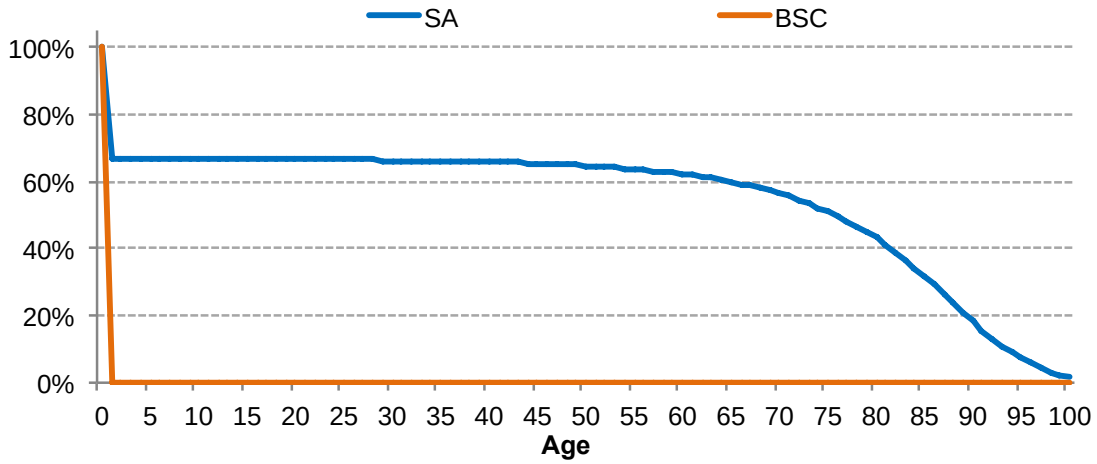
Survival differences appear in Figure D12.8 for the base case analysis. Sebelipase alfa patients are estimated to live for 70.70 years (undiscounted). BSC-treated patients are estimated to live for 29.99 years (undiscounted), leading to a gain of 40.71 years (undiscounted) for sebelipase alfa treated patients. The discounted gain in life years for sebelipase alfa-treated patients is 21.16 years.

Figure D12.8: Survival with sebelipase alfa and BSC in the base case



Survival differences appear in Figure D12.9 for the infant only analysis. Infant sebelipase alfa patients are expected to gain 53.13 years (undiscounted) or 30.90 years (discounted).

Figure D12.9: Survival with sebelipase alfa and BSC in the infant only analysis



12.5.4 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table D12.17: Model outputs by clinical outcomes

Outcome	Life years	QALYs
Best supportive care	22.08	19.24
Sebelipase alfa	43.24	39.73
Incremental	21.16	20.48

12.5.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Table D12.18: Summary of QALY gain by health state

Health state	Sebelipase alfa	Best supportive care	Increment	Absolute increment	% Increment
LAL Deficiency without CC, DCC, or HCC	39.29	14.37	24.92	24.92	**84.9%**
CC	0.44	3.49	-3.05	3.05	**10.4%**
DCC	0.00	1.01	-1.01	1.01	**3.4%**
HCC	0.00	0.27	-0.27	0.27	**0.9%**
Liver transplant	0.00	0.11	-0.11	0.11	**0.4%**
Death	0.00	0.00	0.00	0.00	**0.0%**
Total	**39.73**	**19.24**	**20.48**	**29.36**	**100.0%**

Base-case analysis

12.5.6 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis.

Table D12.19: Base-case results

	Total per patient cost (£)
Sebelipase alfa	[redacted]
Best supportive care	46,748

12.5.7 Report the total difference in costs between the technology and comparator(s).

The incremental costs for sebelipase alfa over best supportive care are [redacted] per patient.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost.

Table D12.20: Summary of costs by category of cost per patient

Cost category	Sebelipase alfa (£)	Best supportive care (£)	Increment (£)	Absolute increment (£)	% Increment
Direct medical costs	26,993	46,748	-19,755	19,755	**0.11%**
Drug costs	[redacted]	0	[redacted]	[redacted]	**99.89%**
Total	[redacted]	**46,748**	[redacted]	[redacted]	**100.0%**

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state.

Table D12.21: Summary of costs by health state per patient

Health state	Sebelipase alfa (£)	Best supportive care (£)	Increment (£)	Absolute increment (£)	% Increment
LAL Deficiency without CC, DCC, or HCC	26,480	9,685	16,796	16,796	[redacted]
CC	512	4,095	-3,582	3,582	[redacted]
DCC	0	21,066	-21,066	21,066	[redacted]
HCC	0	4,090	-4,090	4,090	[redacted]
Liver transplant	0	7,813	-7,813	7,813	[redacted]
Drug Costs	[redacted]	0	[redacted]	[redacted]	[redacted]
Total	[redacted]	**46,748**	[redacted]	[redacted]	**100.0%**

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not applicable. Adverse events were not included in the cost-consequence analysis.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Figure D12.10: Tornado diagram of incremental QALYs

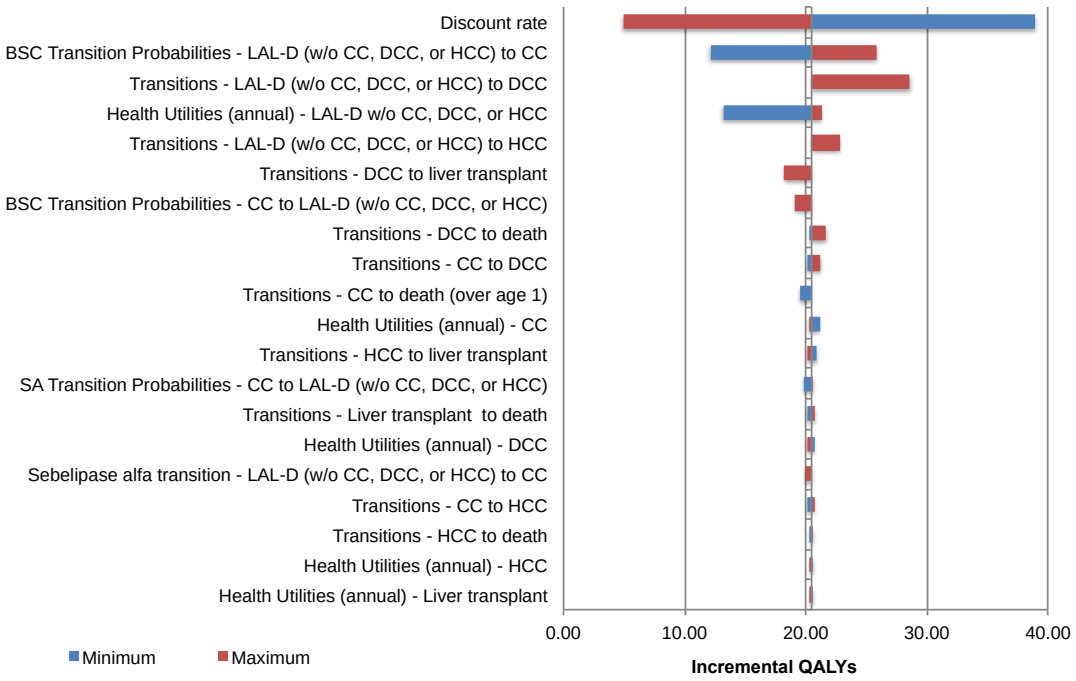


Figure D12.11: Tornado diagram of incremental life years (undiscounted)

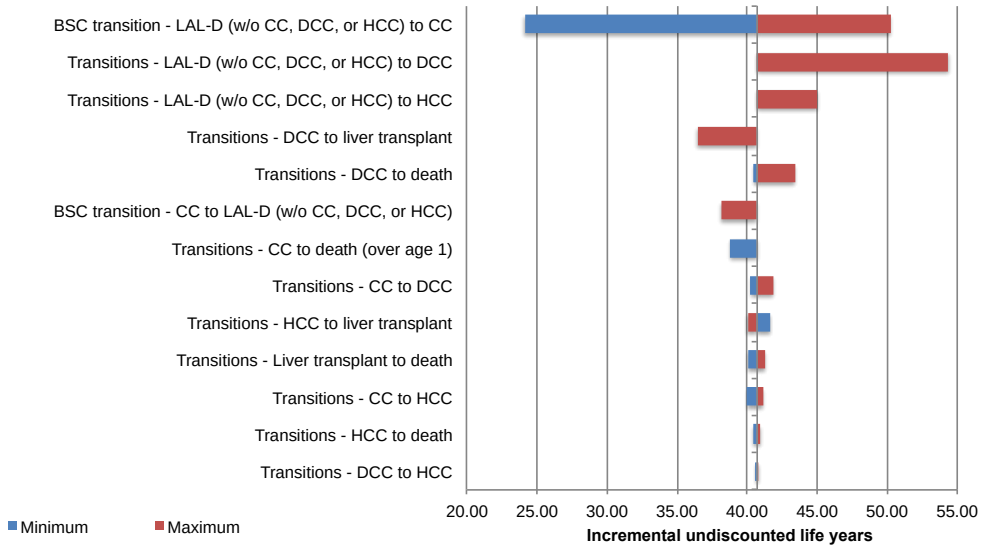


Figure D12.12: Tornado diagram of incremental costs

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Table D12.22: Results of deterministic multi-way scenario sensitivity analysis of patient scenarios

	Incremental costs (£)	Incremental QALYs	Incremental life years (undiscounted)
Base case	[redacted]	20.5	40.7
Infants	[redacted]	28.6	54.1
Full ARISE cohort	[redacted]	20.4	38.2

Table D12.23: Results of deterministic multi-way scenario sensitivity analysis of transition probabilities

	Incremental costs (£)	Incremental QALYs	Incremental life years (undiscounted)
Sebelipase alfa alternative transitions			
Scenario 1: FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)	[redacted]	19.9	40.7

	Incremental costs (£)	Incremental QALYs	Incremental life years (undiscounted)
Scenario 2: FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)	[redacted]	20.5	40.7
Scenario 3: Potentially Significant Fibrosis (Forns>4.2)	[redacted]	19.8	40.7
Scenario 4: Potentially Significant Fibrosis (APRI>1.5)	[redacted]	20.5	40.7
Best supportive care and sebelipase alfa alternative transitions			
BSC scenario 1 vs. sebelipase base case	[redacted]	10.2	20.8
BSC scenario 2 vs. sebelipase scenario 1	[redacted]	24.9	49.6
BSC scenario 3 vs. sebelipase scenario 3	[redacted]	20.6	42.1
BSC scenario 4 vs. sebelipase scenario 4	[redacted]	15.2	30.5

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Table D12.24: Mean and 95% CI probabilistic sensitivity analysis results

	Total costs (£)	Total QALYs	Total life years (undiscounted)
Best supportive care	45,093 (29,721 – 75,624)	20.6 (10.9 – 31.8)	33.0 (16.8 – 52.7)
Sebelipase alfa	[redacted]	39.8 (31.5 – 44.6)	71.0 (59.8 – 77.7)

Figure D12.13: Resulting total costs from PSA

[redacted]

Figure D12.14: Resulting total QALYs from PSA

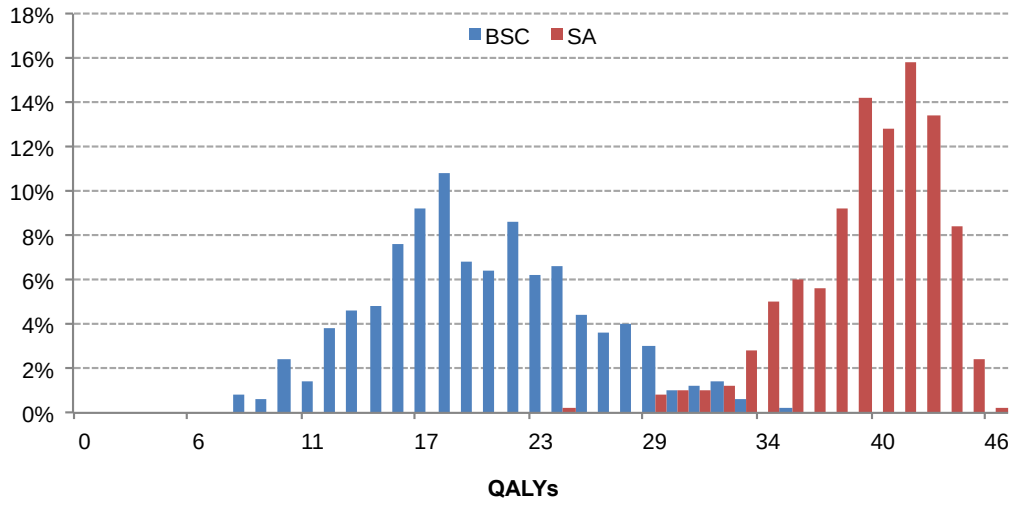
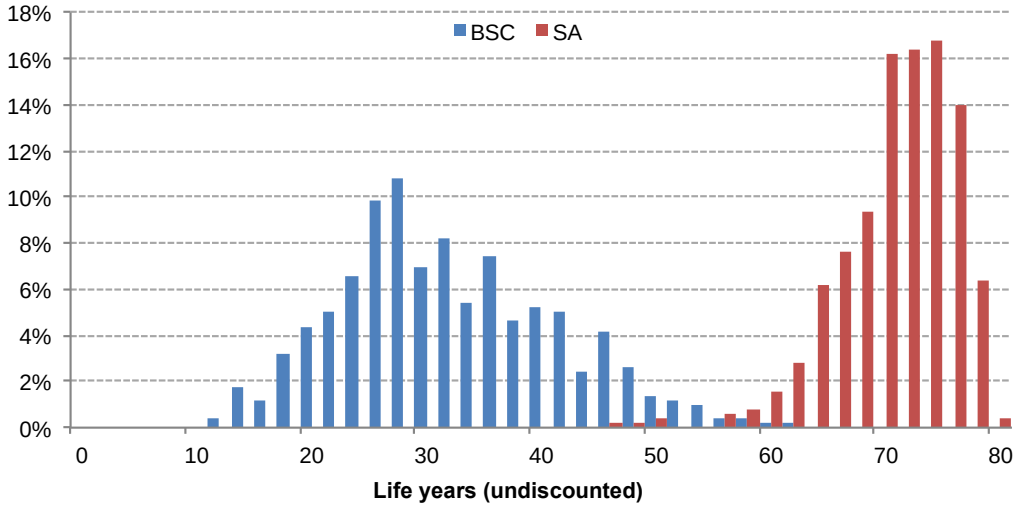


Figure D12.15: Resulting total life years from PSA



12.5.14 What were the main findings of each of the sensitivity analyses?

Results were most sensitive to discount rates, as expected. QALY and survival results were also sensitive to the transition probabilities to and from the 'LAL Deficiency without CC, DCC and HCC' state. Treating the youngest patients has the highest QALY gains. QALY gains are large in all analyses.

12.5.15 What are the key drivers of the cost results?

Discount rates and the cost of sebelipase alfa are the greatest drivers of the results.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

No subgroup analysis was performed.

12.6.2 Define the characteristics of patients in the subgroup(s).

No subgroup analysis was performed.

12.6.3 Describe how the subgroups were included in the cost-consequence analysis.

No subgroup analysis was performed.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis).

No subgroup analysis was performed.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

No subgroup analysis was performed.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The technical aspects of the model were reviewed to ensure internal consistency.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-consequence analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published literature on cost-effectiveness or related topics for LAL Deficiency.

12.8.2 Is the cost-consequence analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The analysis for sebelipase alfa has a number of weaknesses:

- Extreme difficulty exists with using a standard health technology assessment approach in modelling an ultra-orphan condition due to varied care pathways with poorly defined standard of care, lack of data specific to LAL Deficiency, and the limited number of patients in clinical trials. For example, there are short follow-up times for BSC in the trials.
- The measurement of time to CC from 'LAL Deficiency without CC, DCC, or HCC' is likely biased downwards owing to the fact that eight of the patients with CC first had their CC identified at the baseline of the trials. Patients who died from their disease owing to rapid progression are omitted from the analysis; thus a survival bias likely also pushes transition time estimates lower than they actually are.
- There is no liver or other outcome data for LAL Deficiency patients in the published literature that can be used in a model. Bernstein et al. (2013) presented data illustrative of the high comorbidity and mortality burden of LAL Deficiency, but as a series of case studies, cannot be used to parameterize the model. Thus, there are no outside cohorts for external validity assessment of a LAL Deficiency model.
- LAL Deficiency affects multiple organ systems, and manifestations of LAL Deficiency can vary substantially; the model is unable to capture all these effects. For instance, cardiovascular effects, failure to thrive (growth failure),

severe malabsorption, other gastrointestinal symptoms, pulmonary hypertension associated with intimal lipid deposition in pulmonary arteries, severe hypersplenism, mesenteric lipodystrophy, anaemia, and thrombocytopenia are excluded from the model owing to lack of data. Nevertheless, patients with LAL Deficiency face damage and complications related to involvement of multiple vital organs including the liver, intestines, spleen and heart. It is estimated that 87% of patients with LAL Deficiency experience manifestations in more than one organ (Bernstein, 2013). These omissions of important clinical aspects of LAL Deficiency are insurmountable owing to data limitations but likely bias model outcomes against the value of sebelipase alfa.

- The economic model does not include educational attainment, productivity benefits or other indirect costs, though these are expected to be large and in favour of sebelipase alfa.
- There have been no health utility or direct medical cost studies that have been published in LAL Deficiency.

These issues are in addition to those affecting all ultra-orphan drugs, including small sample sizes (with the consequent statistical issues in describing small samples), no randomized controlled trials with long term follow-up, thin knowledge bases about the natural history of the disease prior to the trials, lack of established databases or algorithms from which to extrapolate trial data to life-time outcomes, and little evidence outside of case series.

Caution should be used when attempting to interpret these analyses due to the relatively small body of LAL Deficiency disease information used to estimate patient outcomes over a lifetime.

Instead of relying on an economic model that is inherently flawed due to the reasons listed above, the factors most important for NICE to consider when assessing the value of sebelipase alfa in the treatment of LAL Deficiency include:

- The devastating and life-threatening nature of LAL Deficiency
- The clinical and life-saving benefits of sebelipase alfa
- The very small number of patients with LAL Deficiency
- The clear lack of available and effective treatment alternatives
- The ethical imperative to provide access to treatment to the sickest citizens and to ensure such access is provided fairly and without discrimination between patients with rare diseases and those with more common diseases.

Best supportive care is associated with poor HRQL in all analyses, and extreme mortality in infant patients. Conversely, sebelipase alfa is associated with very high QALY gains over a patient's lifetime, regardless of which patient group is treated. Sebelipase alfa is expected to extend life in all patients.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Enrolling patients into the LAL Deficiency UK registry and capturing the effects of sebelipase alfa will validate and enhance the results of the cost-consequence analysis.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

An epidemiological approach, based on the overall population of England, was used to determine the expected financial implications, commonly known as "budget impact", associated with public funding for sebelipase alfa for the treatment of LAL Deficiency over a five-year time period, from the start of Year 1 (i.e., 2016) to Year 5 (i.e., 2020).

Two scenarios were modelled: 1) sebelipase alfa with market access in England, and 2) sebelipase alfa without market access in England. The budget impact difference between these two scenarios is the net budget impact. The parameters and calculations used in the budget-impact model (BIM) are described in detail in the sections below. Please also see Appendix 7 for a copy of the budget impact model (BIM) itself.

Note about Rounding: Please note that throughout this section, and in the corresponding Excel spreadsheet that contains the BIM itself, exact calculations were computed in the assessment of budget impact (i.e., no rounding was performed). However, numbers presented in outputs from the model may be displayed as integers with zero decimal places showing. As a result, some computations may appear incorrect in the spreadsheet and seem to be off by a single unit; however, this is due to rounding for presentation purposes only.

Patient Groups Included in BIM and Population of England

Two groups of patients are modelled to capture differences in the epidemiology of LAL Deficiency in the published literature, and differences in dosing for sebelipase alfa based on age of presentation of the disease. The two groups modelled include: 1) patients with presentation of LAL Deficiency between birth and age 1 ("Age 0-1 presentation" group); and 2) patients with presentation of LAL Deficiency at age greater than 1 year ("Age 1+ presentation" group). Of note, these groups reflect the age that a patient presents with LAL Deficiency, not necessarily their "current" age in the model or related outputs, as patients age over the five-year period of the model.

Population of England

Population size data for the two groups are based on estimates for England in 2013, the latest year reported by the Office of National Statistics (ONS) (ONS, 2013a). Average population growth for the two groups is assumed to be 0.63% based on analysis by ONS in 2013 (ONS, 2013b). The BIM starts in 2016. Therefore, relying on the 2013 estimate from ONS, and applying the average growth estimate of 0.63%, we determine the estimated 2016 population size for England as highlighted in Table D13.1 below.

Table D13.1: Estimated Population of England, 2013-2020

Year	Age 0-1 presentation	Age 1+ presentation
2013	676,586	53,189,231
2014	680,848	53,524,323
2015	685,138	53,861,526
2016 (Year 1 of BIM)	689,454	54,200,854
2017 (Year 2 of BIM)	693,798	54,542,319
2018 (Year 3 of BIM)	698,169	54,885,936
2019 (Year 4 of BIM)	702,567	55,231,717
2020 (Year 5 of BIM)	706,993	55,579,677

Source: ONS, 2013a)

Estimated Epidemiology of LAL Deficiency in England

Variable estimates of the epidemiology of LAL Deficiency exist in the published literature. Published prevalence rates vary from 1:40,000 to 1:300,000 or 1:400,000 (Grabowski, 2012; Muntoni, 2007; Scott, 2013). The presentation of LAL Deficiency in infants is even rarer with an estimated incidence of approximately 1:704,000 births (Meikle, 1999).

One study in particular, Scott et al. (2013), studied the prevalence of LAL Deficiency using the Exon 8 Splice Junction Mutation (E8SJM) in different populations, including healthy African-American, Asian, Caucasian, Hispanic, and Ashkenazi Jewish individuals from the greater New York metropolitan area (10,000 LIPA alleles) and from African-American, Caucasian, and Hispanic subjects enrolled in the Dallas Heart Study (6,578 LIPA alleles) (Scott, 2013). Using Hardy-Weinberg equilibrium (H-WE), and reflecting the ethnicity mix of England, the authors' model estimates the prevalence of LAL Deficiency in the population of England to be 1:99,000.

For purposes of modelling the budget impact of treatment for LAL Deficiency, the following epidemiological rates are used:

Prevalence: Amongst patients in the Age 0-1 presentation group, a prevalence rate is unnecessary to determine the existing patient population with LAL Deficiency in Year 1 of the BIM. Prior to Year 1, it is assumed that treatment with sebelipase alfa is not available; the mortality rate for patients presenting with LAL Deficiency between birth and age 1 is therefore 100% (see the description of mortality below).

Consequently, all patients in the Age 0-1 presentation group in Year 1 are incident patients.

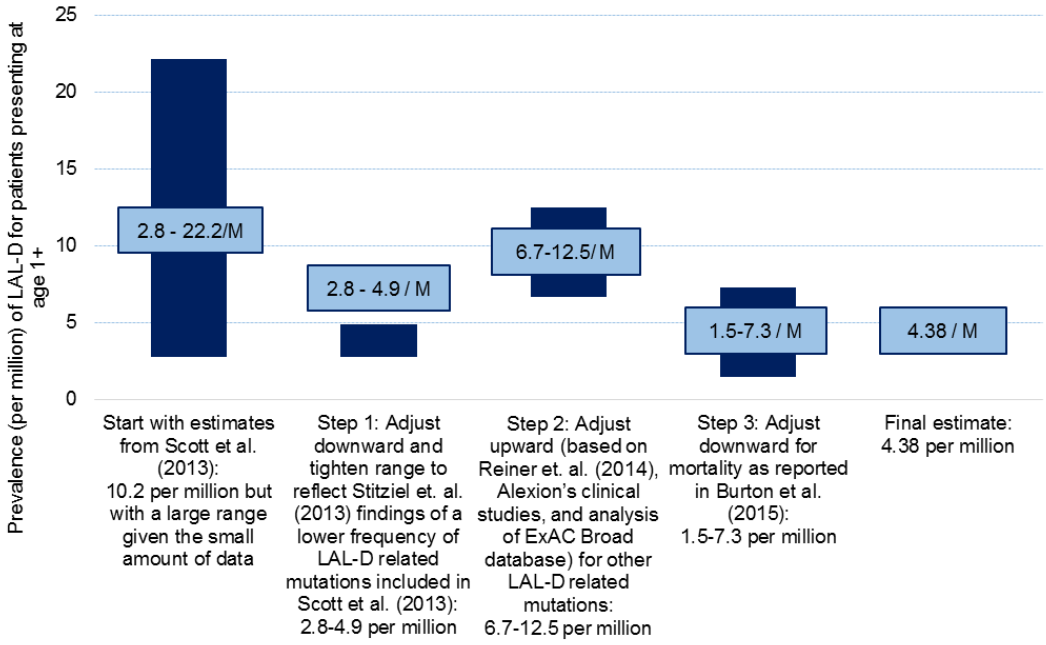
Amongst patients in the Age 1+ presentation group, prevalence of LAL Deficiency is estimated to be 4.38 per million (or 1:228,311), based on internal Alexion modelling, as outlined below.

Starting with a prevalence-rate estimate from Scott et al. (2013), adjusted for the ethnicity mix of England, one would estimate 10.1 cases per million. However, this approach analyses a subset of LAL-D causal mutations (those related only to the exon 8 splice junction mutation E8SJM) and has a broad estimate range given the small number of E8SJM carriers found in the study. We take three steps to refine and improve this estimate further:

- **Step 1: Strengthen E8SJM Data**: Include a larger number of E8SJM carriers in the analysis from Stitziel et al. (2013) and the Exome Aggregation Consortium (ExAC) Broad database (ExAC, 2015) which tightens the range and reduces the estimate to 2.8-4.9 cases per million.
- **Step 2: Add Causal Mutations**: Consider all causal mutation combinations with or without E8SJM, which contribute to LAL Deficiency. Combining mutations from Reiner et al. (2014), Alexion's clinical studies, and analysis of the ExAC database, this increases the estimate to 6.7-12.5 cases per million.
- **Step 3: Incorporate Mortality**: Scott et al.'s original analysis did not consider the reduced life-span of patients with LAL Deficiency. Incorporating mortality as it is reported in Burton et al. (2015c), and also observed in Alexion's clinical studies, leads to an estimate of 1.5-7.3 cases per million.

These three steps as outlined in Figure D13.1 incorporate the ethnicity mix of England, the latest understanding of mutations which contribute to LAL-D, and our current understanding of reduced life-span to arrive at a final prevalence estimate of 4.38 cases per million in England.

Figure D13.1: Prevalence Estimates for Age 1+ Presentation LAL Deficiency Patients



Incidence: Amongst patients in the Age 0-1 presentation group, incidence of LAL Deficiency is estimated to be 1.52 per million (or 1:657,895); this estimate is based on the frequency analysis from Scott et al. (2013) combined with null-allele assessment from Reiner et al. (2014), which enable an assessment of incidence of presentation of symptoms at birth. In the Age 1+ presentation group, incident patient counts are estimated based on the prevalence estimate described above, and the distribution of age of presentation from Bernstein et al. (2013).

Patient progression throughout the model

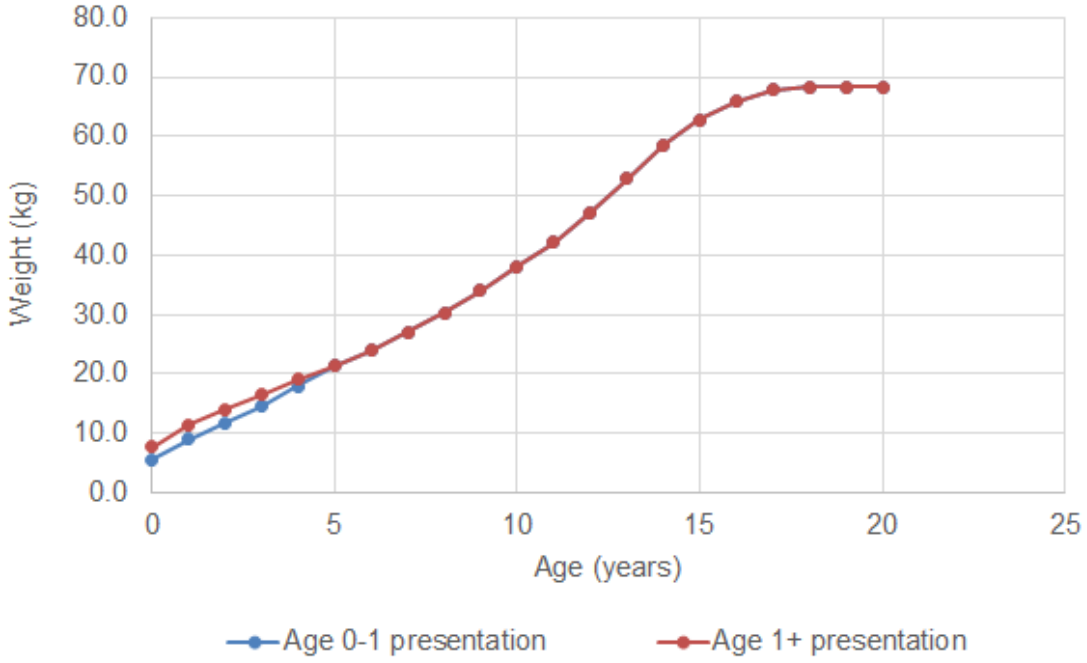
Given the above epidemiological assumptions, the budget-impact analysis assumes that there will be 237 prevalent patients in the Age 1+ presentation group in 2016 (Year 1). In each of the five years modelled, it is estimated that there will be 1 incident patient in the Age 0-1 presentation group, and between 5 and 8 incident patients in the Age 1+ presentation group.

In order to determine the dosing for these patients over the five-year horizon, we model patient weight and the progression of the weight over this period using a correspondence of age to weight for UK children of ages 0 to 20 years constructed by the Royal College of Paediatrics and Child Health (RCPCH) and based on World Health Organisation (WHO) Child Growth Standards (RCPCH, 2015). We use actual weights and ages from patients in the sebelipase alfa clinical trial programme to determine which percentile curves to apply for patients with LAL Deficiency.

Gender-specific weights from the RCPCH data are averaged based on the gender balance observed in the sebelipase alfa ARISE trial (Data on File, CSR LAL-CL02). In ARISE, of the total study population, 50% of the patients were female (33/66), and also 50% for each arm (18/36 for sebelipase alfa, 15/30 for placebo). Based on input from Alexion's clinical team, incident patients in the Age 0-1 presentation group are modelled as starting at the 2nd percentile of weight for their age, and if they receive sebelipase alfa treatment, grow to the 75th percentile by Year 5. The analysis assumes that patients in the Age 1+ presentation group are consistently in the 75th percentile of weight.

Figure D13.2 depicts the age-to-weight correspondence, by age of presentation group, for LAL Deficiency patients receiving treatment with sebelipase alfa.

Figure D13.2: Age-to-weight correspondence by age of presentation group for LAL Deficiency patients receiving sebelipase alfa



Source: RCPCH, 2015

Values of the age-to-weight correspondence for LAL Deficiency patients receiving treatment with sebelipase alfa are also presented in Table D13.2.

Table D13.2: Age to weight correspondence by age of presentation group for LAL Deficiency patients receiving sebelipase alfa

	Weight (kg)	
Age	**Age 0-1 presentation**	**Age 1+ presentation**
Age: 0-1	5.6	7.7
Age: 1-2	9.0	11.4
Age: 2-3	11.7	14.1
Age: 3-4	14.6	16.5
Age: 4-5	18.0	19.0
Age: 5-6	21.4	21.4
Age: 6-7	24.0	24.0
Age: 7-8	27.1	27.1
Age: 8-9	30.3	30.3
Age: 9-10	34.0	34.0
Age: 10-11	38.1	38.1
Age: 11-12	42.2	42.2
Age: 12-13	47.2	47.2
Age: 13-14	52.9	52.9
Age: 14-15	58.5	58.5
Age: 15-16	62.9	62.9
Age: 16-17	65.9	65.9
Age: 17-18	67.8	67.8
Age: 18-19	68.3	68.3

	Weight (kg)	
Age	**Age 0-1 presentation**	**Age 1+ presentation**
Age: 19-20	68.3	68.3
Age: 20-100	68.3	68.3

Source: RCPCH, 2015

Of note, an age-to-weight correspondence is not presented for patients treated with BSC, as patient weight is only required in order to model sebelipase alfa dosing, and is therefore not relevant to patients assumed to receive BSC.

For purposes of accounting for patient weight gain over the five-year horizon of the model, the Age 1+ presentation group is further divided into 20 age ranges (i.e., “Age 1-2”, “Age 2-3”, … , “Age 20+”). Each range has a unique patient weight sourced from the age-to-weight correspondence described above (see Figure D13.2, Table D13.2). Prevalent and incident patients in the Age 1+ presentation group are allocated to these age ranges based on the age distribution of LAL Deficiency patients at onset reported in Bernstein et al. (2013), as presented in Table D13.3.

Table D13.3: Age distribution of LAL Deficiency patients at presentation, based on Bernstein et al. (2013)

Age Range	Percent
Age: 1-2	19.1%
Age: 2-3	9.7%
Age: 3-4	9.7%
Age: 4-5	9.7%
Age: 5-6	9.7%
Age: 6-7	3.6%
Age: 7-8	3.6%
Age: 8-9	3.6%
Age: 9-10	3.6%
Age: 10-11	3.6%
Age: 11-12	3.6%
Age: 12-13	3.6%
Age: 13-14	0.8%
Age: 14-15	0.8%
Age: 15-16	0.8%
Age: 16-17	0.8%
Age: 17-18	0.8%
Age: 18-19	0.8%
Age: 19-20	0.8%
Age: 20+	11.5%
Total	100.0%

As a sensitivity analysis (see Section 13.7), we also consider the assumption that at presentation of LAL Deficiency, patients in the Age 1+ presentation group have age according to the baseline age distribution observed in ARISE, as presented in Table D13.4.

Table D13.4: Age distribution of LAL Deficiency patients at presentation, based on ARISE

Age Range	Percent
Age: 1-2	0%
Age: 2-3	0%
Age: 3-4	0%
Age: 4-5	3%
Age: 5-6	0%
Age: 6-7	5%
Age: 7-8	3%
Age: 8-9	5%
Age: 9-10	5%
Age: 10-11	3%
Age: 11-12	14%
Age: 12-13	8%
Age: 13-14	12%
Age: 14-15	6%
Age: 15-16	5%
Age: 16-17	3%
Age: 17-18	2%
Age: 18-19	5%
Age: 19-20	2%
Age: 20+	23%
Total	100.0%

Over the course of the model's five-year horizon, patients age and gain weight. For example, incident patients in the Age 0-1 presentation group in Year 1 will reach age range Age: 4-5 by Year 5 of the model if treated with sebelipase alfa, moving from a weight of 5.6 kg in Year 1 to 18.0 kg in Year 5. However, while incident patients in the Age 0-1 presentation group effectively "age out" of the 0-1 age range in their second year in the model, they continue to be tracked in the Age 0-1 presentation group due to dosing differences depending on age of presentation of LAL Deficiency (see section 13.3).

Mortality

Mortality is based on the LAL-CL03 (infant) clinical trial. In LAL-CL03, 6 of 9 infants with rapidly progressing LAL Deficiency treated with sebelipase alfa survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). Assessing treatment beyond 12 months of age, 1 additional patient died at age 15 months. A primary control group identified from a historical cohort (LAL-1-NH01) revealed no survival

beyond 8 months of age (implying 0% survival at 12 months, the unit of time in the model) (Jones, 2015a). Consequently, a mortality rate of 33% is applied to Age 0-1 presentation patients in their first year, if treated with sebelipase alfa, and 100% if treated with BSC.

For patients in the Age 1+ presentation group, it is assumed that mortality risk for those treated with sebelipase alfa is the same as those treated with BSC, and is set to 0% to be conservative (i.e., to reflect the higher estimate of net budget impact). Results from clinical studies were not available to support a definitive difference in mortality risk between treatment options for this patient group.

Patient counts over time

Applying the aging/weight-gain and mortality dynamics described above to the patients progressing through the model, we calculate patient counts by age range, for scenarios with sebelipase alfa with and without market access in England, as presented in Tables D13.5-D13.8.

As mentioned above, the age group labels reflect the age when a patient presented with LAL Deficiency (and consequently, their dosing regimen). For example, by Year 5, 3.9 patients treated with sebelipase alfa who at one point in time presented with LAL Deficiency as infants are still receiving Age 0-1 presentation group dosing; they are not all of age 0-1, however, as reflected in Table D13.5.

Table D13.5: Age 0-1 presentation group patient counts, scenario with sebelipase alfa with market access in England

Age 0-1 presentation patients, with sebelipase alfa	Year 1	Year 2	Year 3	Year 4	Year 5
Age: 0-1	1.0	1.1	1.1	1.1	1.1
Age: 1-2		0.7	0.7	0.7	0.7
Age: 2-3			0.7	0.7	0.7
Age: 3-4				0.7	0.7
Age: 4-5					0.7
Age: 5-6					
Age: 6-7					
Age: 7-8					
Age: 8-9					
Age: 9-10					
Age: 10-11					
Age: 11-12					
Age: 12-13					
Age: 13-14					
Age: 14-15					
Age: 15-16					
Age: 16-17					
Age: 17-18					
Age: 18-19					

Age 0-1 presentation patients, with sebelipase alfa	Year 1	Year 2	Year 3	Year 4	Year 5
Age: 19-20					
Age: 20-100					
Total	**1.0**	**1.8**	**2.5**	**3.2**	**3.9**

Table D13.6: Age 0-1 presentation group patient counts, scenario with sebelipase alfa without market access in England

Age 0-1 presentation patients, without sebelipase alfa	Year 1	Year 2	Year 3	Year 4	Year 5
Age: 0-1	1.0	1.1	1.1	1.1	1.1
Age: 1-2					
Age: 2-3					
Age: 3-4					
Age: 4-5					
Age: 5-6					
Age: 6-7					
Age: 7-8					
Age: 8-9					
Age: 9-10					
Age: 10-11					
Age: 11-12					
Age: 12-13					
Age: 13-14					
Age: 14-15					
Age: 15-16					
Age: 16-17					
Age: 17-18					
Age: 18-19					
Age: 19-20					
Age: 20-100					
Total	**1.0**	**1.1**	**1.1**	**1.1**	**1.1**

Table D13.7: Age 1+ presentation group patient counts, scenario with sebelipase alfa with market access in England

Age 1+ presentation patients, with sebelipase alfa	Year 1	Year 2	Year 3	Year 4	Year 5
Age: 0-1	-	-	-	-	-
Age: 1-2	47	2	1	1	1
Age: 2-3	24	47	2	2	1
Age: 3-4	24	25	48	3	2
Age: 4-5	24	25	25	49	3
Age: 5-6	24	25	25	26	49
Age: 6-7	9	24	25	25	26
Age: 7-8	9	9	24	25	26
Age: 8-9	9	9	9	25	25
Age: 9-10	9	9	9	10	25
Age: 10-11	9	9	9	10	10

Age 1+ presentation patients, with sebelipase alfa	Year 1	Year 2	Year 3	Year 4	Year 5
Age: 11-12	9	9	9	10	10
Age: 12-13	9	9	9	10	10
Age: 13-14	2	9	9	9	10
Age: 14-15	2	2	9	9	9
Age: 15-16	2	2	2	9	9
Age: 16-17	2	2	2	2	9
Age: 17-18	2	2	2	2	2
Age: 18-19	2	2	2	2	2
Age: 19-20	2	2	2	2	2
Age: 20-100	28	31	33	36	39
Total	**244**	**252**	**259**	**264**	**269**

Table D13.8: Age 1+ presentation group patient counts, scenario with sebelipase alfa without market access in England

Age 1+ presentation patients, without sebelipase alfa	Year 1	Year 2	Year 3	Year 4	Year 5
Age: 0-1	-	-	-	-	-
Age: 1-2	47	2	1	1	1
Age: 2-3	24	47	2	2	1
Age: 3-4	24	25	48	3	2
Age: 4-5	24	25	25	49	3
Age: 5-6	24	25	25	26	49
Age: 6-7	9	24	25	25	26
Age: 7-8	9	9	24	25	26
Age: 8-9	9	9	9	25	25
Age: 9-10	9	9	9	10	25
Age: 10-11	9	9	9	10	10
Age: 11-12	9	9	9	10	10
Age: 12-13	9	9	9	10	10
Age: 13-14	2	9	9	9	10
Age: 14-15	2	2	9	9	9
Age: 15-16	2	2	2	9	9
Age: 16-17	2	2	2	2	9
Age: 17-18	2	2	2	2	2
Age: 18-19	2	2	2	2	2
Age: 19-20	2	2	2	2	2
Age: 20-100	28	31	33	36	39
Total	**244**	**252**	**259**	**264**	**269**

Total patient counts for both scenarios are presented in Table D13.9.

Table D13.9: Total LAL Deficiency prevalent patients, by age presentation group and scenario

Patients	Year 1	Year 2	Year 3	Year 4	Year 5
Age 0-1 presentation					

with sebelipase alfa	1	2	2	3	4
w/o sebelipase alfa	1	1	1	1	1
Age 1+ presentation					
with sebelipase alfa	244	252	259	264	269
w/o sebelipase alfa	244	252	259	264	269

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

In order to calculate the budget impact of sebelipase alfa treatment amongst the prevalent and incident patients described above, uptake and utilization must be determined. Expected treatment uptake is a function of diagnosis and treatment rates; utilization is based on treatment continuation and compliance with dosing.

Diagnosis rate

Table D13.10 presents the diagnosis rate of LAL Deficiency patients in England for the two scenarios: 1) sebelipase alfa with market access in England and 2) sebelipase alfa without market access in England. These diagnosis rates are based on Alexion's experience in ultra-rare diseases and the expected diagnosis rate of patients with LAL Deficiency in England based on current knowledge of the healthcare system and discussions with clinical experts.

Table D13.10: Diagnosis rate of LAL Deficiency

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario: **sebelipase alfa with market access in England**					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: **sebelipase alfa without market access in England**					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment rate with sebelipase alfa

We assume all patients diagnosed with LAL Deficiency receive either best supportive care (BSC) or sebelipase alfa; it is assumed that any patient not treated with sebelipase alfa would receive BSC. Treatment rates for sebelipase alfa are

presented in Table D13.11 for the two scenarios. As with the diagnosis rates, these treatment rates are based on Alexion's experience in ultra-rare disease, particularly the company's experience with launching eculizumab (Soliris®) for two ultra-rare diseases in over 40 countries world-wide.

Table D13.11: Treatment rate amongst diagnosed LAL Deficiency patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario: **sebelipase alfa with market access in England**					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: **sebelipase alfa without market access in England**					
Age 0-1 presentation	0%	0%	0%	0%	0%
Age 1+ presentation	0%	0%	0%	0%	0%

Applying the diagnosis and treatment rates to the total LAL Deficiency prevalent patient counts (see Section 13.1) yields estimates of the total treated patients per year, as presented in Table D13.12.

Table D13.12: Total treated patients, by scenario, treatment type, and age presentation group

Patients	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario: **sebelipase alfa with market access in England**					
Sebelipase alfa					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: **sebelipase alfa without market access in England**					
Sebelipase alfa					
Age 0-1 presentation	0	0	0	0	0
Age 1+ presentation	0	0	0	0	0
BSC					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment continuation rate

In the sebelipase alfa clinical trials, discontinuation of treatment with sebelipase alfa and dose modifications due to adverse events were uncommon, and the majority of adverse events were mild to moderate in severity (See Section 9.7.3). However, based on Alexion's experience in other ultra-rare diseases, we assume that over a period of years, some patients will not continue treatment, with highest continuation

rates in the first year of treatment. The assumed treatment continuation rate, by age group, is presented in Table D13.13. Amongst the Age 1+ presentation group (which will likely include children, adolescents, and adults treated on an outpatient basis, and whose most serious underlying manifestations may not be the most troublesome for them on a daily basis), we might expect higher rates of discontinuation than amongst infants managed on an in-patient basis.

Table D13.13: Treatment continuation rate amongst treated patients, by years from start of treatment

	Years from patient's start of treatment				
	1st	2nd	3rd	4th	5th
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Compliance rate

As expected with all therapies, even an infused biologic like sebelipase alfa, some may not comply with prescribed dosing. The compliance rates assumed are based on Alexion's experience with eculizumab, another infused treatment for ultra-rare diseases. The compliance rates also are expected to be high in England as a result of the homecare service available to patients with lysosomal storage disorders in England.

Table D13.14: Compliance with recommended dosing

	Year 1	Year 2	Year 3	Year 4	Year 5
Age 0-1 presentation	100%	100%	100%	100%	100%
Age 1+ presentation	85%	85%	85%	85%	85%

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures).

Sebelipase alfa Treatment Costs

As mentioned in Section 1.3, the BIM is structured to model two groups (i.e., the Age 0-1 presentation and Age 1+ presentation groups, reflecting the age of presentation with LAL Deficiency) in part to account for differences in dosing depending on age of presentation.

The following is the recommended dosing of sebelipase alfa for each age presentation group (Kanuma SPC, 2015):

- **Age 0-1 presentation**: The recommended starting dose for infants (< 6 months of age) presenting with rapidly progressive LAL Deficiency is 1 mg/kg administered once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response. In the LAL-CL03 clinical trial, patients < 6 months of age presenting with rapidly progressive LAL Deficiency were dose escalated to 3 mg/kg once weekly during their first year of treatment, based on clinical response. Of these patients, escalation from 1 mg/kg per week to 3 mg/kg per week was required between 2-10 weeks from the start of treatment for 60% of patients of age 0-1, and between 6 months and a year from the start of treatment for the remaining 40%. We therefore estimate that the time-weighted average weekly dosing required by a patient in the Age 0-1 presentation group in the first year of life is:

  60% x ((6/52) x 1mg/kg + (46/52) x 3mg/kg) + 40% x ((9/12) x 1mg/kg + (3/12) x 3mg/kg) = 2.3mg/kg

  Time weights assume that escalation occurs at the midpoint of the time range of escalation (i.e., 2-10 weeks = 6 weeks, 6 months to a year = 9 months). In clinical studies, no reversion from 3 mg/kg to 1 mg/kg was observed after escalation, so it is assumed in the BIM that all Age 0-1 presentation patients continue to receive 3 mg/kg every week in subsequent years of their lifetimes.

- **Age 1+ presentation:** The recommended dosing in children and adults presenting with LAL Deficiency is 1 mg/kg administered once every other week.

  For patients treated with sebelipase alfa, in Year 1 (2016), we calculate average annual drug costs assuming that a 20 mg vial of sebelipase alfa is available at an ex-factory price of £6,286.00. In Years 2-5 (2017-2020), it is

assumed that a 5 mg vial will become available, priced at one-fourth of the 20 mg, or £1,571.50. For purposes of modelling, it is assumed that all patients use the 5 mg vial starting in 2017; given the assumption of linear pricing (i.e., that the 5 mg vial is priced at one-fourth the price of the 20 mg), this equates to assuming that purchased mg will be the least costly combination to achieve required dosing. The resulting average annual drug costs by age presentation group, for the scenario with sebelipase alfa with market access in England, are presented in Table D13.15.

Table D13.15: Average annual drug costs per patient, by age group

	Year 1	Year 2	Year 3	Year 4	Year 5
Avg. annual drug costs per patient					
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As a sensitivity analysis, the net budget impact is also calculated assuming that over the five-year horizon of the model only the 20 mg vial is available.

Sebelipase alfa is administered via an intravenous infusion (Kanuma SPC, 2015) Age 0-1 presentation patients receive 1 infusion administration per week, and Age 1+ presentation patients receive 1 infusion administration every other week. As a result, patients in the Age 0-1 presentation group receive 52 administrations annually, and patients in the Age 1+ presentation group receive 26. The cost of an administration is £68.66 per unit, based on the average NHS reference cost for 2013-2014 of "outpatients - non consultant led" costs (NHS, 2015).

Non-drug direct medical costs

Patients also incur non-drug-related direct medical costs for care for LAL Deficiency, differing by treatment option (sebelipase alfa vs. BSC) and age of presentation group (Age 0-1 vs. Age 1+). These costs are derived from the cost-consequence model, presented in section 12.

- **Patients in the Age 0-1 presentation group:**

  Costs for patients in the Age 0-1 presentation group were generated based on LAL-1-NH01, NHS reference costs, and assumptions. The mean survival time of untreated LAL Deficiency infants in LAL-1-NH01 was 3.45 months, so the annual cost for infants who die is assumed to consist of the costs of 3.45 months of hospitalisation. Infant patients who survive following treatment with sebelipase alfa still require a significant proportion of time in hospital from birth, so it is assumed that 3 months of hospitalisation would be required. The cost per day of hospitalisation was sourced as £1,001 from NHS reference costs 2013-14 "Paediatric Critical Care, Basic Critical Care" [XB07Z] (NHS,

2015). This equated to a total cost of £103,604 for infant patients dying from LAL Deficiency and a cost of £90,090 for surviving infants. The averages of these costs, based on the survival rates for infants treated with BSC vs. sebelipase alfa, are used in the BIM, and presented in Table D13.16 below.

- **Patients in the Age 1+ presentation group:**

  Costs for patients in the Age 1+ presentation group reflect the expected distributions of sebelipase alfa and BSC patients across five liver-disease-related health states: fibrosis, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplant. For each treatment type, the average of costs over the five years following the average baseline age in ARISE (16.6 years) was used. Please refer to Section 12 of Appendix G of Alexion's complete NICE submission for a detailed description of the calculation of these costs, which are also presented in Table D13.16 below.

Direct medical costs by health state, as well as by age of presentation group and treatment type, are summarized in Table D13.16.

Table D13.16: Non-drug direct medical costs, by treatment option and age of presentation group

	Mean cost	Source
Health state		
LAL Deficiency without CC, DCC or HCC	£620	Backx, 2014; ONS, 2015
Compensated Cirrhosis	£962	Backx, 2014; ONS, 2015
Decompensated Cirrhosis	£12,523	Shepherd, 2007; ONS, 2015
HCC	£11,159	Shepherd, 2007; ONS, 2015
Liver Transplant	£50,515	Shepherd, 2007; ONS, 2015
1st year cost for dying infants	£103,604	Jones, 2015a; National Health Service, 2014
1st year cost for surviving infants	£90,090	NHS, 2015 and assumption
Age 0-1		
BSC	£103,604	Calculation (see section 12.3.7)
Sebelipase alfa	£94,586	Calculation (see section 12.3.7)
Age 1+		
BSC	£1,699	Calculation (see section 12.3.7)
Sebelipase alfa	£668	Calculation (see section 12.3.7)

13.4 Describe any estimates of resource savings associated with the use of the technology.

There are two sources of resource savings associated with the use of the technology, broadly. First, sebelipase alfa reduces the disease burden of patients, allowing them to enter less severe states. The second is mortality, including the infant lives saved by sebelipase alfa, as described in Section 13.1. Non-drug direct medical costs for these sources of resource savings are presented in Section 13.3 (see Table D13.16).

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The cost-effectiveness model tracks patients through their severity stages over time; the budget impact model only approximates this, so all cost offsets from alleviation of the disease burden are not captured in the budget impact model.

Additionally, the ultra-rare nature of LAL Deficiency makes resource utilization analysis difficult. The treatment of LAL Deficiency occurs across a range of specialists. All resources related to the holistic care of the disease are not likely included.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Costs related to care-giver burden, lost productivity, higher absenteeism and presenteeism, and lost home production are likely, especially for severe patients. Patients likely face disadvantages with regards to educational attainment and human capital formation. Parents whose children die prematurely bear a high economic and psychological burden.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Base case budget impact

As mentioned in Section 13.1, two base case scenarios were modelled for purposes of the BIM: 1) sebelipase alfa with market access in England, and 2) sebelipase alfa without market access in England. It was assumed that in the Age 1+ presentation group (patients presenting with LAL Deficiency at age 1 and over), prevalent patients

in Year 1 and incident patients in all years had age distributed according to Bernstein et al. (2013).

Total costs, including drug costs and other non-drug direct medical costs for patients treated with sebelipase alfa and those treated with BSC, for both the scenarios with and without sebelipase alfa market access, appear in Tables D13.17 and D13.18.

The net budget impact is the total budget in the scenario where sebelipase alfa receives market access minus the total budget in the scenario where sebelipase alfa does not receive market access. These estimates appear in Table D13.19.

Table D13.17: Total costs, scenario with sebelipase alfa with market access in England

Costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
Sebelipase alfa costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-drug costs:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA-treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC-treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	£4,418,612	£7,038,926	£10,140,215	£13,828,533	£18,608,038	£54,034,324

Table D13.18: Total costs, scenario with sebelipase alfa without market access in England

Costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
Sebelipase alfa costs	£0	£0	£0	£0	£0	£0
Non-drug costs:						
SA-treated patients	£0	£0	£0	£0	£0	£0
BSC-treated patients	£126,476	£86,751	£89,136	£90,841	£92,547	£485,752
Total costs	£126,476	£86,751	£89,136	£90,841	£92,547	£485,752

Table D13.19: Net budget impact of sebelipase alfa with market access in England

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	£4,418,612	£7,038,926	£10,140,215	£13,828,533	£18,608,038	£54,034,324
SA without market access	£126,476	£86,751	£89,136	£90,841	£92,547	£485,752
Net budget impact	**£4,292,136**	**£6,952,175**	**£10,051,079**	**£13,737,692**	**£18,515,491**	**£53,548,573**

Sensitivity analyses

As sensitivity analyses, the same scenarios (i.e., 1) sebelipase alfa with market access in England, and 2) sebelipase alfa without market access in England) were modelled and compared as above, but with certain variations from the base case. These variations are described below.

In a first sensitivity, it was assumed that in contrast to the base case, in the Age 1+ presentation group, prevalent patients in Year 1 and incident patients in all years had age distributed according to the baseline age distribution observed in ARISE, rather than that reported in Bernstein et al. (2013). The ARISE baseline age distribution is on average older than in Bernstein et al., which increases the average annual drug costs for patients in the Age 1+ presentation group. Table D13.20 presents the net budget impact for this sensitivity.

In a second sensitivity, it was assumed that only the 20 mg vial of sebelipase alfa is available over the five-year horizon over the model, in contrast to the base case in which a 5 mg vial becomes available in Year 2 (i.e., 2017). Table D13.21 presents the net budget impact for this sensitivity.

Finally, a sensitivity analysis was considered in which an annual per-patient cost cap of [redacted] was applied, in order to ensure that cost remains consistent with the clinical benefit and value of sebelipase alfa, as addressed below. Table D13.22 presents the net budget impact for this sensitivity.

Table D13.20: Net budget impact of sebelipase alfa with market access in England, assuming age of presentation according to ARISE clinical trial

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	£7,051,022	£11,492,508	£15,882,731	£21,064,283	£27,189,375	£82,679,919
SA without market access	£126,476	£86,751	£89,136	£90,841	£92,547	£485,752
Net budget impact	**£6,924,546**	**£11,405,757**	**£15,793,595**	**£20,973,441**	**£27,096,829**	**£82,194,168**

Table D13.21: Net budget impact of sebelipase alfa with market access in England, assuming availability of only 20 mg vial

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	£4,418,612	£8,554,699	£12,044,376	£16,573,120	£22,761,259	£64,352,066
SA without market access	£126,476	£86,751	£89,136	£90,841	£92,547	£485,752
Net budget impact	**£4,292,136**	**£8,467,948**	**£11,955,240**	**£16,482,279**	**£22,668,712**	**£63,866,314**

Table D13.22: Net budget impact of sebelipase alfa with market access in England, with annual per-patient cost cap of [redacted]

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA without market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example, quality of data inputs and sources and analysis).

A chief limitation of the budget impact analysis is that assumptions regarding the age of presentation of LAL Deficiency have considerable influence on the five-year projected budget impact. Given that dosing for sebelipase alfa is dependent on patient weight, which increases with age (through 20 years of age in this analysis), costs associated with treatment for sebelipase alfa increase significantly when a higher age of presentation is assumed. Comparison of the base case analysis using the distribution of age of presentation from Bernstein et al. (2013) vs. the sensitivity analysis using the distribution of baseline age in ARISE reflects this. In the former, the net budget impact of sebelipase alfa with market access in England vs. without is estimated to range between £4,292,136 and £18,515,491 (in Years 1 and 5, respectively), and totals £53,548,573 over the five-year time period. In the latter, a higher average age of presentation increases the net budget impact estimates significantly to a range between £6,924,546 and £27,096,829 (in Years 1 and 5, respectively), and totalling £82,194,168 over the five-year time period.

As noted in Section 13.7, Alexion intends to bring forward proposals in the form of a Patient Access Scheme (PAS) to cap the cost of treating the heaviest patients and ensure that cost remains consistent with the clinical benefit and value of sebelipase alfa, irrespective of patient weight. We intend to begin discussions with the relevant authorities about the parameters for a PAS as soon as possible.

Another limitation of the budget impact analysis is omission of potentially significant resource savings that might be achieved with treatment with sebelipase alfa. Non-drug direct medical costs included in the budget impact analysis only include costs associated with liver disease, although treatment with sebelipase alfa may also reduce other costs (e.g., cardiovascular-related). In addition, the costs of undiagnosed patients are not included, given that we are not aware of data addressing these costs.

Section E – Impact of the technology beyond direct health benefits and on the delivery of the specialised service

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

Section 15 is aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

It is expected that sebelipase alfa treatment will result in cost savings incurred outside of the NHS.

Affected infants with rapidly progressive disease die before the age of 6 months after suffering from diarrhoea, vomiting, anaemia and thrombocytopenia (which may require transfusion support), and failure to thrive (Anderson, 1999; Mayatepek, 1999). Literature and modelling suggests that affected paediatric and adult patients are unlikely to survive beyond 40 years of age as their life is impacted by portal hypertension, chronic liver failure and premature atherosclerosis (Elleder, 2000;

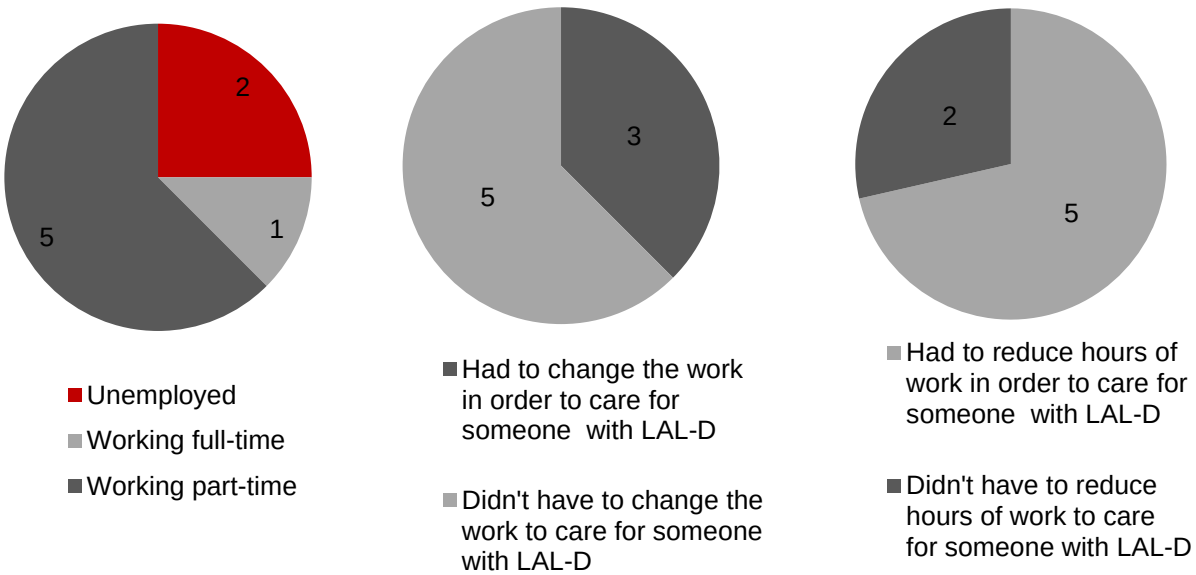
Smith, 2015). Therefore it is often the case that those affected do not enter adulthood and become a productive member of society.

No published studies reporting the wider societal burden of LAL Deficiency were identified, therefore data from the patient/carer survey described in Section 7.1 are provided.

LAL Deficiency may negatively affect patients' employment and ability to work full time. Of the three adult participants in the EU LAL-D Survey (see Section 7.1), two patients indicated their working status and provided relevant information. Both reported LAL Deficiency had some impact on their productivity. One patient worked full time, 37 hours per week. This patient reported missing one hour during the previous week because of problems associated with LAL Deficiency. She also indicated a moderate impact (score 4 of 10, where 0 equals "no effect" on work and 10 equals "completely prevented" work) on her ability to work. The other patient retired early due to LAL Deficiency at the age of 48 years.

LAL Deficiency also impacts on the productivity of carers. Seven carers of children with LAL Deficiency and one carer of an adult patient took part in survey. All carers were parents of the LAL Deficiency patient. Two of eight carers were unemployed, five were working part-time and only one was working full-time (Figure E14.1). Five of seven carers (one did not respond) had to reduce hours of work and three of eight carers had to change their work in order to care for a patient with LAL Deficiency. One of the unemployed carers reported that changes in work were because of caring for a patient with LAL Deficiency; however, this was not the reason for the other carer who was unemployed. Four of five part-timer workers indicated they had to reduce working hours because of taking care of a patient with LAL Deficiency (details in Table E14.1).

Figure E14.1: Impact of LAL Deficiency on employment of carers



On average, carers worked 21.2 hours per week (n=6: median: 20 hours; range: 7–35 hours; 35 hours for full-time worker) and, on average, working hours were reduced by 13.3 hours per week (n=4). Carers also reported providing an average of 11.5 hours of care for their children with LAL Deficiency. Further details are provided in Table E14.1.

Table E14.1: Changes in hours of work and professions for carers (n=8)

Employment status	Hours worked in the past week	Number of hours reduced per week	Had to reduce hours of work?	Had to change work?	Hours / week spent providing care for LAL Deficiency patients
Working part-time	16	Full time to part time	Yes	Yes	70
	24	8	Yes	No	NR
	7	30	Yes	Yes	NR
	20	NR	No	No	3
	20	12	Yes	No	
Working full-time	35	3	Yes	No	24
Unemployed	N/A	N/A	N/A	Yes	5
	N/A	N/A	N/A	No	14
MEAN	**21.2**	**14.6**			**11.5**

N/A-not applicable

The carer who was working full-time was a father of the child, while all other carers were mothers. The ages of the patients being cared for were similar in employed and unemployed carers.

The unemployment rate of 25% among those caring for a patient with LAL Deficiency (two unemployed carers were from Spain and were females) is similar to the unemployment rate (25.4%) for females of the general population in Spain (age 15-64) (Eurostat, 2014b) but higher than the general EU28 unemployment rate of 9.5% (Eurostat, 2015). In addition, in the survey sample, the proportion of carers working part-time (five out of six – 83%), who were all females (one from Netherlands, two from Spain and two from UK) is substantially higher compared to proportion of females working part-time in the EU-28 (32.2%) (Eurostat, 2014a).

The employment status of carers is considerably affected by caring for patients with LAL Deficiency. Carers have to reduce the time they spend working, change their job or even quit their job because of their relative's or child's needs. Carers were unable to fully fulfil their employment obligations:

"It becomes really hard to do a full- time job or accept some kind of work that required being away from home at night or at weekend or for a long hours. I cannot get a full time job because my daughter required my attention and care to keep track of her treatment and take medication."

"Full time job had to go as amount of time spent at hospital either for general appointment or emergency. I was unable to carry on. Care has to be provided for my daughter while I work shorter hours in case of a bleed."

"I have to organise my working agenda according to the medical visits and I have to work during weekends in order to compensate/ replenish for the workings hours I missed."

"It reduces my job possibilities because of my psychological restlessness."

However, visits to hospital for treatment may also affect the ability to work:

"I work one day less (because we need to go to the hospital for infusion every two weeks)."

"I could not have a new job because I have to take care of my daughter every 15 days I have to travel to another city for treatment with alpha sebelipase."

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Sebelipase alfa may result in savings to the welfare budget – the more independent and capable the patient is, the less dependent they – or their caregivers - are on respite care, or on disability and other welfare payments.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

LAL Deficiency may impose a financial burden to patients and their families. In the patient survey, seven families / adult patients gave their insight into out-of-pocket expenses. Examples of out-of-pocket expenses mentioned by families participating in the survey included the following:

- Cost of special dietary requirement: due to the nature of the disease, some patients were required to adjust their dietary intake. For example, one adult patient from the UK not treated with sebelipase alfa needed a low fat diet – this may cost more than a regular meal.
- Travel expenses: family members accompanying patients to hospital / doctor visits; furthermore, carers may be required to take time off work to accompany their relative to the hospital.

Receiving treatment with sebelipase alfa may incur some out-of-pocket expenses for carers and families. Three carers reported that out-of-pocket expenses increased after the patient started taking sebelipase alfa, which included travelling expenses to receive treatment. Alexion anticipate that administration of sebelipase alfa will be transitioned to homecare thereby reducing these costs to patients and their families.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

The majority of informal care is provided by parents and is expected to be significant, with the amount of time spent is likely to reflect the severity of disease. In the EU LAL-D Survey carers reported providing an average of 11.5 hours of care for their children with LAL Deficiency. 38% of carers took fewer holidays to support or care for someone with LAL Deficiency, and 63% reported spending less time with other children and family members. As described above carers have to reduce the time they spend working, change their job or even quit their job because of their relative's or child's needs.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Sebelipase alfa is the first targeted therapy to be approved for treating patients with LAL deficiency and studies LAL-CL03 and LAL-CL02 are the first registration studies in LAL Deficiency. Across these studies along with the phase 1/2 study and extension study (LAL-CL01 and LAL-CL04), a total of 84 subjects with LAL Deficiency have received treatment with sebelipase alfa, including 9 infants, 47 children and 28 adults. Fifty-six of 84 patients (67%) who received sebelipase alfa during clinical trials (LAL-CL01/LAL-CL04, LAL-CL02 and LAL-CL03) were in the paediatric and adolescent age range (1 month up to 18 years).

The clinical study programme was designed to provide evidence of efficacy and safety across the full spectrum of patients with LAL Deficiency and has therefore contributed a great deal in terms of study design and choice of endpoints in this ultra-rare and heterogeneous condition.

In addition, two non-interventional studies completed by Alexion have provided invaluable knowledge on progression of the disease and the rate of clinically important events:

- The natural history study, LAL-1-NH01, evaluated data on 35 infants with confirmed LAL Deficiency. The study provided the first systematic evaluation of the natural history of LAL Deficiency 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.

- LAL-2-NH01 was an observational study of children and adults with LAL Deficiency designed to characterize the key aspects of clinical presentation and progression of the disease in order to improve the understanding of the clinical phenotype. An associated, prospective sub-study was conducted to assess hepatic and splenic volume and fat content using standardized methodologies. This study represents the largest case record review of patients with LAL Deficiency, and is the first that combined both retrospective and prospective data collection. Overall, retrospective chart data were collected from 48 living patients with LAL Deficiency and prospective data were generated in a subset of 24. Data from this study confirm previously published findings that the disease is predominantly of paediatric onset resulting in liver injury and persistent dyslipidaemia, with serious complications that can require liver transplant or lead to early death.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Alexion believes that the clinical programme for sebelipase alfa and subsequent reimbursement and use in the NHS will advance knowledge, foster clinical leadership and encourage research initiatives in rare diseases in the UK as well as encourage investment in the UK biotechnology and pharmaceutical industry.

Sebelipase alfa represents the first effective treatment for an ultra-rare and devastating disease that affects patients all around the world. Whilst patient numbers are relatively small in England, we benefit from expertise of specialist clinical centres. The UK is world-leading with 12 clinical trial centres in England all managing patients from inside and outside the UK who travel to the UK to receive treatment across the full age spectrum of the disease.

3 of the 9 infant patients treated in LAL-CL03 were treated at St Mary's Hospital, Central Manchester Foundation Trust, University of Manchester, Manchester and the centre continues to gain experience as they are currently have enrolled 5 infants into LAL-CL08. Clinical trials in children and adults with LAL Deficiency were led from Cambridge University Hospitals & Evelina Children's Hospital, where 3 patients were enrolled into LAL-CL02 (ARISE).

Following access in England to sebelipase alfa, Alexion will seek to enrol additional centres in England into the LAL Deficiency Registry. This project will enable the collection and sharing of data to inform clinicians and authorities about the progression of the disease and the impact of treatment. UK centres will likely

continue to contribute to the global knowledge base for LAL Deficiency through the management of patients receiving treatment with sebelipase alfa.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

A registry has been set-up to collect data on key outcomes, including liver transplants of LAL Deficiency patients. Patients are currently being enrolled for this purpose. Registry protocol and other details will be made available upon request.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Treatment is ongoing in LAL-CL03 and in the open-label extension phase of LAL-CL02. The final analysis of these studies is expected in 2017. Additional data from the two open-label studies initiated in 2014, LAL-CL06 and LAL-CL08 (see Section 4.1) will be available in June 2017 and December 2018 respectively. Clinical safety and efficacy data for those between 2 and 4 years of age will be generated from LAL-CL06.

In addition, a global LAL Deficiency registry exists. Although it is understood that no patients in the UK are currently enrolled, it is expected that in the future patients treated with sebelipase alfa in the UK will participate in this registry.

15 Impact of the technology on delivery of the specialised service

15.1 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The Summary of Product Characteristics for sebelipase alfa states that treatment should be supervised by an experienced healthcare professional experienced in the management of patients with LAL deficiency, other metabolic disorders, or chronic liver diseases (Kanuma SPC, 2015). Sebelipase alfa is administered by intravenous infusion. The total volume of the infusion should be administered over approximately 2 hours however a 1-hour infusion may be considered after patient tolerability is established. The infusion period may be extended in the event of dose escalation or

infusion related events. Appropriate medical support must be readily available when sebelipase alfa is administered (Kanuma SPC, 2015). In England, it is expected that initiation of the infusions and stabilisation of the patient will occur at specialist LSD centres followed by transition to local hospital outpatient clinics or homecare arrangements, as is the case for currently available enzyme replacement therapies.

15.2 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No additional infrastructure is anticipated, since sebelipase alfa will be administered and monitored within existing services for LSDs. However, management of infants is more complex than in older children and adults, with the requirement for prolonged hospital stay and multi-disciplinary treatment approaches which may impact on resource requirements for the expert centres managing these infants.

16 References

Abdallah M, Wang K, Magnuson E, et al. Quality of Life After PCI vs CABG Among Patients With Diabetes and Multivessel Coronary Artery Disease. JAMA. 2013;310(15):1581. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2013.279208\nhttp://www.ncbi.nlm.nih.gov/pubmed/24129463

Abel F , Whitley C, Valayannopoulos V, et al. Effect of sebelipase alfa after 2 years in adults with lysosomal acid lipase deficiency. Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, SSIEM 2014 Innsbruck Austria. Journal of Inherited Metabolic Disease 2014; 37 (1 SUPPL. 1): S160.

Alkhouri N, Sedki E, Alisi A, et al. Combined paediatric NAFLD fibrosis index and transient elastography to predict clinically significant fibrosis in children with fatty liver disease. Liver Int. 2013;33(1):79–85.

Anderson RA, Bryson GM, Parks JS. Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. Mol Genet Metab. 1999;68(3):333–45.

Angulo P, Keach JC, Batts K, Lindor KD. Independent Predictors of Liver Fibrosis in Patients With Nonalcoholic Steatohepatitis. Hepatology. 1999;30(507):1356–62.

Backx M, Lewszuk A, White JR et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1–infected patients who do or do not achieve sustained virological response to therapy. Journal of Viral Hepatitis, 2014; 21:208–215.

Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet [Internet]. Elsevier Ltd; 2010;376:1670–81. Available from: http://dx.doi.org/10.1016/S0140-6736(10)61350-5

Baigent C, Keech A, Kearney P, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.

Balwani M et al. Long term safety and clinical activity of SBC-102, a recombinant human lysosomal acid lipase (rhLAL), in patients with late onset LAL deficiency. 9th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium, 2013 Orlando, FL United States. Molecular Genetics and Metabolism 2013b; 108 (2): S22-S23.

Balwani M, Breen C, Enns G, et al. Clinical Effect and Safety Profile of Recombinant Human Lysosomal Acid Lipase in Patients With Cholesteryl Ester Storage Disease. Hepatology 2013a; 58: 950-957

Balwani M, Quinn AG, Burton B. Phase 3 randomized controlled trial assessing efficacy and safety of sebelipase alfa in children/adults with lysosomal acid lipase deficiency. Hepatology. 2014;60:1 Suppl.

Bentley TS, Hanson SG. 2011 U.S. organ and tissue transplant cost estimates and discussion. Milliman Res Rep. 2011;(April):1–16.

Bernstein D, Hulkova H, Bialer M, et al. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. European Association for

the Study of the Liver; 2013;58(6):1230–43. Available from: http://dx.doi.org/10.1016/j.jhep.2013.02.014

Bhala N, Angulo P, van der Poorten D, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology. 2011;54(4):1208-1216. doi:10.1002/hep.24491.

Bugianesi E. Non-alcoholic fatty liver disease. Orphanet. 2013 [cited 2015 Aug 1]. Available from: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=10315&Disease(s)/group of diseases=Non-alcoholic-steatohepatitis&title=Non-alcoholic-steatohepatitis&search=Disease_Search_Simple.

Burton B, Balwani M, Feillet F, et al. A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency. N Engl J Med 2015a;373:1010-20.

Burton B, on behalf of the ARISE Investigators. Results of a global phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of sebelipase alfa as an enzyme replacement therapy in children and adults with lysosomal acid lipase deficiency. Conference: 11th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium, 2015 Orlando, FL United States. Molecular Genetics and Metabolism 2015b; 114 (2): S27.

Burton BK, Deegan PB, Enns GM et al. Clinical Features of Lysosomal Acid Lipase Deficiency − a Longitudinal Assessment of 48 Children and Adults. 2015c. J Pediatr Gastroenterol Nutr (Epub ahead of print]

Cagle PT, Ferry GD, Beaudet AL, Hawkins EP. Pulmonary hypertension in an 18-year-old girl with cholesteryl ester storage disease (CESD). Am J Med Genet. 1986;24(4):711-722. doi:10.1002/ajmg.1320240416.

Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94(2):528–38.

Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012;142(7):1592–609.

Chen C-J, Yang H-I, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology. 2009;49(5 Suppl):S72–84.

Chong CAKY, Gulamhussein A, Heathcote EJ, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol. 2003;98(3):630-638. http://www.ncbi.nlm.nih.gov/pubmed/12650799.

Crocker AC, Vawter GF, Neuhauser EB et al. Wolman'S Disease: Three New Patients With a Recently Described Lipidosis. Pediatrics. 1965;35:627–40.

Crosby J, Peloso G, Auer PL, et al. Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease. N Engl J Med. 2014;371(1):22–31. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1307095

Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease:

systematic review and economic evaluation. Health Technol Assess. 2015;19(9):1-409, v - vi. doi:10.3310/hta19090.

D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-753. doi:10.1161/CIRCULATIONAHA.107.699579.

Data on File: Summary of Clinical Safety

Data on File. LAL-1-NH01 Clinical Study Report (2014).

Data on FIle. LAL-2-NH01 Clinical Study Report (2014).

Data on File. LAL-CL01 Clinical Study Report (2014).

Data on File. LAL-CL02 Clinical Study Report (2014).

Data on File. LAL-CL03 Clinical Study Report (2014).

Data on File. LAL-CL04 Clinical Study Report (2014).

David K, Kowdley K V, Unalp A, Kanwal F, Brunt EM, Schwimmer JB. Quality of life in adults with nonalcoholic fatty liver disease: baseline data from the nonalcoholic steatohepatitis clinical research network. Hepatology. 2009;49(6):1904-1912. doi:10.1002/hep.22868.

Do R, Willer CJ, Schmidt M, Sengupta S, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet. 2013;45(11):1345–52.

Donnan PT, McLernon D, Dillon JF, et al. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). Health Technol Assess. 2009;13(25):iii - iv, ix - xi, 1-134. doi:10.3310/hta13250.

Du H, Schiavi S, Wan N, et al. Reduction of Atherosclerotic Plaques by Lysosomal Acid Lipase Supplementation. Arterioscler Thromb Vasc Biol. 2004;24(1):147–54.

Elleder M, Chlumska A, Hyanek J, et al. Subclinical course of cholesteryl ester storage disease in an adult with hypercholesterolemia, accelerated atherosclerosis, and liver cancer. J Hepatol. 2000;32:528–34.

Elleder M, Ledvinová J, Cieslar P, Kuhn R. Subclinical course of cholesterol ester storage disease (CESD) diagnosed in adulthood - Report on two cases with remarks on the nature of the liver storage process. Virchows Arch A Pathol Anat Histopathol. 1990;416(4):357–65.

Enns G, Balwani M, Deegan P, et al. Initial human experience with SBC-102, a recombinant enzyme replacement therapy in adults with lysosomal acid lipase deficiency.. 8th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium 2012 San Diego, CA United States. Molecular Genetics and Metabolism 2012; 105 (2): S29.

Eurostat. Proportion of part-time workers among females in EU28 (2014a). Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Employment_statistics

Eurostat. Unemployment among females (age 15-64) for Spain (2014b). Available from http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Table_3_Unemployment_rate_by_gender_and_age,_2007-2014_(%25).png

Eurostat. Unemployment rate for EU28 (2015). Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Unemployment_rates,_seasonally_adjusted,_July_2015.png

Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org). Accessed Oct 2015.

Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S et al. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut. 2009;58(11):1538–44.

Ferry GD, Whisennand HH, Finegold MJ, et al. Liver transplantation for cholesteryl ester storage disease. J Pediatr Gastroenterol Nutr. 1991;12(3):376–8.

Forns X, Ampurdanès S, Llovet JM, Aponte J, Quintó L, Martínez-Bauer E, Bruguera M, Sánchez-Tapias JM, Rodés J. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology. 2002;36(4):986-92.

Gasche C, Aslanidis C, Kain R, et al. A novel variant of lysosomal acid lipase in cholesteryl ester storage disease associated with mild phenotype and improvement on lovastatin. J Hepatol. 1997;27(4):744–50.

Grabowski, GA. The Wolman disease / cholesteryl ester storage disease spectrum. The Online Metabolic and Molecular Basis of Inherited Disease,2012; 142.

Grundy SM, Cleeman JI, Bairey Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110(2):227–39.

Hamilton J, Jones I, Srivastava R, et al. A new method for the measurement of lysosomal acid lipase in dried blood spots using the inhibitor Lalistat 2. Clin Chim Acta; 2012;413(15-16):1207–10. Available from: http://dx.doi.org/10.1016/j.cca.2012.03.019

Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess. 2011;15(17):i - xii, 1-210. doi:10.3310/hta15170.

Hoeg JM, Demosky SJ, Pescovitz OH, et al. Cholesteryl ester storage disease and Wolman disease: phenotypic variants of lysosomal acid cholesteryl ester hydrolase deficiency. Am J Hum Genet. 1984;36(6):1190–203.

Hossain N, Afendy A, Stepanova M, et al. Independent Predictors of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol; 2009;7(11):1224–9.e2. Available from: http://dx.doi.org/10.1016/j.cgh.2009.06.007

Iorio R, Giannattasio A, Cirillo F, et al. Long-term outcome in children with chronic hepatitis B: a 24-year observation period. Clin Infect Dis. 2007;45(8):943–9.

Janssen and Szende. Chapter 3. Population Norms for the EQ-5D. Szende et al. (eds.), Self-Reported Population Health: An International Perspective based on EQ-5D (2014)

Jones S, Enns G, Balwani M, et al. Enzyme replacement with recombinant human lysosomal acid lipase (rhLAL) in patients with cholesteryl ester storage disease, the late onset form of LAL deficiency, produces sustained decreases in transaminases and reduction in liver fat content. 63rd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2012 Boston, MA United States. Hepatology 2012a; 56: 824A-825A.

Jones S, Enns G, Balwani M, et al. Recombinant human lysosomal acid lipase (LAL) demonstrates pharmacodynamic activity in Cholesteryl Ester Storage Disease (CESD), the late onset form of lal deficiency. Annual Symposium of the Society for the Study of Inborn Errors of

Metabolism, SSIEM 2012 Birmingham United Kingdom. Journal of Inherited Metabolic Disease 2012b; 35 (1 SUPPL. 1): S11.

Jones S, Ghosh A, Breen C, et al. Effect of sebelipase alfa on survival and liver function in infants with rapidly progressive lysosomal acid lipase deficiency. 11th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium, 2015 Orlando, FL United States. Molecular Genetics and Metabolism 2015b; 114 (2): S59.

Jones S, Valayannopoulos V, Schneider E, et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. Genetics in Medicine (2015a) doi:10.1038/gim.2015.108. Available from:http://www.nature.com/doifinder/10.1038/gim.2015.108

Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med. 2014;371(1):32–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24941082

Kanuma Summary of Product Characteristics, September 2015.

Kim C, Bernstein SJ. Quality of life assessment for chronic stable angina. Expert Rev Pharmacoecon Outcomes Res. 2003;3(5):637–50.

Koloski N a, Talley NJ, Boyce PM. The impact of functional gastrointestinal disorders on quality of life. Am J Gastroenterol. 2000;95(1):67–71

Konno T, Fujii M, Watanuki T, Koizumi K. Wolmans Disease: The first case in Japan. Tohoku J Exp Med. 1966;90:375–89.

Krivit W, Peters C, Dusenbery K, et al. Wolman disease successfully treated by bone marrow transplantation. Bone Marrow Transplant. 2000;26(5):567–70.

LaBrecque D, Zaigham A, Anania F, et al. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. World Gastroenterol Organ Glob Guidel. 2012; Available from: http://www.ncbi.nlm.nih.gov/pubmed/23971751\nhttp://www.ncbi.nlm.nih.gov/pubmed/23198569\nhttp://www.ncbi.nlm.nih.gov/pubmed/23971751\nhttp://www.ncbi.nlm.nih.gov/pubmed/23198569

Levy AR, Kowdley KV, Iloeje U, et al. The impact of chronic hepatitis B on quality of life: A multinational study of utilities from infected and uninfected persons. Value Heal [Internet]. International Society for Pharmacoeconomics and Outcomes Research (ISPOR); 2008;11(3):527–38. Available from: http://dx.doi.org/10.1111/j.1524-4733.2007.00297.x

Lin Z-H, Xin Y-N, Dong Q-J, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53(3):726-736. doi:10.1002/hep.24105.

Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Ávila F, Vargas-Vorackova F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. Annals of hepatology. 2007; 7 (4): 350-357.

Mahady SE, Wong G, Craig JC, George J. Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis. Hepatology. 2012;56(6):2172-2179. doi:10.1002/hep.25887.

Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013; 381: 468–75

Marcellusi A, Viti R, Capone A, Mennini FS. The economic burden of HCV-induced diseases in Italy. A probabilistic cost of illness model. European Review for Medical and Pharmacological Science. 2015; 19: 1610-1620

Marshall WC, Ockenden BG, Fosbrooke AS, Cumings JN. Wolman's disease. A rare lipidosis with adrenal calcification. Arch Dis Child. 1969;44:331–41.

Mayatepek E, Seedorf U, Wiebusch H, et al. Fatal genetic defect causing Wolman disease. J Inherit Metab Dis. 1999;22(1):93–4.

Mazariegos G, Shneider B, Burton B, et al. Liver transplantation for pediatric metabolic disease. Mol Genet Metab; 2014;111(4):418–27. Available from: http://dx.doi.org/10.1016/j.ymgme.2014.01.006

McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making. 2008; 28(4):582-592. doi:10.1177/0272989X08315240.

Meikle P, Hopwood J, Clague A, Carey W. Prevalence of Lysosomal Storage Disorders. JAMA. 1999;281(3):249–54.

Meyers WF, Hoeg JM, Demosky SJ,et al. The use of parenteral hyperalimentation and elemental formula feeding in the treatment of Wolman Disease. Nutr Res. 1985;5:423–9.

Mulcahy AW, Predmore Z, Mattke S. The Cost Savings Potential of Biosimilar Drugs in the United States. 2014. http://www.rand.org/pubs/perspectives/PE127.html. Accessed September 18, 2015.

Muntoni S, H Wiebusch, M Jansen-Rust, et al. Prevalence of cholesteryl ester storage disease. Arterioscler Thromb Vasc Biol. 2007; 27(8): 1866-1868.

National Health Service. "NHS schedule of reference costs: The main schedule" 2013-2014. (2015). Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014.

NHS Blood and Transplant. Annual Activity Report 2014-15.Available at: http://www.odt.nhs.uk/uk-transplant-registry/annual-activity-report/

NHS England. 2013/14 NHS Standard Contract for Lysosomal Storage Disorders (children) 2013a. Available at: http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf

NHS England. 2013/14 NHS Standard Contract for metabolic Disorders (Adult). 2013b. Available at: http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-metab-disorders-adult.pdf

NHS England. Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children).

NICE. Guide to the methods of technology appraisal (2013). Available at: http://publications.nice.org.uk/pmg9

Office for National Statistics. Consumer Price Inflation, (2015b). Available at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-323653.

Office for National Statistics. England, National Life Tables, 1980-82 to 2012-14. (2015a). Available at: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Life+Tables#tab-data-tables

Office for National Statistics. Population Estimates Analysis Tool, mid-2013. 2013a [cited 2015 Sept. 09]. Available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/sty-population-estimates.html

Office for National Statistics. Release: Population estimates for UK, England and Wales, Scotland and Northern Ireland, mid-2013. 2013b [cited 2014 Oct 31]. Available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/index.html

Ouimet M, Franklin V, Mak E, et al. Autophagy regulates cholesterol efflux from macrophage foam cells via lysosomal acid lipase. Cell Metab; 2011;13(6):655–67. Available from: http://dx.doi.org/10.1016/j.cmet.2011.03.023

Ouimet M, Marcel YL. Regulation of lipid droplet cholesterol efflux from macrophage foam cells. Arterioscler Thromb Vasc Biol. 2012;32(3):575–81.

Quinn AG, Burton B, Deegan P, et al. Sustained elevations in LDL cholesterol and serum transaminases from early childhood are common in lysosomal acid lipase deficiency. Mol Genet Metab [Internet]. Elsevier B.V.; 2014a;111(2):S89. Available from: http://www.sciencedirect.com/science/article/pii/S1096719213006471

Quinn, AG, Yang Y, Eckert S, et al. Results of a global, phase 3, randomized, double-blind, placebo controlled trial evaluating the efficacy and safety of sebelipase alfa as an enzyme replacement therapy in children and adults with lysosomal acid lipase deficiency. Hepatology 2014b: 60 (1 Suppl).

Ratcliffe J. Assessing health-related quality of life pre[ndash] and post[ndash]liver transplantation: A prospective multicenter study. Liver Transplant. 2002;8(3):263-270. doi:10.1053/jlts.2002.31345.

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.

Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. Hepatology. 2009;49(3):1017–44

Rojas-Caro S , Whitley C, Valayannopoulos V et al. Effect of sebelipase alfa after 2 years in adults with lysosomal acid lipase deficiency. 11th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium, 2015 Orlando, FL United States. Molecular Genetics and Metabolism 2015; 114: (2) S99).

Royal College of Paediatrics and Child Health (RCPCH). UK-WHO growth charts, 0-18 years [Internet]. 2015 [cited 2015 Oct 06]. Available at: http://www.rcpch.ac.uk/improving-child-health/public-health/uk-who-growth-charts/uk-who-growth-charts-0-18-years

Saab S, Gordon SC, Park H, Sulkowski M, Ahmed A, Younossi Z. Cost-effectiveness analysis of sofosbuvir plus peginterferon/ribavirin in the treatment of chronic hepatitis C virus genotype 1 infection. Aliment Pharmacol Ther. 2014 Sep;40(6):657-75. doi: 10.1111/apt.12871.

Scott SA, Liu B, Nazarenko I, Martis S, et al. Frequency of the cholesteryl ester storage disease common LIPA E8SJM mutation (c.894G>A) in various racial and ethnic groups. Hepatology. 2013;58(3):958–65.

Shah D, Bower AG, Yang Y, Rojas-Caro S. Cardiovascular risk of patients with lysosomal acid lipase (LAL) deficiency. In: AMCP. 2015.

Shepherd J, Jones J, Hartwell D, Davidson P, Price A and Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technology Assessment 2007; Vol. 11: No. 11.

Sheth SG, Chopra S. Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults. 2014 [cited 2014 Dec 1]. Available from: http://www.uptodate.com/contents/epidemiology-clinical-features-and-diagnosis-of-nonalcoholic-fatty-liver-disease-in-adults

Siebert U, Sroczynski G, Rossol S, et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut. 2003;52(3):425-432. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1773554&tool=pmcentrez&rendertype=abstract. Accessed September 18, 2015.

Singh S, Allen AM, Wang Z, et al. Fibrosis Progression in Nonalcoholic Fatty Liver vs Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis of Paired-Biopsy Studies. Clin Gastroenterol Hepatol 2015;13(4):643–54.e9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1542356514006028

Smith C, Aggarwal J, Bower AG, et al. Predictive Analysis of Disease Burden and Cost of Lysosomal Acid Lipase Deficiency in a US Commercial Health Plan. In: AMCP. 2015

Stein J, Zion Garty B, Dror Y, et al. Successful treatment of Wolman disease by unrelated umbilical cord blood transplantation. Eur J Pediatr. 2007;166(7):663–6.

Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-1325. doi:10.1002/hep.21178.

Stitziel NO, SW Fouchier, B Sjouke, et al. Exome sequencing and directed clinical phenotyping diagnose cholesterol ester storage disease presenting as autosomal recessive hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2013; 33(12): 2909–2914.

Thelwall PE, Smith FE, Leavitt MC, et al. Hepatic cholesteryl ester accumulation in lysosomal acid lipase deficiency: Non-invasive identification and treatment monitoring by magnetic resonance. J Hepatol. European Association for the Study of the Liver; 2013;59(3):543–9.

Tolar J, Petryk a, Khan K, et al. Long-term metabolic, endocrine, and neuropsychological outcome of hematopoietic cell transplantation for Wolman disease. Bone Marrow Transplant. 2009;43(1):21–7.

Tomlinson PS, Harbaugh BL, Kotchevar J, Swanson L. Caregiver mental health and family health outcomes following critical hospitalization of a child (1995). Issues in mental health nursing 16(6).

Tripuraneni R, Sharma R, Balwani Mm et al. Sebelipase alfa improves dyslipidemia in patients with cholesteryl ester storage disease. 2013 Annual Scientific Sessions of the National Lipid Association Las Vegas, NV United States. Journal of Clinical Lipidology 2013; 7 (3): 286.

Tsochatzis E, Papatheodoridis G V, Manesis EK, Kafiri G, Tiniakos DG, Archimandritis AJ. Metabolic syndrome is associated with severe fibrosis in chronic viral hepatitis and non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2008;27(1):80-89. doi:10.1111/j.1365-2036.2007.03538.x.

Vajro P, Lenta S, Socha P, et al. Diagnosis of Nonalcoholic Fatty Liver Disease in Children and Adolescents. J Pediatr Gastroenterol Nutr. 2012;54(5):700–13.

Valayannopoulos V, Malinova V, Honzik T, et al. Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. Journal of Hepatology 2014a; 61: 1135–1142

Valayannopoulos V, Malinova V, Sharma R, et al. Effect of sebelipase alfa after 90 weeks in adults with lysosomal acid lipase deficiency. 82nd European Atherosclerosis Society Congress, EAS 2014 Madrid Spain. Atherosclerosis 2014b; 235: (2) e19.

Valayannopoulos V, Malinova V, Sharma R, et al. Long term effect of sebelipase alfa after one year in patients with late onset lysosomal acid lipase deficiency (LAL deficiency). 12th International Congress of Inborn Errors of Metabolism, ICIEM 2013 Barcelona Spain.. Journal of Inherited Metabolic Disease 2013; 36 (2 SUPPL. 1): S301.

Valayannopoulos V, Plantaz D, Vara R, et al. Clinical effect of sebelipase alfa on survival and growth in infants with lysosomal acid lipase deficiency (Wolman disease). 10th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium, 2014 San Diego, CA United States. Molecular Genetics and Metabolism 2014c; 111 (2): S108.

Varni JW, Limbers C a. The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. J Health Psychol. 2009;14(4):611–22.

Varni JW, Limbers C, Burwinkle TM. Literature Review : Health-related Quality of Life Measurement in Pediatric Oncology : Hearing the Voices of the Children. J Pediatr Psychol. 2007;32(9):1151–63.

Vernon G, Baranova a., Younossi ZM. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34(3):274–85.

Whitley C, Valayannopoulos V, Malinova V, et al. Long-term clinical effect and safety of sebelipase alfa in adults with lysosomal acid lipase deficiency. 10th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium, 2014 San Diego, CA United States. Molecular Genetics and Metabolism 2014; 111 (2): S113-S114).

Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. Pharmacoeconomics. 2013 Jun; 31(6): 489–500. doi: 10.1007/s40273-013-0040-y

Wright, M, Grieve R, et al. "Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation." Health Technol Assess. 2006; 10(21): 1-113, iii.

Yang HR, Kim HR, Kim MJ, Ko JS, Seo JK. Noninvasive parameters and hepatic fibrosis scores in children with nonalcoholic fatty liver disease. World J Gastroenterol. 2012;18(13):1525-1530. doi:10.3748/wjg.v18.i13.1525.

Yang HR, Kim HR, Kim MJ, Ko JS, Seo JK. Noninvasive parameters and hepatic fibrosis scores in children with nonalcoholic fatty liver disease. World J Gastroenterol. 2012;18(13):1525-1530. doi:10.3748/wjg.v18.i13.1525.

Yanir A, Allatif MA, Weintraub M, Stepensky P. Unfavorable outcome of hematopoietic stem cell transplantation in two siblings with Wolman disease due to graft failure and hepatic complications. Mol Genet Metab [Internet]. Elsevier Inc.; 2013;109(2):224–6. Available from: http://dx.doi.org/10.1016/j.ymgme.2013.03.007

Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. Am J Gastroenterol. 2001;96(7):2199-2205. doi:10.1111/j.1572-0241.2001.03956.x.

Younossi ZM, Guyatt G, Kiwi M, et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut. 1999;45(2):295–300.

Zhang B, Porto AF. Cholesteryl Ester Storage Disease: Protean Presentions of Lysosomal Acid Lipase Deficiency. J Pediatr Gastroenterol Nutr [Internet]. 2013;56(6):682–5. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005176-201306000-00020

17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Table 17.1: Databases searched in clinical systematic review

Database	Year	Platform
EMBASE	1974 to 2015 Week 22	Ovid
Cochrane Central Register of Controlled Trials	Up to April 2015	Ovid
Cochrane Database of Abstracts of Reviews of Effects	Up to 2nd Quarter 2015	Ovid
Health Technology Assessment	Up to 2nd Quarter 2015	Ovid
NHS Economic Evaluation Database	Up to 2nd Quarter 2015	Ovid
Medline (R)	1946 to May Week 4 2015	Ovid
Medline complete	1865 to current	EBSCO

17.1.2 The date on which the search was conducted.

The search was conducted on the 1st June 2015.

17.1.3 The date span of the search.

No date limit was placed on the search thus the date span was from inception of each database to 1st June 2015.

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 17.2: Search strategy used in the Ovid platform for the clinical systemic review

Index	Search terms	Search limits	Hits
1	sebelipase alfa	Explode Free text: all fields	29
2	sebelipase		37
3	SBC-102 OR SBC102		14
4	recombinant human lysosomal acid lipase		16
5	1 OR 2 OR 3 OR 4	Human	47
6	5	Deduplicate	39

Table 17.3: Search strategy used in the EBSCO host platform for the clinical systemic review

Index	Search terms	Search limits	Hits
1	sebelipase	Boolean search, All text [TX]	7
2	SBC 102 OR SBC-102 OR SBC102		10
3	recombinant human lysosomal acid lipase		16
4	1 OR 2 OR 3		23

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Not applicable.

17.1.6 The inclusion and exclusion criteria.

See Table C9.2.

17.1.7 The data abstraction strategy.

Two reviewers assessed the publication title and abstracts for inclusion in the review, followed by review of the full text articles (where available). A third reviewer resolved

contradictory decisions. Included RCTs were quality assessed according to criteria adapted from Centre for Reviews and Dissemination guidance for systematic reviews (CRD, 2008) and included cohort non-RCTs were quality assessed according to Critical Appraisal Skills Programme (CASP) tool. Key aspects of study methodology and results were extracted.

17.2 Appendix 2: Search strategy for adverse events

The following information should be provided.

17.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Adverse events were captured within the clinical systematic review detailed in section 17.1.

17.2.2 The date on which the search was conducted.

Adverse events were captured within the clinical systematic review detailed in section 17.1.

17.2.3 The date span of the search.

Adverse events were captured within the clinical systematic review detailed in section 17.1.

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Adverse events were captured within the clinical systematic review detailed in section 17.1.

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Adverse events were captured within the clinical systematic review detailed in section 17.1.

17.2.6 The inclusion and exclusion criteria.

Adverse events were captured within the clinical systematic review detailed in section 17.1.

17.2.7 The data abstraction strategy.

Adverse events were captured within the clinical systematic review detailed in section 17.1.

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Table 17.4: Databases searched in economic systematic review

Database	Year	Platform
EMBASE	1974 to 2015 Week 22	Ovid
Cochrane Central Register of Controlled Trials	Up to April 2015	Ovid
Cochrane Database of Abstracts of Reviews of Effects	Up to 2nd Quarter 2015	Ovid
Health Technology Assessment	Up to 2nd Quarter 2015	Ovid
NHS Economic Evaluation Database	Up to 2nd Quarter 2015	Ovid
Medline (R)	1946 to May Week 4 2015	Ovid
Medline complete	1865 to current	EBSCO
EconLit	All available	EBSCO

17.3.2 The date on which the search was conducted.

The search was conducted on the 1st June 2015.

17.3.3 The date span of the search.

No date limit was placed on the search thus the date span was from inception of each database to 1st June 2015.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 17.5: Search strategy used in the Ovid platform for the economic systemic review

Index	Search terms	Search limits	Hits
1	exp "Cholesterol Ester Storage Disease"/		444
2	exp "Wolman disease"/		471
3	Cholesterol Ester Storage Disease	Free text: all fields, human	424
4	Cholesteryl Ester Storage disease		285
5	Wolman		624
6	LAL deficiency		108
7	lysosomal acid lipase deficiency		122
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	Human	795
9	8	Deduplicate	542
10	exp socioeconomics/ or exp "cost benefit analysis"/ or exp "cost control"/ or exp "cost effectiveness analysis"/ or exp "cost minimization analysis"/ or exp "cost of illness"/ or exp "cost utility analysis"/ or exp "health care cost"/ or exp "economic aspect"/ or exp "health economics"/ or exp "economic evaluation"/ or exp "financial management"/ or exp "health care distribution"/ or exp "health care financing"/ or exp "hospital cost"/ or exp "resource allocation"/ or exp productivity/ or exp absenteeism/ or exp "work disability"/ or exp "work capacity"/ or exp caregiver/ or exp "caregiver burden"/ or exp "caregiver support"/	Human	1,131,312
11	"resource use" or "resource utilisation" or "resource utilization" or presenteeism or "indirect cost"	Free text: all fields, human	33,259
12	10 or 11		1,144,136
13	exp "quality of life"/ or exp "quality of life assessment"/ or exp "quality of life index"/ or exp "quality adjusted life year"/ or exp questionnaire/ or exp "rating scale"/ or exp "health survey"/ or exp "health status"/ or exp "outcomes research"/ or exp "scoring system"/	Human	2,663,291
14	qaly$ or qald or qale or qtime or "disability adjusted life" or daly or hql$ or hqol$ or h$qol or hye$ or "health utilit$"	Free text: all fields, human	24,912
15	13 or 14		2,669,629
16	(12 OR 15) AND 9		17

Table 17.6: Search strategy used in the EBSCO host platform for the economic systemic review

Index	Search terms	Search limits	Hits
1	(MH "Cholesterol Ester Storage Disease+")	Major heading: Explode	209
2	TX "Cholesteryl Ester Storage disease"	Boolean search, All text [TX]	190
3	TX "Wolman#s disease"		224
4	TX "LAL deficiency"		50
5	TX "lysosomal acid lipase deficiency"		74
6	1 OR 2 OR 3 OR 4 OR 5	Human	447
7	(MH "Economics+") OR (MH "Models, Statistical+") OR (MH "Health Care Costs+") OR (MH "Health Resources+") OR (MH "Psychology, Industrial+") OR (MH "Disability Evaluation+") OR (MH "Caregivers+") OR (MH "Patient Care+") OR (MH "Socioeconomic Factors+")	Major heading: Explode	1,650,839
8	TX socioeconomics or TX economic aspect or TX health care financing or TX health economics or TX resource use or TX resource utili#ation or TX presenteeism or TX work disability or TX work capacity or TX caregiver burden or TX caregiver support or TX indirect cost	Boolean search, All text [TX]	239,236
9	7 OR 8	Boolean search, Limit to Human	1,523,474
10	(MH "Quality of life+") OR (MH "Value of life+") OR (MH "Quality-Adjusted Life Years+") OR (MH "Health Surveys+") OR (MH "Health Status+") OR (MH "Health Care Surveys+") OR (MH "Questionnaires+") OR (MH "Health Impact Assessment+") OR (MH "Outcome Assessment (Health Care)+")	Major heading: Explode	1,523,474
11	TX qald OR TX qale OR TX qtime OR TX disability adjusted life OR TX daly OR TX hql* OR TX hqol* OR TX h#qol OR TX hye* OR TX health * year equivalent OR TX health utility* OR TX rating scale* OR TX scoring system	Boolean search, All text [TX]	322,930
12	10 OR 11	Boolean search, Limit to Human	1,641,250
13	(9 OR 12) AND 6	Boolean search, Limit to Human	34

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Due to a rarity of the disease, resource identification, measurement and valuation were captured within the economic systematic review - see section 17.3.

17.4.2 The date on which the search was conducted.

Due to a rarity of the disease, resource identification, measurement and valuation were captured within the economic systematic review - see section 17.3.

17.4.3 The date span of the search.

Due to a rarity of the disease, resource identification, measurement and valuation were captured within the economic systematic review - see section 17.3.

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Due to a rarity of the disease, resource identification, measurement and valuation were captured within the economic systematic review - see section 17.3.

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Due to a rarity of the disease, resource identification, measurement and valuation were captured within the economic systematic review - see section 17.3.

17.4.6 The inclusion and exclusion criteria.

Due to a rarity of the disease, resource identification, measurement and valuation were captured within the economic systematic review - see section Table D11.2.

17.4.7 The data abstraction strategy.

Due to a rarity of the disease, resource identification, measurement and valuation were captured within the economic systematic review - see section Table D11.2.

17.5 Appendix 5 Patient Questionnaires

LAL-D Survey (Adult Version)

Adult version, patients 18 years old and above - to be completed by the patient.
Thank you for taking part in this survey. It will take about 30 to 45 minutes to complete.

Purpose and content of the survey
This survey is being conducted to better understand lysosomal acid lipase deficiency (LAL-D) and its impact on the lives of patients and their carers. The anonymised results of this survey will be shared with Alexion Pharmaceuticals in order to inform its submission to the National Institute for Health and Care Excellence (NICE), the organisation that recommends whether medicines - including those for rare conditions - should be available on the National Health Service (NHS) in England.

How to answer the survey?

Please answer the questions as best you can. You only need to answer questions you feel comfortable answering. If you do not wish to answer a particular question, skip to the next question. Any personal information you provide will remain confidential; only anonymised information will be shared with Alexion Pharmaceuticals.

By clicking on the button you are confirming that you have LAL-D and providing consent for your anonymised information to be used as described.

Patient Information

1. How old are you? ____ years old

2. Are you male or female? ☐ Male ☐ Female

3. In which country do you live? _____

5. Please indicate whether you have children:

   ☐ Yes
   ☐ No

6. If "Yes", how many children do you have? _____

7. Do any of your children suffer also from LAL-D?

   ☐ Yes
   ☐ No

8. Do you have a carer?

   ☐ Yes
   ☐ No

9. Are you currently receiving treatment with sebelipase alfa?

   ☐ Yes
   ☐ No

10. If yes for how long you have been treated with sebelipase alfa? ___months

11. If no, have you ever been given sebelipase alfa?

☐ Yes
☐ No

If you are not taking sebelipase alfa, please answer all questions, including questions that mention "before your treatment with sebelipase alfa" and skip the questions that mention "after your treatment with sebelipase alfa".

Lysosomal acid lipase deficiency (LAL-D) status

The next section will cover questions about the symptoms you experience and the severity of these symptoms.

11. How old were you when you were told you had LAL-D? ___years old

12. Please specify the first symptom you experienced and what age you were when you first experienced it?

    First symptom: _____
    Age at first symptom: _____

13. How many visits to the doctor or hospitalizations did you have before you were told you had LAL-D? _____

14. Thinking about the **time before you started taking sebelipase alfa**, could you indicate how frequently you suffered from any of the following symptoms

Symptoms	Never	Occasionally	Frequently
Abdominal / tummy pain			
Vomiting			
Nausea			
Diarrhoea			
Anaemia			
Bleeding, bruising easily			
Coughing up blood			
Shortness of breath			
Difficulty in swallowing			
Fatigue			
Fluid accumulation in your abdomen (ascites)			
"Big belly" (not fluid accumulation)			
Itchy skin			
Yellow discoloration in the skin and eyes (jaundice)			
Loss of appetite			
Swelling in your legs			
Weight loss / difficulty gaining weight			
Confusion, drowsiness and slurred speech (hepatic encephalopathy)			
Spider-like blood vessels on your skin			
Other (please specify_____)			

15. Thinking about the time **before you started taking sebelipase alfa**, please score how burdensome these symptoms were for you (as detailed in Question 13). *If you did not experience a symptom, please select 'Not relevant'*

Symptoms	Not relevant	Not burdensome	Quite burdensome	Very burdensome
Abdominal / tummy pain				
Vomiting				
Nausea				
Diarrhoea				
Anaemia				
Bleeding, bruising easily				
Coughing up blood				
Shortness of breath				
Difficulty in swallowing				
Fatigue				
Fluid accumulation in your abdomen (ascites)				
"Big belly" (not fluid accumulation)				
Itchy skin				
Yellow discoloration in the skin and eyes (jaundice)				
Loss of appetite				
Swelling in your legs				
Weight loss / difficulty gaining weight				
Confusion, drowsiness and slurred speech (hepatic encephalopathy)				
Spider-like blood vessels on your skin				
Other (please specify_____)				

16. Do you suffer from any other long term conditions?

☐ Yes
☐ No
If YES, please specify _____

17. Have you been diagnosed with any of the following conditions?

	Yes	No
Coronary artery disease		
Aneurysm (swelling of blood vessels)		
Stroke		

Myocardial infarction		
Liver failure		
Liver cirrhosis		
Liver cancer		
Enlarged liver (hepatomegaly)		
Enlarged spleen (splenomegaly)		

18. Are you currently taking any medication or receiving treatment for your LAL-D? Please tick one or more options corresponding to your situation from the list below.

☐ Not taking any medication
☐ Lipid lowering drugs (statins, niacin, ezetimibe, bile acids and resins)
☐ Pain relief medication/narcotics (eg morphine, codeine, etc)

☐ Drugs to reduce nausea (antiemetics)
☐ Vitamin E
☐ Other (please specify _____)

19. Have you received a liver transplant in the past?

☐ Yes
☐ No

20. If you have received the liver transplant was it before or after treatment with sebelipase alfa?

☐ Before starting the treatment with sebelipase alfa
☐ After starting the treatment with sebelipase alfa

21. If you have received the liver transplant, how many have you received?

☐ One
☐ More than one

22. Have you received hematopoietic stem cell transplant?

☐ Yes
☐ No

23. If yes, was it before or after you started treatment with sebelipase alfa?

☐ Before starting the treatment with sebelipase alfa
☐ After starting the treatment with sebelipase alfa

24. Did you require surgery to remove your spleen?

☐ Yes
☐ No

25. If yes, was it before or after you started treatment with sebelipase alfa?

☐ Before starting the treatment with sebelipase alfa
☐ After starting the treatment with sebelipase alfa

Impact of LAL-D on quality of life
The aim of this section is to assess how and to what extent LAL-D impacts your life.

Thinking about **before you started taking sebelipase alfa** which of these statements best describe your health at that time? Please tick one option for each of the five categories below

26. Mobility

☐ I had no problems in walking about
☐ I had slight problems in walking about
☐ I had moderate problems in walking about
☐ I had severe problems in walking about
☐ I was unable to walk about

27. Self-Care (ie looking after oneself day-to-day)

☐ I had no problems with washing or dressing myself
☐ I had slight problems with washing or dressing myself
☐ I had moderate problems with washing or dressing myself

☐ I had severe problems with washing or dressing myself

☐ I was unable to wash or dress myself

28. Usual Activities (eg work, study, housework, family or leisure activities)

☐ I had no problems with performing my usual activities

☐ I had slight problems with performing my usual activities

☐ I had moderate problems with performing my usual activities

☐ I had severe problems with performing my usual activities

☐ I was unable to perform my usual activities

29. Pain/Discomfort

☐ I had no pain or discomfort

☐ I had slight pain or discomfort

☐ I had moderate pain or discomfort

☐ I had severe pain or discomfort

☐ I had extreme pain or discomfort

30. Anxiety/Depression

☐ I was not anxious or depressed

☐ I was slightly anxious or depressed

☐ I was moderately anxious or depressed

☐ I was severely anxious or depressed

☐ I was extremely anxious or depressed

31. Thinking about **before you started taking sebelipase alfa**, please describe how LAL-D impacted your everyday life

Now, **thinking about how you feel TODAY**, which of these statements best describes your health today? Please tick one option for each of the five categories below.

32. Mobility

☐ I have no problems in walking about
☐ I have slight problems in walking about
☐ I have moderate problems in walking about
☐ I have severe problems in walking about
☐ I am unable to walk about

33. Self-Care (ie looking after oneself day-to-day)

☐ I have no problems with washing or dressing myself
☐ I have slight problems with washing or dressing myself
☐ I have moderate problems with washing or dressing myself
☐ I have severe problems with washing or dressing myself
☐ I am unable to wash or dress myself

34. Usual Activities (eg work, study, housework, family or leisure activities)

☐ I have no problems with performing my usual activities
☐ I have slight problems with performing my usual activities
☐ I have moderate problems with performing my usual activities
☐ I have severe problems with performing my usual activities
☐ I am unable to perform my usual activities

35. Pain/Discomfort

☐ I have no pain or discomfort
☐ I have slight pain or discomfort
☐ I have moderate pain or discomfort
☐ I have severe pain or discomfort
☐ I have extreme pain or discomfort

36. Anxiety/depression

☐ I am not anxious or depressed
☐ I am slightly anxious or depressed
☐ I am moderately anxious or depressed

☐ I am severely anxious or depressed
☐ I am extremely anxious or depressed

37. Could you please describe how your health has changed **since you started sebelipase alfa treatment?**

Impact of LAL-D on work/employment/student life

The aim of the next section is to assess how - and to what extent LAL-D affects your employment or education.

38. In the table below, please tick the relevant box.

☐ Working full-time
☐ Working part-time
☐ Studying full-time
☐ Studying part-time
☐ Retired
☐ Unemployed

39. If not working, please indicate the reason for your situation. Select the option that best reflects your situation.

☐ Unable to work due to LAL-D
☐ Sick leave due to LAL-D
☐ Temporarily laid off due to LAL-D
☐ Early retirement due to LAL-D
☐ Early retirement due to other reasons than LAL-D
☐ Retired normally
☐ Unemployed due to reasons other than LAL-D
☐ Other, please specify

40. If you retired early, at what age did you retire? _____ years old

41. If you currently work or study, approximately how many hours have you worked/studied **in the past week**?

_____ hours

42. If you currently work, please provide your job title or describe your job.

43. During the last week, approximately how many hours in total did you miss from work or education because of problems associated with LAL-D?

(Please include all hours you missed as a result of sick days, times you went to work late, left early, etc., because of LAL-D)

_____ hours

44. During the last week, please consider how much LAL-D affected your ability while you were working or attending college/school. Do not take other activities apart from working or attending college/school into account when answering this question. Please circle a number on the scale below, where 0 equals "no effect" on work/studies and 10 equals "completely prevented" work/studies.

LAL-D had no effect on my work/studies	0	1	2	3	4	5	6	7	8	9	10	LAL-D completely prevented me from work/studies

45. Please describe how your working / studying situation changed after diagnosis with LAL-D

46. How has your ability to work /study been affected by your sebelipase alfa treatment?

Use of NHS resources

The next section covers questions about the types and frequency of community medical care you require as a LAL-D patient

47. How many **times in a month** do you use the following NHS service? Please enter a number for each type of support in the table below.

Type of support	Number of times in a month
GP	
Dietician	
Physiotherapist	
Other (specify)	

48. How many **times in a month** do you require NHS and other services? Please enter a number in the table below for each type of support and insert the **number of hours you receive that support in a week**.

Type of support	Number of times in a	Number of hours of

	month	care received in a week
Home nurse		
Home help		
Social service personal assistant		
Other (specify)		

Patient out-of-pocket expenses

49. Could you describe expenses associated with LAL-D that you have to pay out of your pocket (not funded by the NHS)?

Examples of out-of-pocket expenses are expenses of moving home, adapting home or car, travelling to receive healthcare, buying medication, hiring home help, etc...

50. How have your out-of-pocket expenses been affected since taking sebelipase alfa treatment?

LAL-D Survey (Child Version)

Child version, patients below 18 years old - to be completed by the parent/guardian of the child that has HPP.

Note: It is advised that the questionnaires should be answered by the parent or the guardian on behalf of the child that has LAL-D. However, it is left to the discretion of the parent/guardian to include the child in the completion of the survey if the child is considered old enough to take part.

Thank you for taking part in this survey. It will take about 30 to 45 minutes to complete.

Purpose and content of the survey

This survey is being conducted to better understand lysosomal acid lipase deficiency (LAL-D) and its impact on the lives of patients and their carers. The anonymised results of this survey will be shared with Alexion Pharmaceuticals in order to inform its submission to the National Institute for Health and Care Excellence (NICE), the organisation that recommends whether medicines - including those for rare conditions - should be available on the National Health Service (NHS) in England.

How to answer the survey?

Please answer the questions as best you can on behalf of the child. You only need to answer questions you feel comfortable answering. If you do not wish to answer a particular question, skip to the next question. Any personal information you provide will remain confidential; only anonymised information will be shared with Alexion Pharmaceuticals.

By clicking on the button you are confirming that you have LAL-D and providing consent for your anonymised information to be used as described.

Patient Information

4. How old is your child? ____ years old

5. Please tick whether your child is male or female: ☐ Male ☐ Female

6. In which country does your child live? _____

7. Is your child currently receiving treatment with sebelipase alfa?
   ☐ Yes
   ☐ No

12. If yes, for how long has your child been treated with sebelipase alfa? ___months

13. If no, has your child ever been given sebelipase alfa?
   ☐ Yes
   ☐ No

If your child is not taking sebelipase alfa, please answer all questions, including questions that mention "before your child's treatment with sebelipase alfa" and skip the questions that mention "after your child's treatment with sebelipase alfa".

Lysosomal acid lipase deficiency (LAL-D) status

The next section will cover questions about the symptoms your child experiences and the severity of these symptoms.

14. How old was your child when he/she was told he/she had LAL-D? ___years old

15. Please specify the first symptom your child experienced and what age he/she was when he/she first experienced it?

    First symptom: _____
    Age at first symptom: _____

16. How many visits to the doctor or hospitalizations did your child have before he/she was told he/she had LAL-D? _____

17. Thinking about the time **before your child started taking sebelipase alfa**, could you indicate how frequently your child suffered from any of the following symptoms

Symptoms	Never	Occasionally	Frequently
Abdominal / tummy pain			
Vomiting			
Nausea			

Diarrhoea			
Anaemia			
Bleeding, bruising easily			
Coughing up blood			
Shortness of breath			
Difficulty in swallowing			
Fatigue			
Fluid accumulation in your abdomen (ascites)			
“Big belly” (not fluid accumulation)			
Itchy skin			
Yellow discoloration in the skin and eyes (jaundice)			
Loss of appetite			
Swelling in your legs			
Weight loss / difficulty gaining weight			
Confusion, drowsiness and slurred speech (hepatic encephalopathy)			
Spider-like blood vessels on your skin			
Other (please specify_____)			

51. Thinking about the time **before your child started taking sebelipase alfa**, please score how burdensome these symptoms were for your child (as detailed in Question 10). *If your child did not experience a symptom, please select ‘Not relevant’*

Symptoms	Not relevant	Not burdensome	Quite burdensome	Very burdensome
Abdominal / tummy pain				
Vomiting				
Nausea				
Diarrhoea				
Anaemia				
Bleeding, bruising easily				
Coughing up blood				
Shortness of breath				
Difficulty in swallowing				
Fatigue				
Fluid accumulation in your abdomen (ascites)				
“Big belly” (not fluid accumulation)				
Itchy skin				
Yellow discoloration in the skin and eyes (jaundice)				
Loss of appetite				
Swelling in your legs				
Weight loss / difficulty gaining weight				
Confusion, drowsiness and slurred speech (hepatic encephalopathy)				
Spider-like blood vessels on your skin				
Other (please specify_____)				

52. Does your child suffer from any other long term conditions?

☐ Yes

☐ No
If YES, please specify _____

53. Has your child been diagnosed with any of the following conditions?

	Yes	**No**
Coronary artery disease		
Aneurysm (swelling of blood vessels)		
Stroke		
Myocardial infarction		
Liver failure		
Liver cirrhosis		
Liver cancer		
Enlarged liver (hepatomegaly)		
Enlarged spleen (splenomegaly)		

54. Is your child currently taking any medication or receiving treatment for LAL-D? Please tick one or more options corresponding to your child's situation from the list below

☐ Not taking any medication
☐ Lipid lowering drugs (statins, niacin, ezetimibe, bile acids and resins)
☐ Pain relief medication/narcotics (eg morphine, codeine, etc)

☐ Drugs to reduce nausea (antiemetics)
☐ Vitamin E
☐ Other (please specify _____)

55. Has your child received a liver transplant in the past?

☐ Yes
☐ No

56. If your child has received the liver transplant, was it before or after treatment with sebelipase alfa?

☐ Before starting the treatment with sebelipase alfa
☐ After starting the treatment with sebelipase alfa

57. If your child has received the liver transplant, how many has he/she received?

☐ One
☐ More than one

58. Has your child received hematopoietic stem cell transplant?

☐ Yes
☐ No

59. If yes, was it before or after your child started treatment with sebelipase alfa?

☐ Before starting the treatment with sebelipase alfa
☐ After starting the treatment with sebelipase alfa

60. Did your child require surgery to remove his/her spleen?

☐ Yes
☐ No

61. If yes, was it before or after your child started treatment with sebelipase alfa?

☐ Before starting the treatment with sebelipase alfa
☐ After starting the treatment with sebelipase alfa

Impact of LAL-D on quality of life
The aim of this section is to assess how and to what extent LAL-D impacts your child's life.
Thinking about **before your child started taking sebelipase alfa,** which of these statements best describe your child's health at that time? Please tick one option for each of the five categories below

62. <u>Mobility</u>

☐ My child had no problems in walking about

- ☐ My child had slight problems in walking about
- ☐ My child had moderate problems in walking about
- ☐ My child had severe problems in walking about
- ☐ My child was unable to walk about

63. Self-Care (ie looking after oneself day-to-day)

- ☐ My child had no problems with washing or dressing
- ☐ My child had slight problems with washing or dressing
- ☐ My child had moderate problems with washing or dressing
- ☐ My child had severe problems with washing or dressing
- ☐ My child was unable to wash or dress

64. Usual Activities (eg work, study, housework, family or leisure activities)

- ☐ My child had no problems with performing usual activities
- ☐ My child had slight problems with performing usual activities
- ☐ My child had moderate problems with performing usual activities
- ☐ My child had severe problems with performing usual activities
- ☐ My child was unable to perform usual activities

65. Pain/Discomfort

- ☐ My child had no pain or discomfort
- ☐ My child had slight pain or discomfort
- ☐ My child had moderate pain or discomfort
- ☐ My child had severe pain or discomfort
- ☐ My child had extreme pain or discomfort

66. Anxiety/Depression

- ☐ My child was not anxious or depressed
- ☐ My child was slightly anxious or depressed
- ☐ My child was moderately anxious or depressed
- ☐ My child was severely anxious or depressed
- ☐ My child was extremely anxious or depressed

67. Thinking about **before your child started taking sebelipase alfa**, please describe how LAL-D impacted his/her everyday life

Now, **thinking about how your child feels TODAY**, which of these statements best describes his/her health today? Please tick one option for each of the five categories below.

68. Mobility

- ☐ My child has no problems in walking about
- ☐ My child has slight problems in walking about
- ☐ My child has moderate problems in walking about
- ☐ My child has severe problems in walking about
- ☐ My child is unable to walk about

69. Self-Care (ie looking after oneself day-to-day)

- ☐ My child has no problems with washing or dressing
- ☐ My child has slight problems with washing or dressing
- ☐ My child has moderate problems with washing or dressing
- ☐ My child has have severe problems with washing or dressing
- ☐ My child is unable to wash or dress

70. Usual Activities (eg work, study, housework, family or leisure activities)

- ☐ My child has no problems with performing usual activities
- ☐ My child has slight problems with performing usual activities
- ☐ My child has moderate problems with performing usual activities
- ☐ My child has severe problems with performing usual activities
- ☐ My child is unable to perform usual activities

71. Pain/Discomfort

- ☐ My child has no pain or discomfort
- ☐ My child has slight pain or discomfort
- ☐ My child has moderate pain or discomfort
- ☐ My child has severe pain or discomfort

☐ My child has extreme pain or discomfort

72. Anxiety/depression

☐ My child is not anxious or depressed
☐ My child is slightly anxious or depressed
☐ My child is moderately anxious or depressed
☐ My child is severely anxious or depressed
☐ My child is extremely anxious or depressed

73. Could you please describe how your child's health has changed **since he/she started sebelipase alfa treatment?**

Impact of LAL-D on education

The aim of the next section is to assess how - and to what extent LAL-D affects your child's education.

74. Regarding your child's school/college attendance. Please tick the option that best corresponds to your child's situation.

i. Full-time attendance
ii. Part-time attendance
iii. Full-time attendance with educational support
iv. Part-time attendance with educational support
v. Full-time attendance in school/college with special adaptation and educational support
vi. Home-based education
vii. Other (specify) _____

75. If attending school/college part-time, how many days per week is your child able to attend on average? _____days

76. In the past month, how often has your child had problems with keeping up with school/college work as a result of LAL-D? Please tick the option that best corresponds to your child's situation.

i. Never ☐
ii. Almost never ☐
iii. Sometimes ☐
iv. Often ☐
v. Almost always ☐

77. In the past month, how often has your child missed school/college because not feeling well as a result of LAL-D? Please tick the option that best corresponds to your child's situation.

i. Never ☐

ii. Almost never
iii. Sometimes
iv. Often
v. Almost always

78. In the past month, how often has your child missed school/college to go to the doctors or hospital as a result of LAL-D? Please tick the option that best corresponds to your child's situation.

i. Never ☐
ii. Almost never ☐
iii. Sometimes ☐
iv. Often ☐
v. Almost always ☐

79. Please describe how your child's schooling situation changed after diagnosis with LAL-D

80. How has your child's ability at school been affected by his/her sebelipase alfa treatment?

Use of NHS resources

The next section covers questions about the types and frequency of community medical care your child requires as a LAL-D patient

81. How many **times in a month** does your child use the following NHS service? Please enter a number for each type of support in the table below.

Type of support	Number of times in a month
GP	
Dietician	
Physiotherapist	
Other (specify)	

82. How many **times in a month** does your child require NHS and other services? Please enter a number in the table below for each type of support and insert the **number of hours your child receives that support in a week**.

Type of support	Number of times in a month	Number of hours of care received in a week

Home nurse		
Home help		
Social service personal assistant		
Other (specify)		

Patient out-of-pocket expenses

83. Could you describe expenses associated with LAL-D that you have to pay out of your pocket (not funded by the NHS) to cover your child's needs?

Examples of out-of-pocket expenses are expenses of moving home, adapting home or car, travelling to receive healthcare, buying medication, hiring home help, etc...

84. How have your out-of-pocket expenses been affected since your child is taking sebelipase alfa treatment?

LAL-D Carer Survey – Online Version

To be completed by anyone living with or supporting a LAL-D patient

Introduction

Thank you for taking part in this survey. It will take about 15 minutes to complete.

Purpose and content of the survey

This survey is being conducted to better understand LAL-D and its impact on the lives of patients and their carers. The results of this survey will be shared with Alexion Pharmaceuticals in order to inform its submission to the National Institute for Health and Care Excellence (NICE), the organisation that recommends whether medicines - including those for rare conditions - should be available on the National Health Service (NHS) in England

How to answer the survey?

Please answer the questions as best you can. You only need to answer questions you feel comfortable answering. If you do not wish to answer a particular question, skip to the next question. Any personal information you provide will remain confidential; only anonymized information will be shared with Alexion Pharmaceuticals.

By clicking on the button you are providing consent for your anonymised information to be used as described.

Caregiver information

1. How old are you? _____years old

2. Please tick whether you are male or female: ☐ Male ☐ Female

3. Please specify the relationship you have with the LAL-D patient. Tick the most relevant option below or specify.

   ☐Spouse/Partner
   ☐Mother/Father
   ☐Brother/Sister
   ☐Relative (other)
   ☐Other, please specify_____

4. What is the age of the LAL-D patients you are taking care of? _____years old

5. Does the LAL-D patient you are caring for currently receive treatment with sebelipase alfa?

   ☐ Yes
   ☐ No

Impact of LAL-D on carer's quality of life

The aim of the next section is to assess how and to what extent taking care of the LAL-D patient impacts your life.

❖ **General quality of life**

6. Please consider how much taking care of the LAL-D patient affected your ability to do regular daily activities (housework, shopping, childcare, exercising, etc…), other than your work over the last week. Please circle a number on the scale below, where 0 means LAL-D had no effect on your daily activities and 10 means LAL-D completely prevented your daily activities

Caring for someone with LAL-D had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Caring for someone with LAL-D completely prevented my daily activities

7. Please consider only how much taking care of the LAL-D patient affected your ability to do leisure activities over the last week. Please circle a number on the scale below, where 0 means LAL-D had no effect on your leisure activities and 10 means LAL-D completely prevented you in engaging in leisure activities.

Caring for someone with LAL-D had no effect on my leisure activity

0 1 2 3 4 5 6 7 8 9 10

Caring for someone with LAL-D completely prevented me from engaging in leisure activities

❖ **Disease-specific quality of life**

Please indicate how much you agree with the following statements in the context of your relative affected with LAL-D. Please tick the option that best corresponds to your situation.

8. "I have reduced the time I spend with my other children or other family members due to the need to care for or support someone with LAL-D"
   - ☐ Strongly agree
   - ☐ Agree
   - ☐ Disagree
   - ☐ Strongly disagree

9. "I take fewer holiday because of the need to care for or support someone with LAL-D"
   - ☐ Strongly agree
   - ☐ Agree
   - ☐ Disagree
   - ☐ Strongly disagree

10. Please think about your experience as a carer of a LAL-D Patient within the last week. Read the statements in the table below. Please indicate by ticking the relevant column which applies to you for each statement below.

	Never	Some of the time	A lot of the time	Always
I feel worn out as a result of caring				
I am mentally exhausted by caring				
I am physically exhausted by caring				
I feel stressed as a result of caring				

I feel anxious due to caring				

28. Please provide any other comment to describe how taking care of a patient affected by LAL-D impacts your overall quality of life and everyday life

Impact of LAL-D on the carer's work and employment

This section will assess how - and to what extent - caring for someone with LAL-D affects your employment status.

12. What is your work status? Please tick one box below.

☐ Working full-time
☐ Working part-time
☐ Retired
☐ Unemployed

13. If you currently work, approximately how many hours have you worked in the past week?

_____ hours

14. If you currently work, please provide your job title or describe your job.

_____
_____
_____

15. Have you had to reduce your hours of work in order to care for or support someone with LAL-D?

☐ Yes
☐ No

16. If yes, please estimate the number of hours of work reduced per week. If you have had an increase in hours at work, please enter 0h/week and write increase in ii below:

_____hours/week
Comment (if any):_____

17. Have you had to change your work in order to take care of or support someone with LAL-D.

☐ Yes
☐ No

18. How many hours per week do you need to spend to care for the LAL-D patient?

_____hours/week

19. Please provide any other comment to describe how taking care of a patient affected by LAL-D impacts your work and employment situation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Highly Specialised Technology Evaluation
Sebelipase alpha for patients with lysosomal acid lipase deficiency [ID737]

Dear Sarah,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have now had an opportunity to take a look at the submission received on 14 October by Alexion. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Monday 16 November**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Mary Hughes, Technical Lead (mary.hughes@nice.org.uk). Any procedural questions should be addressed to Leanne Wakefield, Project Manager (leanne.wakefield@nice.org.uk) in the first instance.

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Literature searching

1. Please describe the strategies and resources used to retrieve the grey literature and conference publications documented in Figure C9.1 for published and unpublished clinical evidence.

Alexion Response:
An additional search was carried out in PubMed to identify relevant reviews (using the search terms "Wolman Disease"[Mesh] OR "Lysosomal acid lipase deficiency" [Supplementary Concept] OR lysosomal acid lipase deficiency). Reference lists of papers (both reviews and any primary studies identified by the database searches) were scanned to identify further studies meeting the inclusion criteria.

Searches conducted in Ovid SP and EBSCO resulted in some results that related to conference proceedings (e.g., Hepatology, Molecular Genetics and Metabolism). As a cross-check additional searches were carried out in websites of journals publishing conference proceedings (e.g., Hepatology, Molecular Genetics and Metabolism, Gastroenterology for Digestive Disease Week).

A search of www.clinicaltrials.gov was also completed with the search term sebelipase.

2. Please describe the strategies and resources used to retrieve the conference publications documented in Figure D11.1 for economic studies.

Alexion Response:
Searches conducted in Ovid SP and EBSCO resulted in some results that were conference proceedings (e.g. Program and Abstracts for the 2012 Meeting of the Society for Inherited Metabolic Disorders, SIMD 2012). The PDFs of the resulting conference proceedings were searched for keywords to identify relevant abstracts. Some conference proceedings were not electronically searchable so were hand searched.

Section A: Clarification on effectiveness data

A1. **Priority Question**: Please provide full Clinical Study Reports for all included studies (intervention [LAL-CL01, LAL-CL02, LAL-CL03, LAL-CL04] and control studies [LAL-1-NH01 and LAL-2-NH01]); including all demographic data and full patient data listings. These should include at least all baseline clinical and demographic data, all efficacy data (including related to liver disease) and adverse event data.

Alexion Response:
The clinical study reports requested are provided in the attached ZIP file.

A2. **Priority Question**: On page 105 of the company submission, a comparison is presented between 9 patients from LAL-CL03 and 21 from Study LAL-1-NH01 (with 'failure to thrive within 1st 6 months based on objective criteria similar to those used in LAL-CL03'). Please present full patient characteristics for the 21 patients from Study LAL-1-NH01, including all variables reported in Table C9.9 (company submission, page 93).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Alexion Response:
Full patient characteristics for the 21 patients from Study LAL-1-NH01, including all variables reported in Table C9.9 of our initial submission, are included in the table below. We have included the CL03 data for comparison purposes:

Characteristics	LAL-CL03	LAL-1-NH01
	All (N = 9)	All (n=21)
Males, n (%)	5 (56)	10 (47.6)
White, n (%)	[redacted]	[redacted]
Not Hispanic or Latino, n (%)	[redacted]	[redacted]
Age at Onset of LAL Deficiency-related abnormality (years) Mean ± SD (Median)	[redacted]	[redacted]
Age at Randomisation/First Dose (years) Mean ± SD (Median)	[redacted]	N/A
Age < 12 years, n (%)	9 (100)	21 (100)
Mutation		
Homozygous Common	0	0 (0)
Heterozygous Common	0	1 (16.7[c])
Other[b]	6 (100[c])	0 (0)
Baseline transaminases (U/L) Mean ±SD		
ALT	[redacted]	NR
AST	[redacted]	NR
Baseline serum lipids (mg/dL) Mean ±SD	[redacted]	
LDLc	[redacted]	NR
Non-HDL-c	[redacted]	NR
TG	[redacted]	NR
HDL-c	[redacted]	NR
Liver fat content (%) at baseline, Mean ±SD	NR	NR
Baseline LLM use, n (%)	NA	NA

[a] Ethnicity was not reported in the other 3 subjects
[b] 'Other' mutation: at least one of the alleles has a defined mutation, nether allele has the common mutation
[c] Only 6 of the 9 patients in LAL-Cl03 and 12 of the 35 patients in LAL-1-NH01 had data on LIPA genetic testing
NR = Not reported.

A3. **Priority Question**: On page 105 of the company submission, a comparison is presented between 9 patients from LAL-CL03 and 25 from Study LAL-1-NH01 ('all patients who have not received haematopoietic stem cell transplantation or liver transplant, irrespective of whether these patients met objective criteria for early failure to thrive'). Please present full patient characteristics for the 25 patients from Study LAL-1-NH01, including all variables reported in Table C9.9 (company submission, page 93).

Alexion Response:
Full patient characteristics for the 21 patients from Study LAL-1-NH01, including all variables reported in Table C9.9 of our initial submission, are included in the table below. We have included the CL03 data for comparison purposes:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Characteristics	LAL-CL03	LAL-1-NH01
	All (N = 9)	All (n=25)
Males, n (%)	5 (56)	13 (52.0)
White, n (%)	[redacted]	[redacted]
Not Hispanic or Latino, n (%)	[redacted]	[redacted]
Age at Onset of LAL Deficiency-related abnormality (years) Mean ± SD (Median)	[redacted]	[redacted]
Age at Randomisation/First Dose (years) Mean ± SD (Median)	[redacted]	N/A
Age < 12 years, n (%)	9 (100)	25 (100)
Mutation		
Homozygous Common	0	0 (0)
Heterozygous Common	0	2 (8.0[c])
Other[b]	6 (100[c])	1 (4.0[c])
Baseline transaminases (U/L) Mean ±SD		
ALT	[redacted]	NR
AST	[redacted]	NR
Baseline serum lipids (mg/dL) Mean ±SD		
LDLc	[redacted]	NR
Non-HDL-c	[redacted]	NR
TG	[redacted]	NR
HDL-c	[redacted]	NR
Liver fat content (%) at baseline, Mean ±SD	NR	NR
Baseline LLM use, n (%)	NA	NA

[a] Ethnicity was not reported in the other 3 subjects
[b] 'Other' mutation: at least one of the alleles has a defined mutation, nether allele has the common mutation
[c] Only 6 of the 9 patients in LAL-Cl03 and 12 of the 35 patients in LAL-1-NH01 had data on LIPA genetic testing
NR = Not reported.

A4. **Priority Question**: On page 119 of the company submission, subgroup analyses are mentioned. However, no results are reported. Please present a table with results from study LAL-CL02 (presented in the same way as Table c9.11 company submission page 107) for the following outcomes:

- mortality
- cholesterol level (total, LDL and HDL)
- triglycerides level
- transaminase level,
- liver fat content
- adverse effects of treatment
- health-related quality of life (for patients and carers)

Please provide these results for both treatments arms for the following subgroups:

- age (separate results for <12y and ≥12y)
- gender
- genetic mutation category
- ALT level
- liver volume
- presence of cirrhosis

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

- LDL-c level
- use of LLMs
- ADA status at baseline

Alexion Response:
Please find the tables requested below.

Subgroup Analysis: Gender=Male

Endpoint, Statistic	Sebelipase alfa (N = 18)	Placebo (N = 15)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa (N = 18)**	**Placebo (N = 15)**	**Total (N = 33)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	[redacted]	[redacted]	[redacted]
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Subgroup Analysis: Gender=Female

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 18)	(N = 15)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 18)	**(N = 15)**	**(N = 33)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Age<12 Years

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 14)	(N = 10)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 14)	(N = 10)	(p-value)[a]
Relative reduction in triglyceride, Mean (SD)[d]	■	■	■
Relative increase in HDL-c, Mean (SD)[d]	■	■	■
Relative reduction in liver fat content, Mean (SD)[d]	■	■	■
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 14)	**(N = 10)**	**(N = 24)**
Subjects with at least one			
TEAE	■	■	■
Related TEAE[1]	■	■	■
Infusion related reaction (IRR)	■	■	■
TEAE leading to study termination	0	0	0
Serious TEAE	0	0	0
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Age≥12 to <18 Years

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 9)	(N = 14)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	■	■	■
Relative reduction in LDL-c, Mean (SD)[d]	■	■	■
Relative reduction in Non-HDL-c , Mean (SD) [d]	■	■	■
Normalisation of AST, % (n/N)[e]	■	■	■
Relative reduction in triglyceride, Mean (SD)[d]	■	■	■
Relative increase in HDL-c, Mean (SD)[d]	■	■	■
Relative reduction in liver fat content, Mean (SD)[d]	■	■	■
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 9)	(N = 14)	(p-value)[a]
	(N = 9)	(N = 14)	(N = 23)
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	[redacted]	[redacted]	[redacted]
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Age≥18 Years

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 13)	(N = 6)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 13)	(N = 6)	(N = 19)
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa (N = 13)	Placebo (N = 6)	Difference (p-value)[a]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Homozygous for Common Mutation

Endpoint, Statistic	Sebelipase alfa (N = 11)	Placebo (N = 10)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa (N = 11)**	**Placebo (N = 10)**	**Total (N = 20)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Heterozygous for Common Mutation

Endpoint, Statistic	**Sebelipase alfa**	**Placebo**	**Difference**
	(N = 17)	**(N = 18)**	**(p-value)[a]**
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 17)	**(N = 18)**	**(N = 35)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	[redacted]	[redacted]	[redacted]
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Subgroup Analysis: Other Mutation

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 8)	(N = 2)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 8)	**(N = 2)**	**(N = 10)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	0	0	0
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: ALT level <3xULN

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 26)	(N = 22)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa (N = 26)	Placebo (N = 22)	Difference (p-value)[a]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa (N = 26)**	**Placebo (N = 22)**	**Total (N = 48)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: ALT level ≥3xULN

Endpoint, Statistic	Sebelipase alfa (N = 10)	Placebo (N = 8)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 10)	(N = 8)	(p-value)[a]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 10)	**(N = 8)**	**(N = 18)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	[redacted]	[redacted]	[redacted]
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Liver Volume <1.25MN

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 14)	(N = 7)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 14)	**(N = 17)**	**(N = 21)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa (N = 14)	Placebo (N = 7)	Difference (p-value)[a]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Liver Volume ≥1.25MN to <1.58MN

Endpoint, Statistic	Sebelipase alfa (N = 11)	Placebo (N = 10)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 11)	**(N = 10)**	**(N = 21)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	[redacted]	[redacted]	[redacted]
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Liver Volume ≥1.58MN

Endpoint, Statistic	**Sebelipase alfa**	**Placebo**	**Difference**
	(N = 11)	**(N = 11)**	**(p-value)[a]**
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 11)	**(N = 11)**	**(N = 22)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	0	0	0
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Subgroup Analysis: Fibrosis/Cirrhosis Status= Fibrosis

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 14)	(N = 8)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 14)	**(N = 8)**	**(N = 22)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Fibrosis/Cirrhosis Status= Cirrhosis

Endpoint, Statistic	Sebelipase alfa	Placebo	Difference
	(N = 5)	(N = 5)	(p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa (N = 5)	Placebo (N = 5)	Difference (p-value)[a]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa (N = 5)**	**Placebo (N = 5)**	**Total (N = 10)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	0	0	0
TEAE leading to study termination	0	0	0
Serious TEAE	0	0	0
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: LDL-c level <190mg/dL

Endpoint, Statistic	Sebelipase alfa (N = 18)	Placebo (N = 10)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa (N = 18)	Placebo (N = 10)	Difference (p-value)[a]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa (N = 18)**	**Placebo (N = 10)**	**Total (N = 28)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	0	0	0
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: LDL-c level ≥190mg/dL

Endpoint, Statistic	Sebelipase alfa (N = 18)	Placebo (N = 20)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa (N = 18)**	**Placebo (N = 20)**	**Total (N = 38)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa (N = 18)	Placebo (N = 20)	Difference (p-value)[a]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	[redacted]	[redacted]	[redacted]
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Use of Lipid Lowering Medications = Yes

Endpoint, Statistic	Sebelipase alfa (N = 15)	Placebo (N = 11)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa (N = 15)**	**Placebo (N = 11)**	**Total (N = 26)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	0	0	0
TEAE leading to study termination	0	0	0
Serious TEAE	0	0	0

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Endpoint, Statistic	Sebelipase alfa (N = 15)	Placebo (N = 11)	Difference (p-value)[a]
Related serious TEAE[1]	0	0	0
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

Subgroup Analysis: Use of Lipid Lowering Medications = No

Endpoint, Statistic	Sebelipase alfa (N = 21)	Placebo (N = 19)	Difference (p-value)[a]
Normalisation of ALT, % (n/N)[c]	[redacted]	[redacted]	[redacted]
Relative reduction in LDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in Non-HDL-c , Mean (SD) [d]	[redacted]	[redacted]	[redacted]
Normalisation of AST, % (n/N)[e]	[redacted]	[redacted]	[redacted]
Relative reduction in triglyceride, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative increase in HDL-c, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Relative reduction in liver fat content, Mean (SD)[d]	[redacted]	[redacted]	[redacted]
Adverse Events	**Sebelipase alfa**	**Placebo**	**Total**
	(N = 21)	**(N = 19)**	**(N = 40)**
Subjects with at least one			
TEAE	[redacted]	[redacted]	[redacted]
Related TEAE[1]	[redacted]	[redacted]	[redacted]
Infusion related reaction (IRR)	[redacted]	[redacted]	[redacted]
TEAE leading to study termination	0	0	0
Serious TEAE	[redacted]	[redacted]	[redacted]
Related serious TEAE[1]	[redacted]	[redacted]	[redacted]
TEAE leading to death	0	0	0

Source: Data on File, CSR LAL-CL02
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; SD = standard deviation.
[a] p-value for treatment differences (Fisher's exact test for normalisation and Wilcoxon rank sum test for all other endpoints).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

[c] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the subject was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of subjects who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).
[1]: AEs the investigators considered to be related, possible related or AEs with missing relationship to study drug.

A5. Table C9.16 presents the numbers of patients from the UK in each trial. Please complete table 1 below to show the numbers from other countries in each trial.

Alexion Response:
Please find the table requested below.

Please also note that LAL Deficiency is a genetic disease which leads to deficiency of a critical enzyme in intracellular cholesterol metabolism. All the clinical manifestations in the various organs are a consequence of this enzyme deficiency. The country of origin or ethnicity of the patients makes no difference to the metabolic defect or its severity. The severity of the defect is directly related to the amount of residual enzyme activity present. If any country-specific differences exist, these will be related to access to BSC, e.g. liver transplantation, intensive management and care of sick children.

Table 1: Numbers of patients from different countries in each trial

Country Study Name	LAL-CL03	LAL-1-NH01	LAL-CL02	LAL-CL01	LAL-CL04
UK					
Croatia					
Czech Republic					
France					
Germany					
Greece					
Ireland					
Italy					
Poland					
Russia					
Spain					
Turkey					
United States					
Canada					
Mexico					
Argentina					
Saudi Arabia					
Taiwan					
Egypt					
Japan					
Australia					
Total					

A6. **Priority Question**: The full results for health related quality of life (HRQL) from LAL-CL02 do not appear to have been presented in the company submission. Please complete table 2 to provide N, mean and SD for both treatment arms and the differences between arms for all three HRQL scales used (CLDQ, FACIT fatigue,

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

PedsQL), including subscales (the results already reported in the company submission have been included in table 2).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Alexion Response:
Table 2 has been completed below with the requested information.

Table 2: Health related quality of life outcomes from LAL-CL02

	Sebelipase Alfa						Placebo						Difference	
	Baseline			Follow-up (20 wks)			Baseline			Follow-up (20 wks)				
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	Mean	p-value
CLDQ														
AB														
AC														
EM														
FA														
SY														
WO														
FACIT Fatigue														
PedsQL														
PH														
PSY														
PHY														
ES														
SF														
SCH														

CLDQ Subscales: AB=Abdominal Activity, AC=Activity, EM=Emotional Function, FA=Fatigue, SY=Systemic Symptoms, WO=Worry
PedsQL Subscales: PH=Physical Health, PSY=Psychosocial Health, PHY=Physical Score, ES=Emotional Score, SF=Social Functioning, SCH=School Functioning
Difference: Difference between the mean change of sebelipase alfa – Placebo; p-value: Wilcoxon rank sum test for treatment differences.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

A7. The company makes several references to confirmed compensated cirrhosis (CC) and liver biopsies in relation to the LAL-CL02 population. For example on page 171 it states that 'Survival analysis was conducted to approximate the rate of transitioning from fibrosis to CC using the LAL-CL02 trial data.' Failure rate was defined as: '…the earliest mention (either a pre-baseline medical record or at baseline of the LAL-CL02 trial) of a confirmed case of CC…' In relation to biopsies, page 174 states 'This resulted in a potentially unrepresentative set of only 10 placebo patients and 16 sebelipase alfa patients with repeat biopsies in the double-blind phase of LAL-CL02.' Please provide an explanation of how a case of CC was 'confirmed'. Also, did this involve biopsy?

Alexion Response:
There were 10 subjects in LAL-CL02 with biopsy confirmed cirrhosis or early/incomplete cirrhosis assessed by an external pathologist corresponding to an Ishak score of 5 or 6. There were a further two subjects who had pre-trial data confirming cirrhosis, but were considered pre-cirrhotic at screening biopsy. This made up the 12 patients in the compensated cirrhosis subject group.

A8. On p.25 in Table A1.1 it states that the following outcomes are not included in the submission:
- liver synthetic function
- liver disease progression
- liver transplant

The justification is '…there are no new interim data analysis for the following four efficacy outcomes for any of the ongoing sebelipase alfa clinical trials'. However, from the cost-consequence model description it can be seen that some data from the clinical studies was used to estimate liver disease progression. For example, it states on page 170 that 'Preliminary analyses indicate that LAL Deficiency patients progress faster than patients with other liver diseases (Alkhouri, 2013; Angulo, 1999)'. Also, on page 171 it states that 'Survival analysis was conducted to approximate the rate of transitioning from fibrosis to CC using the LAL-CL02 trial data.' Moreover, three different proxy measures of progression are also reported: Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI), Forns Index and FIB-4.

To enable the Evaluation Committee to understand the nature and availability of clinical data relating to liver function and liver disease progression from the LAL clinical trials:

a. Please provide the following outcomes related to liver disease progression at baseline and final follow-up for all trials (and separately for the intervention and placebo arms of the LAL-CL02 at 20 weeks):

   i. the proportion of cases of fibrosis

Alexion Response:
In order to provide clarification on the disease progression analyses referenced in Question A8, none of these analyses relied on biopsy data for patients receiving treatment with sebelipase alfa. The analysis of progression rates relative to other liver diseases was conducted using data from natural history study LAL-2-NH01. As described in the Executive Summary of our initial submission, "Serious liver

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

complications often develop at an early stage of disease and progress at a faster rate than in most other liver diseases (Data on File, CSR LAL-2-NH01; Alkhouri, 2013; Angulo, 1999)." Disease progression results for this study are presented in Figure B6.3 in our initial submission entitled: “Kaplan-Meier Estimate: Paediatric and Adult Patients with LAL Deficiency at Risk for Fibrosis, Cirrhosis, or Liver Transplant”.

The survival analysis conducted to approximate the rate of transitioning from fibrosis to compensated cirrhosis (CC) relied only on pre-treatment biopsy data. As explained immediately following the excerpt above in Section 12 of our initial submission: "Specifically, LAL-CL02 patients with a known baseline Ishak score (N=32) were analysed. An accelerated failure time (AFT) survival model was estimated assuming a constant hazard. [redacted]Study time was defined to begin on the date of a patient’s first record of LAL Deficiency symptom onset, and to end on the earlier of the date of the baseline biopsy or first record of cirrhosis in medical history."

Finally, the proxy measures APRI, Forns Index, and FIB-4 rely on lab measures not biopsy data. The specific components of each measure are outlined in Section 12 of our submission, and results for the double-blind period are presented in Section 9. In addition, results for FIB-4 and all of its components at baseline and week 20 are provided for each treatment arm in Table D12.5 (“Analysis of FIB-4 scores and components, baseline and week 20, in LAL-CL02”).

Though none of the analyses relied on biopsy data for patients while on treatment with sebelipase alfa, to comply with the request from NICE/ERG, please find a summary of disease progression based on biopsy data available from sebelipase alfa trials below.

As a reminder, Study LAL-CL04, the open label extension of the sebelipase alfa first in human LAL-CL01 study, did not have protocol required biopsies. However, in cases where pre-study and follow-up biopsies were taken and recorded in the CSR, details are provided below. No biopsies were taken in study LAL-CL03, which did not have provision for biopsy for multiple reasons, *inter alia* the hazards of performing biopsies in very young children, reluctance of ethics committees to approve the procedure in young children, and technical issues with the procedure in very small and immature livers to mention a few. All details of the liver biopsies performed in the LAL-CL02 study relevant to the questions from NICE/ERG are provided.

ii. the proportion of cases of fibrosis

*[redacted]

iii. the proportion of cases of CC (using both the confirmed case definition and according to biopsy)

[redacted]

Please find these results summarized in the table below:

Table: CL02 subjects with no CC and CC at Baseline and Week 20

	Sebelipase alfa		Placebo		Total
	No CC	CC	No CC	CC	
Baseline					
Week 20					

Source: Table 14.2.7.3 LAL-CL02 CSR

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

The full details of liver disease progression of CL02 subjects comparing baseline with Week 20 as assessed by Ishak scores are presented in the table below. [redacted]

In order to assist review and for a complete picture, the status of all subjects in LAL-CL02 displaying whether their Ishak score stayed the same, improved, or worsened is displayed in the table below:

Table: Ishak score progression for CL02 subjects at Week 20 compared to Baseline

	Sebelipase alfa			**Placebo**			**Total**		
	Same	Improved	Worsened	Same	Improved	Worsened	Same	Improved	Worsened
20 Wks	[redacted]								

In terms of liver disease progression as assessed by liver biopsy, there are many factors that need to be taken into consideration and these apply specifically to study LAL-CL02:

- Short timeframe of analysis: The 20-week duration of treatment of these patients prior to the post-treatment biopsy would have resulted in only 11 doses of sebelipase alfa in the active treatment group and is therefore likely not be of sufficient treatment duration or dosing to reverse the established scarring in the liver. In the design of the trial, it was considered unethical to continue placebo therapy for a longer duration before switching these patients to enzyme replacement therapy with sebelipase alfa.

- Small sample size: Of the 36 sebelipase alfa and 30 placebo subjects in the 2 treatment groups, only 16/36 and 10/30 subjects had paired liver biopsy for the week 20 analysis, so the sample size for assessing changes in liver histology was small.

- Biopsies only required in subjects >18 years of age: Liver biopsies were required, per protocol, only in subjects above 18 years of age or older and were optional in patients less than 18 years of age. [redacted]. Thus, the majority of this subgroup of patients who were biopsied to assess histological changes had the disease for a longer period of time than younger patients, since the genetic defect and consequent enzyme deficiency is present from birth. As a result, the patients with paired liver biopsies disproportionately contained older subjects.

- Sampling variability in liver biopsies: It is well known that there is a sampling variability in liver biopsies that make paired liver biopsies challenging to interpret. Of interest, reduction in hepatic fat content by Multi Echo Gradient Echo Magnetic Resonance Imaging (MEGE-MRI) was statistically significant (-32% vs -4.2%; P <0.001) in 57 patients in whom it was tested. However, reduction in steatosis by liver morphormetry in 26 patients with paired liver biopsies did not reach statistical significance (-62% vs -40%; p= 0.42). MEGE-MRI measures the fat content in the whole liver, whereas histology is only capable of measuring this in a very small sample of the liver. In the AASLD guidelines on Liver Biopsy (Rockey, Hepatology 2009), it is stated that “Although liver biopsy clearly provides important diagnostic and prognostic information and helps define

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

treatment plans, it must be recognized that liver biopsy may be associated with sampling variability. For example, in a study of 124 patients with chronic HCV infection who underwent laparoscopy-guided left and right lobe liver biopsies, 33% of cases had discordant results by at least one histologic stage (modified Scheuer system). A smaller, but substantial, proportion of biopsies were discordant by at least two stages. Similarly, a single liver biopsy specimen may fail to distinguish steatohepatitis from simple steatosis and may mis-stage the disease by one or less frequently two stages if the specimen is much smaller than 2 cm."

Furthermore, the quality and intensity of staining of the liver section also influences the variability in measurement of fibrosis and steatosis, including when special stains such as Sirius Red are used to quantify liver fibrosis.

Taking these multiple factors into consideration, meaningful interpretation of the outcomes related to liver disease progression at baseline and subsequent follow-up biopsies is challenging.

iv. the proportion of cases of decompensated cirrhosis (DCC)

Zero patients had DCC while actively participating in a study. [redacted]

b. Please perform the survival analysis, as illustrated in Figure D12.2: 'Time to compensated cirrhosis state in LAL-CL02 patients', separately for the placebo and the sebelipase alfa arms, plot separate survival curves and estimate separate hazard ratios.

The survival analysis depicted in Figure D12.2 presents the survival curve from the date of symptom onset to diagnosis of compensated cirrhosis for subjects in LAL-CL02. This analysis was conducted using patients with biopsy data collected at baseline, and did not include any data gathered during the treatment period. The purpose of this analysis was to identify the transitional probability for BSC-treated patients to transition from 'LAL Deficiency without CC, DCC or HCC' to 'CC'. As described in Section 12.2.1 of our initial submission:

"Survival analysis was conducted to approximate the rate of transitioning from fibrosis to CC using the LAL-CL02 trial data. Specifically, LAL-CL02 patients with a known baseline Ishak score (N=32) were analysed. An accelerated failure time (AFT) survival model was estimated assuming a constant hazard. [redacted]

Study time was defined to begin on the date of a patient's first record of LAL Deficiency symptom onset, and to end on the earlier of the date of the baseline biopsy or first record of cirrhosis in medical history. [redacted]

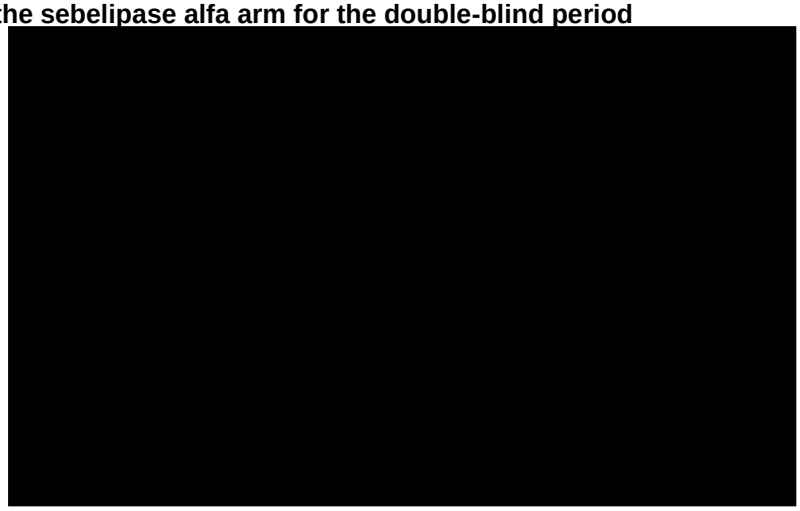
As the referenced survival analysis is performed using data collected prior to the treatment period, it is unclear why the survival analysis should be conducted separately based on the treatment that each subject later received during the double-blind period. Nevertheless, in order to comply with NICE/ERG's request, please find the results of these analyses in the figures below:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Figure 1: Time to compensated cirrhosis state in LAL-2-CL02 subjects in the sebelipase alfa arm for the double-blind period



As discussed in the response to A8.a.ii above, 19 subjects in the sebelipase alfa arm had evaluable liver biopsy data at baseline. [redacted]
The Kaplan Meier curve related to this analysis is shown in Figure 1 above. As noted in Section 12.2.1 of our initial submission, this estimate is expected to be conservative, as the actual date of developing cirrhosis almost certainly preceded the baseline biopsy finding.

Figure 2: Time to compensated cirrhosis state in LAL-2-CL02 subjects in the placebo arm for the double-blind period

Also as discussed in the response to A8.a.ii above, 13 subjects in the placebo arm had evaluable liver biopsy data at baseline, [redacted] The Kaplan Meier curve related to this analysis is shown in Figure 2 above. As noted in Section 12.2.1 of our initial submission, this estimate is expected to be conservative, as

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

the actual date of developing cirrhosis almost certainly preceded the baseline biopsy finding.

In addition, a log-rank test was conducted to compare the survival distributions of the two samples presented above. No statistically significant difference was found [redacted]

c. Please provide the following outcomes at final follow-up for both arms LAL-CL02 at 20 weeks:

i. The proportion of patients who progressed i.e. from no CC at baseline to CC (using both the confirmed case definition and according to biopsy).

All of these assessments are based upon change from Baseline in Ishak score on liver biopsy at Week 20. [redacted]

As mentioned above, it should be noted that biopsies were mandated per LAL-CL02 protocol for adults >18 years of age and optional for children thereby skewing the data towards older subjects with more established and hence more severe disease. The relatively small sample size limits generalizability and small changes in a few subjects can have a major impact on the analysis. The liver biopsy is an important contributor to the disease picture but so are other measures of disease progression such as reduction in hepatic fat content which showed statistically significant differences in favour of the treated subjects.

For these reasons (also described in A8.a.ii above), we believe that the Week 20 liver biopsy results of the double-blind period present a challenge of interpretation.

ii. The proportion of patients who have improved i.e. from CC at baseline to no CC.

Again, all of these assessments are based upon change from Baseline in Ishak score on liver biopsy at Week 20. [redacted]

A9. The natural history study LAL-2-NH01 is cited in several places with regards to liver disease progression, for example on p. 11: 'Serious liver complications often develop at an early stage of disease and progress at a faster rate than in most other liver diseases (Data on File, CSR LAL-2-NH01; Alkhouri, 2013; Angulo, 1999).' Also, a survival analysis is shown in Figure B.3 to support the claim on p.42: 'Deficiency patients progressed to fibrosis, cirrhosis, or liver transplant within 3 years of clinical manifestation onset (Data on File, CSR LAL-2-NH01) (Figure B6.3).' However, there is no analysis of the liver progression data from this study or any comparison with liver progression data from any clinical trial including LAL-CL02 presented in the clinical effectiveness section 9.

To enable the Evaluation Committee to understand the nature and availability of data relating to liver disease, liver disease progression and liver transplant from the natural history study please provide:

a. an analysis of all outcomes related to liver disease progression for LAL-2-NH01 including, at baseline, at 20 weeks and final follow-up:

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

i. the proportion of cases of CC

Alexion Response:
The LAL-2-NH01 study represents the largest case record review of patients with LAL Deficiency, and is the first study that combined both retrospective and prospective data collection. Overall, retrospective chart data were collected from 48 living patients with LAL Deficiency and prospective data were generated in a subset of 24 living patients with LAL Deficiency. Investigators reviewed medical records of patients with LAL Deficiency aged ≥5 years, extracted historical data, and obtained prospective laboratory and imaging data on living patients to develop a longitudinal dataset.

[redacted]
These findings are almost identical to the findings of Bernstein et al (2013) in her review (64% for fibrosis and cirrhosis).

[redacted]
Of note, where data were available in the observational study LAL-2-NH01, there was a rapid decrease in ALT levels following liver transplantation correlating the relationship between serum transaminase levels and liver pathology.

[redacted]

The LAL-2-NH01 subjects were not assessed at baseline/20 weeks and final follow up as the study was based on a retrospective analysis.

ii. the proportion of cases of DCC

Alexion Response:
Please see response to Question A9.a.i above.

iii. the proportion of cases of liver transplant

Alexion Response:
Please see response to Question A9.a.i above.

b. the survival analysis, as illustrated in Figure D12.2: Time to compensated cirrhosis state in LAL-CL02 patients, is performed on the LAL-2-NH01 data for the following separate events:
   i. time to CC

Alexion Response:
The survival analysis depicted in Figure D12.2 presents the survival curve from the date of symptom onset to diagnosis of compensated cirrhosis for subjects in LAL-CL02. This analysis was conducted using patients with biopsy data collected at baseline to minimize potential selection bias. In a natural history study such as LAL-2-NH01, bias could result from historical biopsy data being available for only the more severe subjects. However, to comply with the request, a similar analysis was conducted using the LAL-2-NH01 data for the 31 subjects with hepatic histology data available. As discussed in the response to Question A9.a.i above,

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

[redacted]

The Kaplan Meier curve related to this analysis is shown in Figure 3 below.

Figure 3: Time to compensated cirrhosis state in LAL-2-NH01 subjects

[redacted]

ii. time to DCC

Alexion Response:
The survival analysis depicted in Figure D12.2 is based on the earliest biopsy data available for each subject to minimize bias from adverse selection. No subjects in LAL-2-NH01 had evidence of DCC in their earliest biopsy data, so this analysis was not conducted. As discussed in the response to Question A9.a.i above, [redacted]

iii. time to liver transplant

Alexion Response:
The survival analysis depicted in Figure D12.2 is based on the earliest biopsy data available for each subject to minimize bias from adverse selection. No subjects in LAL-2-NH01 had a transplant prior to their earliest biopsy date, so this analysis was not conducted. Since data in LAL-2-NH01 were gathered both retrospectively and prospectively, it is not clear what the appropriate censoring event would be for subjects that have no record of a transplant. Descriptive statistics on the occurrence of liver transplantation are provided in Section 6 of our submission: "13% had liver transplant (2/3 <18 years)." Additional statistics on liver transplantation in LAL-2-NH01 are provided in Quinn 2014a, referenced throughout our submission:

[redacted]

A10. Three different proxy measures of liver disease progression are also reported in the cost consequence analysis section of the company submission: Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI), Forns Index and FIB-4. However, none of these data are analysed in Section 9 ('published and unpublished clinical evidence'). Table D12.5: 'Analysis of FIB-4 scores and components, baseline

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

and week 20, in LAL-CL02', page 175 summarises some of these data, but there are no data on the changes individual patients score. Please provide for LAL-CL02:

a. the proportion of patients whose FIB-4 scores improve between baseline and 20 weeks

Alexion Response:
FIB-4 and the other non-invasive indices referenced were developed to predict significant fibrosis and cirrhosis in the absence of biopsy data. As such, they have been validated based on specific thresholds indicative of a clinically meaningful change in liver functionality (see, e.g., Sterling et al. (2006)), which are used as the basis for the transition from fibrosis to compensated cirrhosis in the economic model. The significance of continuous changes in FIB-4 scores above or below these threshold values has not been established to the best of our knowledge. However, to comply with the request, we have evaluated patient-specific changes in FIB-4 from baseline to 20 weeks with a cut-off value of 0.4/year representing a minimal clinically meaningful change in fibrosis progression based on Tamaki et al. (2013).

Please note that the applicability of this study has several limitations (e.g., it is a single-centre study of an adult hepatitis C population); however, it is the only publication we are aware of that provides guidance on interpreting continuous within-person changes in FIB-4 scores.

Using the thresholds above, we conducted a new analysis of FIB-4 change from baseline to week 20 to respond to this question. We find that 14% of sebelipase alfa patients and 0% of placebo patients had improvements of at least 0.4. Assuming a constant rate of fibrosis progression, we also calculated a 20-week significant change cut-off as 0.4*(20/52)=0.154. Using this threshold, 41% of sebelipase alfa patients and 3% of placebo patients experienced a meaningful improvement.

b. the proportion of patients whose FIB-4 scores get worse between baseline and 20 weeks

Alexion Response:
Noting the limitations discussed in the response to A10.a, we find that 0% of sebelipase alfa patients and 10% of placebo patients worsened by at least 0.4, and [redacted]

c. the proportion of patients whose FIB-4 scores do not change between baseline and 20 weeks.

Alexion Response:
Again noting the limitations discussed in the response to A10.a, we find that 86% of sebelipase alfa patients and 90% of placebo patients did not have a meaningful change of at least 0.4, and 55% of sebelipase alfa patients and 79% of placebo patients did not have a meaningful change of at least 0.154.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Section B: Clarification on cost model and value for money

Cost Consequence Analysis – Model structure

B1. The model structure consists of six health states, including health states for compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and liver transplant.

1. **i) Priority question:** Please justify why allergic reactions (including anaphylaxis), which were identified as important risks of sebelipase alfa by the EMA, were not incorporated in the model. In the clinical studies 21 of 106 patients (20%) experienced signs and symptoms either consistent with or that may be related to an allergic reaction (9 out of 14 infants (64%) and 12 out of 92 children and adults (13%)).

Alexion Response:
As stated in Section 12.2.4 of the original submission, the adverse events (AEs) related to sebelipase alfa, including allergic reactions, are not included in the cost-consequence study. Sebelipase alfa is generally well tolerated. Adverse reactions in LAL-CL02 were mostly mild to moderate in severity. The most serious adverse reactions experienced by 3% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria. See section 9.7 of the original submission for further detail of adverse events.

Specifically, on page 134 of our initial submission, allergic reactions are described in detail. Review of the AE data during the double-blind period of Study LAL-CL02, showed that [redacted] In other words, the rate of reactions was lower for sebelipase alfa-treated patients than it was for the placebo group. [redacted]
For the infants, there was no control group in the study, so no similar comparison can be made. For both groups, the potential for great morbidity from LAL-D overwhelms their inclusion in the model.

Importantly, no long-term studies of patients treated with best-supportive care (BSC) have been conducted, so AEs related to its use are unknown.

ii) Priority question: Please perform scenario analyses incorporating utility decrements and costs for these allergic reactions.

Alexion Response:
Per the answer to Question B1.1.i above, we do not believe that any scenario analysis is appropriate as the adverse reactions reported were minimal and the costs associated with them are likely to be minimal as well (see below for more detail). The vast majority of these events would be termed Infusion Associated Reactions that occurred during the infusion. In a minority of situations, the reaction may have led to an interruption in the infusion and in an even smaller number of cases a temporary break in treatment;

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

however, the overwhelming majority of cases were dealt with by slowing the infusion rate and administration of appropriate medications such as anti-histamines and antipyretics reflecting the minimal cost involved. However, we included a sensitivity analysis despite the above, assuming that 3% of sebelipase alfa patients get an anaphylaxis reaction. We assume the cost per event is equal to HRG codes WA16W (Shock and Anaphylaxis with CC) and WA16Y (Shock and Anaphylaxis without CC), both of which cost £207. We assume no health utility decrement for anaphylaxis owing to the brief, episodic nature of the events, which is consistent with the literature (Lange, Lars. "Quality of life in the setting of anaphylaxis and food allergy." Allergo Journal International 23.7 (2014): 252-260). Accordingly, the change in the base case output would be an additional £6.27 in incremental costs per sebelipase alfa treated patient.

2. As there is very little evidence available on LALD, we acknowledge that a reference model had to be used as a proxy for modelling the long-term progression of the disease. However, the ERG have identified several reference models could have been chosen from the literature (including Siddique et al, 2011[2], which was also used to model progression in a younger population than Mahady et al., 2012[1]). Please justify why the model (structure, characteristics (including cycle time), transition probabilities etc.) by Mahady et al. 2012 (for non-alcoholic steatohepatitis)[1] was selected instead of other possible models from the literature?

Alexion Response:
Mahady et al., which was used in our model, was the only NAFLD model identified in a literature review published in 2015 sponsored by NICE (Crossan et al., 2015).

The Siddiqui et al. model referred to above is for hepatitis B, which was not identified by the clinical experts as an appropriate analogue to LAL Deficiency. In hepatitis B, a virus is the basis for the underlying pathology, whereas LAL Deficiency and NAFLD are both metabolic and infiltrative diseases with more similar pathology than hepatitis B. Clinical experts identified NAFLD as the most appropriate analogue to LAL Deficiency so Mahady et al was used.

3. The treatment options for HCC (Resection, Locoregional Therapy, Sorafenib & Palliation) that are incorporated in the model by Mahady et al. 2012[1] are omitted from the model as they may not apply for LALD (stated in section 12.1.4 of the company submission). Please justify why these do not apply to LALD.

Alexion Response:
There are no data on the efficacy or effectiveness, or any other outcome measure, on using resection, locoregional therapy, or sorafenib in a LAL Deficiency patient population.

As we state on page 167 of our initial submission, the model for sebelipase alfa excludes states defined as a function of resection, locoregional therapy, or sorafenib treatment because they are a function of treatment decisions and patient access that may not apply to LAL Deficiency patients. Exclusion of these states is consistent with other liver disease models including the HCV models that were published and sponsored by NICE, for example Hartwell et al. (2011).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

4. It is assumed that patients return to the baseline state once they received a liver transplant and can hence have multiple transplants. Please:
    - Justify why patients with liver transplant are assumed to have the same transition probabilities, costs and utilities as patients without liver transplant
    - Clarify what proportion of patients will have liver transplants in the model and whether this is clinically plausible.

Alexion Response:
There are no data to make an assumption that patients with LAL Deficiency, who have a liver transplant, assuming the transplant was a success, face a different set of transition probabilities than those patients who have not had a liver transplant. There is already a paucity of longitudinal data on all patients with LAL Deficiency; there are even less data available on patients with LAL Deficiency who have had a successful liver transplant. The LAL-CL06 study has enrolled two subjects who formerly had liver transplant and another who previously received a hematopoietic stem cell transplant. Their progress on the study is ongoing and will contribute to the data of this subgroup.

The model predicts that in 10 years, 15.6% of BSC-treated patients will have had a successful transplant in the base case, which aligns with the 6/48 (12.5%) subjects from the LAL-2-NH01 natural history study who required a transplant.

Transition probabilities

B2. **Priority question:** Currently, a scenario analysis is performed for an infant population using specific parameters for infants (<1 year). After the first year parameters from Mahady et al. 2012[1] are applied. However, from the CL-03 trial and the historical cohort (LAL-1-NH01), data may be available to inform transition probability parameters after the first year for this scenario analysis.

a. Please provide separate scenario analyses for infants (i.e. the population as defined in LAL-CL03) using the LAL-CL03 trial and the historical cohort (LAL-1-NH01) data to inform the parameters after the first year for this scenario analysis.

Alexion Response:
None of the 21 infants in the natural history study LAL-1-NH01 with LAL Deficiency and evidence of early failure to thrive who were received BSC survived to 12 months of age. Thus, there is no possibility of an analysis of these patients' outcomes after year one.

With regard to LAL-CL03 patients' transition probabilities, no sebelipase alfa patient had worsened by more than 0.154 FIB-4 points; accordingly, there would be no difference from the current transition matrix. Please see the response to Question A10.a for discussion of the 0.154 threshold.

There is no evidence to support the need for different transition probabilities in infants vs. children and adults and this is consistent with the common basis for the disease in all ages—enzyme deficiency of LAL Deficiency.

b. In addition to presenting the results, please provide a detailed description of the methods used in the analyses resulting in the parameters.

Alexion Response:

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Per the above, the transition matrices for an infant study would be the same—namely 0% progression to 'CC' from 'LAL Deficiency without CC, DCC or HCC'.

B3. The transition probabilities (for patients aged >1 year) were mainly derived from a secondary source (Mahady et al 2012)[1] and assumptions.

a. The transition probabilities reported in Tables D12.4 and D12.9 of the company submission are not described transparently. Please describe, for the transition probabilities reported in Tables D12.4 and D12.9:

i. the primary sources
ii. how these transition probabilities and confidence intervals are calculated
iii. on which population these transition probabilities are based
iv. justification why these transition probabilities are applicable for the present assessment in the UK setting.

Please use Table 3 below to support your response to this clarification question.

Alexion Response:

We believe that the transition probabilities reported in Tables D12.4 and D12.9 of the company submission are described transparently. More specifically, our presentation of these data is routine for a NICE HST or STA submission. All of the information requested by NICE/ERG is already in both the Section 12 of Appendix G of our initial submission, as well as the MS Excel model, Appendix 6, that was submitted.

With regard to **(i) the primary sources for the transitional probabilities**, we copy Table D12.4 from our initial submission document below. The complete Markov matrix for BSC- treated patients is presented for patients over age 1 (the matrix for sebelipase-alfa treated patients appears in Table D12.9, also with primary sources). The primary source for each probability is indicated in the last column, under the title "Source".

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Table D12.4: Transition probabilities for best supportive care LAL Deficiency patients over the age of 1

Time point n / Time point n+1	LAL Deficiency without CC, DCC or HCC	CC	DCC	HCC	Liver transplant	Death	Source
LAL Deficiency without CC, DCC or HCC	96%*	3%**	1%**	0%**	0%**	0%***	*LAL-CL02 **Mahady 2012 ***Assumption
CC	0%	86%	6%	3%	0%	4%	Mahady 2012
DCC	0%	0%	76%	3%	5%	16%	Mahady 2012
HCC	0%	0%	0%	37%*	20%**	43%***	*Assumption **Mahady 2012 ***Hartwell 2011
Liver transplant	88%	0%	0%	0%	0%	12%	Mahady 2012

With regard to (**ii), "how these transition probabilities and confidence intervals are calculated"**, pages 169 through 179 of our initial submission describe each transitional probability, including its calculation and that of the range used in the deterministic sensitivity analysis in the model. A review of these probabilities by source is below. The four sources are Mahady et al.; Hartwell et al.; and LAL-CL02 data analysis for BSC-treated patients; and LAL-CL02 data analysis for sebelipase alfa-treated patients.

1. Mahady et al.: The majority of transitional probabilities (i.e., 26 of 30 BSC- and 18 of 30 sebelipase alfa-treated patient transitional probabilities) are based on Mahady et al. Mahady et al. is the best source for the model for a variety of reasons, described on page 166 of our initial submission. It is the only cost-effectiveness model identified in a NICE review in 2015 for NAFLD and is still the only cost-effectiveness model published that assesses treatments for NAFLD; NAFLD is the best analogue disease for LAL-D according to the clinical experts. The calculation of the transitional probabilities in our model that use Mahady et al. as their basis is described on pages 170-171 of our initial submission. All BSC-transitional probabilities and their confidence intervals are taken from Mahady et al. except in four cases, which are described on these pages and reprinted below as a footnote.[1] In other words, these transitional probabilities are

[1] Reprinted from pages 170-171 from Section 12 of Appendix G: "Transitional probabilities for best supportive care patients above the age of 1 were obtained directly from Mahady et al. with four exceptions:

1. The transitional probabilities from the fibrosis and CC states in Mahady et al. (2012) do not sum to 100%. It is therefore assumed that the remainder (0.029 for the fibrosis state and 0.05 for the CC state) would be proportionally allocated across all the other states. For example, the probability of remaining in the CC state is divided by the sum of the total transitional probabilities (i.e. 0.82/0.95) to yield 0.863.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

calculated in our model as Mahady et al. calculated in their own model (see Table D12.3: Transition probabilities for NASH patients used by Mahady et al. (2012) on page 170 in the submission for the exact probabilities used from Mahady et al.). A minor adjustment is made to the Mahady et al. probabilities (per case 1, in the footnote) since the transitional probabilities from the fibrosis and CC states in Mahady et al. (2012) do not sum to 100% (see Table D12.3 in our initial submission). To make these probabilities sum to one, we add to the residual so that they do sum to one, proportionally allocating the residual amount across all transitions (see the example in in the footnote). Again, this is a minor and reasonable interpretation of the data. If the ERG has grounds for a different interpretation, we would be happy to run additional analysis.

2. Hartwell et al.: As described in the submission document, as well as in the answer to question B1.3 in this document, there are no data on the efficacy or effectiveness, or any other outcome measure, on using resection, locoregional therapy, or sorafenib in a LAL Deficiency patient population. Exclusion of these states is consistent with other liver disease models including most HCV models, for example Hartwell et al. (2011). To exclude them, we have to use transition probabilities from Hartwell et al. (2011), the most recent publication based on a NICE-sponsored HCV model reflecting experience treating HCC in the UK. Confidence intervals are taken directly from that paper.

3. LAL-CL02 data analysis for BSC-treated patients: The model uses whatever transitional probabilities could be derived from patients with LAL Deficiency—the only longitudinal data available for the LAL Deficiency patient population come in the form of the clinical trials for sebelipase alfa. Specifically, the model uses the ARISE trial to parameterize several transitional probabilities. For BSC-treated patients, LAL-CL02 data analysis on the pre-trial period is used to measure the time from "LAL Deficiency without CC, DCC or HCC" to CC; this analysis is described on page 171 and 172 of our initial submission, including the probability and confidence interval calculation (N=32; n=12 events). Additionally for BSC-treated patients in sensitivity analysis, the transitions from "LAL Deficiency without CC, DCC or HCC" to CC and back using FIB-4, APRI, and Forns

---

2. Unlike Mahady et al. (2012), it is assumed that there is no excess mortality rate from the 'LAL Deficiency without CC, DCC or HCC' state due to liver-related causes. Note that in reality, owing to the other manifestations of LAL Deficiency aside from liver pathology, there is an excess mortality rate for 'LAL Deficiency without CC, DCC or HCC' patients.
3. Additional HCC treatment states (resection, locoregional treatment, treatment with sorafenib, and palliation) in Mahady et al. were excluded from the model structure, as detailed in section 12.1.4. Consequently, transition probabilities published by Hartwell et al. (Table 38, page 66 of publication) were used for transitions to death from the HCC state (by assuming that costs, health utility and outcome for HCC is the same in LAL Deficiency as HCV) (Hartwell, 2011). The assumption about liver transplant is retained from Mahady et al., and it is assumed that the remainder of the probability is the likelihood of patients remaining in HCC.
4. Mahady et al. uses transition probabilities for the "fibrosis" state to refer to those with advanced liver fibrosis in a patient population with NAFLD/NASH. Preliminary analyses indicate that patients with LAL Deficiency progress faster than patients with other liver diseases (Alkhouri, 2013; Angulo, 1999). To evaluate sebelipase alfa in LAL Deficiency, transition probabilities for patients with LAL Deficiency who have any fibrosis stage is required. Unfortunately, there are no publications in the public domain on this progression rate to CC for LAL Deficiency patients so trial data has been analysed to estimate this probability, as detailed below."

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

measures are also included as sensitivity analyses (see pages 174-178 of our initial submission).

4. LAL-CL02 data analysis for sebelipase alfa-treated patients: For sebelipase alfa-treated patients, LAL-CL02 data analysis was used to parameterize all transitions for patients beginning in the "LAL Deficiency without CC, DCC or HCC" and CC states, since that is where patients started in the trials (see pages 174-179 in our initial submission). The observed rate of transitioning from these states to more severe states based on FIB-4 with threshold of >1.45 (i.e., the base case) was 0% in the trials (Table D12.6; N=29; n=0 events). Therefore, it is unclear what confidence interval should be used on these data (for example, were one to take a Bayesian approach to parameterizing the base case, it is unclear what the basis of the prior distribution would be). We use an outer bound of a 4% progression rate for the LAL-D (w/o CC, DCC, or HCC) to CC in a sensitivity, which would assume a faster rate of progression than for BSC-treated patients. We also look at different levels for FIB-4, APRI and Forns measures in sensitivity analyses (see pages 174-178 of our initial submission).

With regard to: "**iii. on which population these transition probabilities are based**" and "**iv. justification why these transition probabilities are applicable for the present assessment in the UK setting**". The population on which these transitional probabilities are based is explained above. Mahady et al. probabilities are based on NAFLD. Hartwell et al. probabilities are based on patients with HCC likely caused by HCV. LAL-CL02 based probabilities are based on patients with LAL Deficiency. We believe that these probabilities are also broadly representative of expected clinical experience in the UK. LAL Deficiency is a genetic disease which leads to deficiency of a critical enzyme in intracellular cholesterol metabolism. All of the clinical manifestations in the various organs are a consequence of this enzyme deficiency. The country of origin or ethnicity of the patients makes no difference to the metabolic defect or its severity. The severity of the defect is directly related to the amount of residual enzyme activity present. If any country-specific differences exist, these will be related to access to BSC, e.g. liver transplantation, intensive management and care of sick children.

With regard to NICE/ERG's request to "Please use Table 3 below to support your response to this clarification question"; we think this request is overly cumbersome and unnecessary for NICE or the ERG to obtain the data needed. Technically, if using Table 3 below, the information would need to be repeated 60 times for each transitional probability in the model. Moreover, the information requested is already in our initial submission document and the Excel spreadsheet that contains the economic model (Appendix 7). For example, please see the following tables in our initial submission documents:

1. Table D12.4: Transition probabilities for best supportive care LAL Deficiency patients over the age of 1 (Section 12 of Appendix G of the submission);
2. Table D12.9: Base case transition probabilities for patients with LAL Deficiency treated with sebelipase alfa (Section 12 of Appendix G of the submission);
3. Table D12.11: Summary of variables applied in the cost-consequence model (Section 12 of Appendix G of the submission);

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

4. Table D12.14: Variables used in one-way deterministic sensitivity analysis (Section 12 of Appendix G of the submission); and
5. Appendix 6, cells C81:I125 on sheet 'Transition Probabilities' (MS Excel model, Appendix 6).

In order to aid NICE/ERG's review, we provide the location of the requested data in each of the above tables in our main submission document (Appendix G) or the economic model (Appendix 6) in the following table:

Example table to support the response to clarification question B3a"

	Table D12.4: Transition probabilities for best supportive care LAL Deficiency patients over the age of 1	**Table D12.9: Base case transition probabilities for patients with LAL Deficiency treated with sebelipase alfa**	**Table D12.11: Summary of variables applied in the cost-consequence model**	**Table D12.14: Variables used in one-way deterministic sensitivity analysis**	**Appendix 6, cells C81:I125 on sheet 'Transition Probabilities'**
Transition	Yes	Yes	Yes	Yes	Yes
Source	Yes	Yes	Yes	Yes	Yes
Patient population	Mahady et al. based probabilities are based on NAFLD. Hartwell et al. probabilities are based on patients with HCC likely caused by HCV. LAL-CL02 based probabilities are based on patients with LAL-D.				
Number of patients	Based on Mahady et al. or Hartwell et al. or LAL-CL02: LAL-CL02 BSC-treated patient time to CC (N=32; n=12 events); LAL-CL02 sebelipase alfa-treated patient time to CC (N=29; n=0 events); LAL-CL02 sebelipase alfa-treated patient time from CC to DCC or HCC (N=84; n=0 events)				
Number of events	Based on Mahady et al. or Hartwell et al. or LAL-CL02: LAL-CL02 BSC-treated patient time to CC (N=32; n=12 events); LAL-CL02 sebelipase alfa-treated patient time to CC (N=29; n=0 events); LAL-CL02 sebelipase alfa-treated patient time from CC to DCC or HCC (N=84; n=0 events)				
Time period	All modelled time periods are one year; note that probabilities calculated from the study period of LAL-CL02 that were observed to be 0% over the 20 week double blind trial period were assumed to be 0% for one year.				
Annual transition probability	Yes	Yes	Yes	Yes	Yes
Standard error	Mahady et al. and Hartwell et al. presented 95% Cis. LAL-CL02: LAL-CL02 BSC-treated patient time to CC (standard error 0.0313 thus 95% CI 0% - 9%; see page 171); LAL-CL02 sebelipase alfa-treated patient time to CC (N=29; n=0 events; see page 177) has no standard error because 0 events were recorded; LAL-CL02 sebelipase alfa-treated patient time from CC to DCC or HCC (N=84; n=0 events; see page 178) has no standard error because 0 events were recorded			Yes	Yes

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

	Table D12.4: Transition probabilities for best supportive care LAL Deficiency patients over the age of 1	Table D12.9: Base case transition probabilities for patients with LAL Deficiency treated with sebelipase alfa	Table D12.11: Summary of variables applied in the cost-consequence model	Table D12.14: Variables used in one-way deterministic sensitivity analysis	Appendix 6, cells C81:I125 on sheet 'Transition Probabilities'
95%CI	Mahady et al. and Hartwell et al. presented 95% Cis. LAL-CL02: LAL-CL02 BSC-treated patient time to CC (standard error 0.0313 thus 95% CI 0% - 9%; see page 171); LAL-CL02 sebelipase alfa-treated patient time to CC (N=29; n=0 events; see page 177) has no standard error because 0 events were recorded; LAL-CL02 sebelipase alfa-treated patient time from CC to DCC or HCC (N=84; n=0 events; see page 178) has no standard error because 0 events were recorded			It is 2*se +/- the mean	Yes
Justification for applicability (infant population)	Based on expert opinion	Based on expert opinion	Based on expert opinion	Based on expert opinion	Based on expert opinion
Justification for applicability (children / adult population)	Based on expert opinion	Based on expert opinion	Based on expert opinion	Based on expert opinion	Based on expert opinion

b. The company states the natural history transition probabilities for best supportive care and sebelipase alfa were adjusted (in Table D12.11, page 183). Please report how, and justify why, the transition probabilities were adjusted

Alexion Response:
We believe this issue was addressed in our initial submission and also in the answer to the prior question above. Please refer to pages 170-171 from Section 12 of our initial submission where it states: "Transitional probabilities for best supportive care patients above the age of 1 were obtained directly from Mahady et al." with four exceptions. Exception 1: "The transitional probabilities from the fibrosis and CC states in Mahady et al. (2012) do not sum to 100%. It is therefore assumed that the remainder (0.029 for the fibrosis state and 0.05 for the CC state) would be proportionally allocated across all the other states. For example, the probability of remaining in the CC state is divided by the sum of the total transitional probabilities (i.e. 0.82/0.95) to yield 0.863."

c. In section 12.2.1, page 176 of the company submission it is stated "It is assumed that the transition probabilities values using baseline to week 20 data represent transitional probabilities over one year."

   i. Please justify why this assumption is plausible

Alexion Response:

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

We use the ARISE data during the double-blind period, from baseline to week 20, so that we can compare FIB-4, Forns, and APRI outcomes to the placebo arm in a sensitivity analysis, to maximize internal validity. There were no events in this period, in terms of transitions from the LAL-D (w/o CC, DCC, or HCC) state to the CC state, or from CC to HCC or DCC; so we assume a 0% transitional probability for both. We assume that the 0% rate carries forward to one year. We note that there is no empirical basis for another assumption.

ii. Please provide a scenario analysis wherein an annual transition probability is calculated from the 20-week data.

Alexion Response:
Given the lack of events in this period, we are methodologically unsure of the basis for parameterizing such a scenario.

d. A 0% transition probability to transit from the 'LAL deficiency without CC, DCC, HCC' and 'CC' health state to the 'HCC' and 'DCC' health states is assumed for sebelipase alfa (see Table D12.9, page 179 of the company submission).

i. Please justify whether it is (clinically) plausible to assume that with sebelipase alfa no patient will ever transit to the DCC, HCC or liver transplant health states.

Alexion Response:
It is clinically plausible that once the source of hepatocyte injury and necroinflammation is removed or treated, the risk for HCC or DCC is also removed. Hepatocytes are able to regenerate (unlike nerve or kidney cells) and resume the normal functions of the liver, thus restoring normal liver functions of synthesis and metabolism of toxic byproducts. The reduction of ALT levels is a marker of reduced hepatocyte necrosis.

Also, in other diseases that result in chronic hepatic necroinflammation, such as chronic viral hepatitis, the risk of HCC declines dramatically once the viral infection and consequent hepatocyte injury is removed with potent antiviral therapies. For example, HCV models commonly assume a 0% progression rate to DCC or HCC after a sustained viral response (Hartwell et al., 2011).

In "Table D12.8: Observable weeks on sebelipase alfa by trial and overall", we present that there are 2690.57 weeks of study period time for patients are on sebelipase alfa across all trials. There are no recorded instances of HCC or DCC. Thus, we assume a 0% event rate.

[redacted]

ii. Please provide scenario analyses to examine the impact of this assumption (e.g. applying 10% and 25% transition probabilities).

Alexion Response:
Given the lack of any events, we are not sure of the basis for parameterizing such a scenario. Please also see answer to Question B3.d.i above.

B4. In the base case scenario, LAL-CL02 data is used to inform transition probabilities for sebelipase alfa, while transition probabilities from Mahady et al 2012[1] are mainly

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

applied for BSC. However, from the LAL-CL02 trial, comparative data on sebelipase alfa and placebo are available to estimate the transition probabilities.

1. from the 'LAL deficiency without CC, DCC, HCC' health state to the 'CC', 'DCC' and 'HCC' health states and;
2. from the 'CC' health state to the 'LAL deficiency without CC, DCC, HCC', 'CC', 'HCC' and 'DCC' health states.

a. Please justify why, based on the natural history progression of LALD patients, it was deemed that the transition probabilities to the 'CC', 'LAL deficiency without CC, DCC, HCC', 'DCC' and 'HCC' health states from Mahady et al.[1] (2012) were more representative of best supportive care (BSC) than transition probabilities derived from the 20 week placebo data.

Alexion Response:
Liver models have one-year cycles, including Mahady et al., and all HCV models (e.g., Hartwell et al.) that have been sponsored by NICE (or submitted to NICE in the past 10 years). The one-year cycle is used because of the expected frequency of liver events. Mahady et al., as the one model of the disease (NALFD) that clinical experts have stated is the closest analogue, is the basis for our natural history model. We have used transitional probabilities from this model as possible in our submission.

However, we recognize that ARISE was a controlled study and parameterized placebo efficacy with the FIB-4, APRI and Forns measures for assessing the transitional probabilities for BSC-treated patients from the 'LAL deficiency without CC, DCC, HCC' health state to the 'CC' health state. We state on page 176 of our initial submission: "Sensitivity analysis is conducted using the placebo liver scores for BSC from Table D12.6". The placebo versions of these values are reported on pages 177-178 in Table D12.6 and Table D12.7 of our initial submission.

We did not use the placebo data to parameterize the transition from CC to DCC or HCC. There were about 667 study period weeks available from the placebo arm of ARISE. No DCC or HCC cases were observed over this period. In the design of the trial, it was considered unethical to continue placebo therapy for a longer duration before switching these patients to enzyme replacement therapy.

b. **Priority question:** Please describe the calculation and provide the transition probabilities for BSC based on the LAL-CL02 trial (placebo-arm) data (or similar assumptions as for sebelipase alfa based on these data)
    5. from the 'LAL deficiency without CC, DCC, HCC' health state to the 'CC', 'DCC' and 'HCC' health states and;

Alexion Response:
These calculations were described on pages 176-178 of our initial submission.

The results are included on pages 203-204 of our initial submission (see last four rows in table D12.23, also copied below; the rows correspond to head to head comparisons using thresholds defined by FIB-4>0.6, FIB-4≥3.25, Forns>4.2, and APRI>1.5).

Note also that these comparisons are programmed into Appendix 6, the Excel model, in cell Y20 on the sheet labelled 'Inputs'; inputs are on cells B9:G14 on sheet labelled 'Transition Probabilities'.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Table D12.23: Results of deterministic multi-way scenario sensitivity analysis of transition probabilities

	Incremental costs (£)	Incremental QALYs	Incremental life years (undiscounted)
Sebelipase alfa alternative transitions			
Scenario 1: FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)	[redacted]	19.9	40.7
Scenario 2: FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)		20.5	40.7
Scenario 3: Potentially Significant Fibrosis (Forns>4.2)		19.8	40.7
Scenario 4: Potentially Significant Fibrosis (APRI>1.5)		20.5	40.7
Best supportive care and sebelipase alfa alternative transitions			
BSC scenario 1 vs. sebelipase base case	[redacted]	10.2	20.8
BSC scenario 2 vs. sebelipase scenario 1		24.9	49.6
BSC scenario 3 vs. sebelipase scenario 3		20.6	42.1
BSC scenario 4 vs. sebelipase scenario 4		15.2	30.5

6. from the ‘CC’ health state to the ‘LAL deficiency without CC, DCC, HCC’, ‘CC’, ‘HCC’ and ‘DCC’ health states

Alexion Response:
Please see response to Question B4.b above.

c. **Priority question:** Provide a scenario analysis while using the transition probabilities from b.

Alexion Response:
Please see response to Question B4.b above.

B5. (New question sent Nov 11, 2015 from NICE): In Table D12.7 (page 177), in the section “Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)” for Placebo it is stated “Potentially cirrhotic (n=0)”. This n=0 doesn’t seem to correspond with the percentages (25% and 75%) reported next to it. The ERG couldn’t find these numbers in the “Data on File CSR lal-cl02-report-body.pdf” file provided by the Company, nor in the economic model. Please could you clarify whether these data reported in table D12.7 are correct, and the source of these data.

Alexion Response:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

The correct data for this portion of the Table D12.7 (page 177 in our initial submission) are below. The Ns were correct, but the percentages were not; we apologise for this error. Note that this typo does not affect any subsequent analysis, results, or the model. This analysis was not used in the model, and therefore not used to produce results, because there were no observations of placebo patients in the "Potentially cirrhotic" group at baseline. The source of the data is the same as for the rest of Table D12.7.

Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)

		Sebelipase alfa Week 20			*Placebo at Week 20*	
		Non-cirrhotic	Potentially cirrhotic		Non-cirrhotic	Potentially cirrhotic
Baseline	Non-cirrhotic (n=28)	100%	0%	Non-cirrhotic (n=29)	100%	0%
	Potentially cirrhotic (n=1)	100%	0%	Potentially cirrhotic (n=0)	-	-

Health state utilities

B6. **Priority:** The utility of 0.92 for the 'LAL deficiency without CC, DCC, HCC' health state was assumed to be independent of age. However, the UK utility in the general population of persons aged older than 35 is expected to be (substantially) lower. For instance, for sebelipase alfa 90% of the patients is still expected to be alive at age 65 with a utility of 0.92 while the UK utility in the general population of persons aged 65 is expected to be 0.784.(Ward et al 2007)[3]

a. Please justify why the utilities in the model are considered independent of age

Alexion Response:

Assuming that health state transition probabilities are discounted over the future but not otherwise modified for age, is not an unusual assumption in a model submission to NICE. Alexion made this assumption in its previous submissions for use of eculizumab in atypical haemolytic uraemic syndrome (aHUS) and use of asfotase alfa in hypophosphatasia (HPP). Gilead made this base case assumption in its sofosbuvir + peginterferon and ribavirin submission for HCV submission to NICE in 2014, and again in its sofosbuvir + ledipasvir submission HCV submission to NICE in 2015. Moreover, AbbVie made it in its ombitasvir-paritaprevir-ritonavir HCV submission to NICE in 2015. In each of these cases, using utilities independent of age was either not commented upon or not made a requirement in the base case by the ERG or NICE.

Importantly, in the case of sebelipase alfa, the health utilities used to parameterize health states were collected for an older patient population, with HCV or NAFLD (e.g., average age 50 in Mahady et al.), at baseline. The age-adjustment factor for scaling health state health utilities in Ara and Brazier algorithm in Ara and Brazier (2010) (Ara, Roberta, and John E. Brazier. "Populating an economic model with health state utility values: moving toward better practice." Value in Health 13.5 (2010): 509-518.) is:

Age-adjustment factor = 0.9508566 + 0.0212126 * Male - 0.0002587 * age - 0.0000332 * Age^2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Were this factor used to scale our base case health utility, where the average patient age is 11 years old, the health utilities at t=0 in the model would be larger than they are in our submission, reflecting the very healthy status of young persons. It is true that they would decline over time, but not by great increments. Accordingly, using health utilities from Mahady et al. is actually very conservative.

Finally, we respect Ara very much, appreciating her research, but on this matter, we believe that baseline health utilities should be parameterized based on the best available research and then appropriately adjusted in the future via the discount rate. Further adjusting them downward based on age-related trajectories in normal patient populations exacerbates issues regarding creating incentives that disadvantage certain age groups. Further, the message is that the health of males is less important than females. There are other issues about the specification used in the above adjustment factor equation—for example, would race or income improve the model fit, but what factors would those parameters introduce.

b. Please provide a scenario analysis while using age-dependent utility values.

Alexion Response:
Such a scenario would increase the baseline health utilities, as we describe in our response to Question B5.a above. Accordingly, we thought our current presentation of the health utilities to be more valid.

B7. The health state utility values were mainly derived from a secondary source (Mahady et al 2012)[1] and assumptions.

a. The health state utilities reported in Table C10.1, page 156 are not described transparently. Please describe, for the health state utilities reported in Table C10.1
   i. the primary sources

Alexion Response:
We are not sure what is meant by the claim that health state utilities are not described transparently. An NIHR-funded systematic review of quality of life in NAFLD was conducted by Crossan et al. (Crossan, 2015); Mahady et al. was identified as the best source of quality of life inputs for a model. The health state utilities for patients over age 1 come directly from Mahady et al. We listed the primary sources in the fifth bullet on page 155 of our initial submission; we copy them again below. Importantly, each comes directly from Mahady et al., who interpreted the literature and identified these data for their model.

Table: Health utilities of health states

	Base	Low	High	Sources cited in Mahady et al.
Non-cirrhotic (i.e., LAL-D without DCC, HCC or Liver transplant)	0.92	0.65	0.95	Chong et al. (2003)[40] [HCV] Siebert et al. (2003)[41] [HCV] McLernon et al. (2008)[42] [Liver]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

	Base	Low	High	Sources cited in Mahady et al.
CC	0.82	0.65	0.89	Chong et al.(2003) Younossi et al.(2001)[43] [chronic liver disease] Siebert et al. (2003) McLernon et al. (2008)
DCC	0.60	0.46	0.81	Chong et al. (2003) Younossi et al. (2001) Siebert et al. (2003) McLernon et al. (2008)
HCC	0.73	0.50	0.80	Chong et al. (2003)
Liver transplant	0.69	0.62	0.86	Younossi et al. (2001) Ratcliffe et al. (2002)[44]. [Liver] Siebert et al. (2003)
Infant year, survivors	0.5	1.0	0.25	Assumption
Infant year, died	0.07 = 103.5/365* 0.25	0.14 = 103.5/365* 0.5	0	Assumption

ii. how these health state utilities are calculated (e.g. which questionnaire, which valuation function etc.)

Alexion Response:

- Chong et al. (2003) used standard gamble.
- McLernon et al. (2008) used time tradeoff.
- Younossi et al. (2001) used Health Utility Index Mark 2 (scores 0-1), Short Form-36 (scale scores 0-100), and a disease-specific health-related quality of life instrument (Chronic Liver Disease Questionnaire; scores 1-7).
- Ratcliffe et al. (2002) used SF-36 (with the exception of Bodily Pain [P =.686]) and the EQ-5D tariff and visual analogue scale (VAS) scores.
- Siebert et al. (2003) used VAS, EQ-5D and physician expert judgment.

Of note, there has been a substantial literature on HCV health utilities; see Appendix Table 11 in Summary of HCV Health State Utility in the Literature in Liu et al. for an overview (Liu, Shan, Lauren E. Cipriano, Mark Holodniy, Douglas K. Owens, and Jeremy D. Goldhaber-Fiebert. "New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis." Annals of internal medicine 156, no. 4 (2012): 279-290.). We looked to Crossnan et al. (2105) to identify the most appropriate for NAFLD, the best analogue for LAL Deficiency, as determined by the clinical experts in the UK.

iii. on which population these health state utilities are based

Alexion Response:

The patients in these studies primarily had HCV, which led to HCC, DCC and liver transplant, as we noted in our initial submission. On page 156 we stated: “Mahady et al (2012) used utilities from studies based on other causes of liver disease (Chong, 2003; Younossi, 2001; Ratcliffe, 2002; Siebert, 2003; McLernon, 2008) and assumed that cirrhosis, decompensated cirrhosis and HCC represent a common pathway for liver

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

disease and that the decrement in quality of life associated with these conditions is similar irrespective of the initial cause".

iv. justification why these health state utilities are applicable for the present assessment in the UK setting.

Alexion Response:
As noted above, we looked to Crossnan et al. (2105) to identify the most appropriate health states for NAFLD, the best analogue for LAL Deficiency.

b. Please justify why a utility of 0.25 was assumed for permanently hospitalised infants with LALD that die within the first year. Moreover, please justify why a utility of 0.50 was assumed for infants with LALD hospitalised for a significant time that survive the first year. Additionally, clarify why this utility value of 0.50 is considered conservative given that infants will be discharged from the hospital within 1 month when receiving sebelipase alfa (as stated in the company submission, page 156).

Alexion Response:
As we state on page 156 of our initial submission, we assume that infants with LAL Deficiency that die within the first year of life have a low utility of 0.25 as they are permanently hospitalised. Those in the neonatal intensive care unit would be unable to spend extended time with their family and would be in poor health. All of the infants in the N=21 set died on average at about 3.45 months. Thus, we assume that their total utility is ((3.45/12)*0.25) = 0.07.

Infants that survive their first year will have 12 months of life. Based on the beneficial clinical efficacy of sebelipase alfa in the clinical trials, we assume infants receiving sebelipase alfa would be discharged from hospital within 1 month of receiving sebelipase alfa (potentially spending 11 months at home); assuming a utility of 0.5 is likely to be a conservative estimate considering that these infants may have a normal existence for the 11 months that they spend at home. However, we acknowledge that this is an assumption in the absence of any published data on this subject.

c. In section 10.1.10 of the company submission (considering the applicability of valuation of health effects assessed by clinical experts), the company submission refers to the advisory board details described in section 12.2.5 of the company submission. However, the description in section 12.2.5 of the company submission does not consider the valuation of health effects. Please clarify if clinical experts assessed the applicability of utility values available or estimated any values and please provide the details requested by the NICE template for section 10.1.10 of the company submission if applicable.

Alexion Response:
Clinical experts assessed the applicability of utility values at an advisory board; they did not estimate any values. As discussed in section 12.2.5 of the submission, the advisory board participants discussed health utilities in addition to the model framework, assumptions, transition probabilities, and medical resource utilisation parameters. The participants were shown utilities derived from the literature for NASH / NAFLD patients. The experts discussed alternative sources of data, such as the PedsQL data collected in the study, but no mappings were available to transform this data to utilities. In the

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

absence of LAL Deficiency specific utilities, the experts cited that published utilities presented in the literature would be a reasonable representation of LAL Deficiency patients' quality of life. Note that the infant LAL Deficiency population was incorporated into the model until after the advisory board so the experts were only assessing the paediatric and adult population utilities. However, the completed model was reviewed in a follow-up meeting with a clinical expert.

Costs

B8. **Priority question:** Please provide all analyses (base case and sensitivity analyses) of the cost-consequence analysis without the 30% price reduction of Sebelipase alfa after 10 years following loss of data exclusivity (described in section 12.3.5, page 186; table D12.12, page 188 of the company submission).

Alexion Response:

Please find below results from our base case, patient-scenario, and deterministic- and probabilistic-sensitivity analyses, reflecting no price reduction of sebelipase alfa after 10 years. Table labels correspond to the tables in which estimates including the price reduction were included in our initial submission, for ease of comparison. Of note, in the base case, patient-scenario, and deterministic-sensitivity analyses, the impact of no price reduction at 10 years is only on sebelipase-alfa costs. However, in the probabilistic-sensitivity analysis, a new set of draws yields slightly different QALY and life-year results.

Table D12.20: Summary of costs by category of cost per patient

Cost category	Sebelipase alfa (£)	Best supportive care (£)	Increment (£)	Absolute increment (£)	% Increment
Direct medical costs	26,993	46,748	-19,755	19,755	[redacted]
Drug costs	[redacted]	0	[redacted]	[redacted]	[redacted]
Total	[redacted]	**46,748**	[redacted]	[redacted]	**100.0%**

Table D12.22: Results of deterministic multi-way scenario sensitivity analysis of patient scenarios

	Incremental costs (£)	Incremental QALYs	Incremental life years (undiscounted)
Base case	[redacted]	20.5	40.7
Infants	[redacted]	28.6	54.1
Full ARISE cohort	[redacted]	20.4	38.2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Table D12.23: Results of deterministic multi-way scenario sensitivity analysis of transition probabilities

	Incremental costs (£)	Incremental QALYs	Incremental life years (undiscounted)
Sebelipase alfa alternative transitions			
Scenario 1: FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)	[redacted]	19.9	40.7
Scenario 2: FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)	[redacted]	20.5	40.7
Scenario 3: Potentially Significant Fibrosis (Forns>4.2)	[redacted]	19.8	40.7
Scenario 4: Potentially Significant Fibrosis (APRI>1.5)	[redacted]	20.5	40.7
Best supportive care and sebelipase alfa alternative transitions			
BSC scenario 1 vs. sebelipase base case	[redacted]	10.2	20.8
BSC scenario 2 vs. sebelipase scenario 1	[redacted]	24.9	49.6
BSC scenario 3 vs. sebelipase scenario 3	[redacted]	20.6	42.1
BSC scenario 4 vs. sebelipase scenario 4	[redacted]	15.2	30.5

Table D12.24: Mean and 95% CI probabilistic sensitivity analysis results

	Total costs (£)	Total QALYs	Total life years (undiscounted)
Best supportive care	45,884 (29,858 – 74,132)	20.5 (11.0 – 31.0)	32.7 (16.0 – 52.5)
Sebelipase alfa	[redacted]	39.8 (30.9 – 44.7)	70.7 (59.8 – 78.6)

B9. Please provide a full justification for using a discount rate of 1.5% on costs and outcomes in the base case.

Alexion Response:

The NICE guide to the methods of technology appraisal 2013 states the following:

> "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), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

> Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved."(Section 6.2.19 of the NICE Methods Guide to the methods of technology appraisal. NICE. April 2013. http://publications.nice.org.uk/pmg9, Last accessed October 30, 2015.)

For LAL Deficiency, the cost-consequences model estimates incremental QALYs = 20.48 using a 1.5% discount rate. When discounted at 3.5%, these gains fall by more than half to 9.99, representing the situation described above in the NICE Methods Guide where "cost-effectiveness analyses are very sensitive to the discount rate used".

NICE has previously recognised that this special case should be applied in similar situations for other HST evaluations.

In the evaluation of eculizumab in aHUS (HST1), the ERG estimated lifetime gains of 10.14 QALYs (using a 3.5% discount rate) and on this basis NICE agreed that the special case applied so a 1.5% discount rate should be used.

In the evaluation of another HST, elosulfase alfa for MPS IVa (ID744), the ERG estimated an incremental 10.03 QALYs and again NICE agreed that the special case applied and a 1.5% discount rate should be used.

Since the QALYs gained for sebelipase alfa in LAL Deficiency are similar to the QALYs calculated for eculizumab for aHUS and elosulfase alfa for MPS IVa, we assume a 1.5% discount rate should be used.

B10. In section 12.3.7 of the company submission, health state costs are mainly derived from secondary sources (Backx et al, 2014; Shepherd et al, 2007). Furthermore, these costs are based on population with hepatitis C virus (HCV) with an average baseline age above 40 years.

a. Please justify why these costs are applicable to the LAL-D population included in the cost-consequence model (average age at baseline of 11 years).

Alexion Response:
We included costs for an HCV patient population because they are available in a UK setting; costs for LAL Deficiency or NAFLD patients in the UK are not available.

b. Backx et al, 2014, and Sheperd [sic] et al, 2007 both describe costs for 'LAL Deficiency without CC, DCC or HCC', 'CC', and 'DCC'. Please justify why Backx et al, 2014 was used for the 'LAL Deficiency without CC, DCC or HCC' and 'CC 'health state costs and why Shepherd et al, 2007 was used for the 'DCC' health state costs.

Alexion Response:
Backx et al. (2014) costs are the most recent for pre-CC (N=154; which represents 'LAL Deficiency without CC, DCC or HCC') and 'CC' (N=33) liver disease in the UK. However, Backx et al. had only N=12 patients with DCC; the DCC estimates were seen as unreliable compared to those available in Shepherd et al.

c. Please describe how the mean and range of the health state costs of table D12.11, page 184 are calculated based on the sources mentioned.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Alexion Response:
The mean costs come from the cited sources and are inflation adjusted to the most current year. Backx et al. ('LAL Deficiency without CC, DCC or HCC' and 'CC' and 'CC') presented a range which is inflation adjusted to the most current year and used in the model. Shepherd et al. (2007) did not present a range, so we assumed +/-20% around the mean for the range.

B11. Health state costs from table D12.11, page 183 of the company submission are not consistent with health state costs from table D12.13, page 190 (used in the model) of the company submission for the following health states: DCC, HCC, Liver transplant.

a. Please explain these discrepancies and rectify tables and analyses if necessary.

Alexion Response:
The contents of table D12.13 are correct, and the values used in the model are correct. The cost inputs in D12.11 for 'DCC' and 'Liver Transplant' should equal those in D12.13; there is an inconsistency in the input reporting for these two cost inputs. No analyses or reporting of the results are affected by this correction.

Budget impact model:

B12. **Priority:** Table D13.16, page 227 of the company submission displays yearly non-drug direct medical costs used in the budget impact model (BIM). However, it is unclear how these costs have been calculated based on the cost-consequence model.

a. Please provide a detailed explanation and calculation of how the yearly non-drug direct medical costs for Age 1+ BSC and Age 1+ Sebelipase alfa (in table D13.16 of the company submission) have been derived from section 12 (cost-consequence analyses) of the company submission.

Alexion Response:
The BIM models the five-year budget impact of sebelipase alfa receiving market access in England. Accordingly, in the first year, prevalent patients in the Age 1+ presentation group are assumed to be of the average age of patients from the LAL-CL02 (ARISE) trials (which includes patients with presentation of LAL Deficiency after their first year), and are modelled as growing in age over the five-year period.

Annual non-drug direct medical costs for Age 1+ presentation group patients in the BIM are therefore calculated based on the cost-consequence analysis (CCA) model from Section 12 of our initial submission as the average of non-drug direct medical costs for the first full five years in the "Full ARISE cohort" scenario (which uses as baseline patient attributes those of the average patient in the LAL-CL02 (ARISE) trials). The average of costs over the five years is used for simplicity/transparency, as non-drug direct medical costs are small in magnitude relative to drug costs.

These annual costs can be calculated by setting the CCA model's scenario to "Full ARISE cohort" in cell G23 of the "Inputs" sheet, then averaging non-drug direct medical costs in the first full five years of the model on the "BSC Calcs" and "SA Calcs" sheets, i.e., cells BR40:BR44 of each respective sheet, which yields the £1,699 average cost for

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Age 1+ BSC patients and £668 average cost for Age 1+ sebelipase alfa patients included in the BIM.

B13. **Priority question:** In section 13.1 of the company submission, three steps to calculate prevalence and incidence rates based on a number of sources are described. Based on the information provided, the ERG was not able to reproduce these calculations. Please provide a detailed explanation of the calculation of the following rates (methods and results):

a. Prevalence rate for the Age 1 + presentation group

Alexion Response:
As noted in Section 13 of our initial submission, the prevalence rate for the Age 1+ presentation group is estimated to be [redacted] per million (or [redacted]), based on internal modelling performed by Alexion's bioinformatics department. This is in contrast to the 1:130,000 estimate reported by Scott et al. (2013), which reflects prevalence of only a sub-sample of LAL Deficiency causal mutations, and further, one based on a relatively small sample which yields a higher value than suggested by Alexion's best data and estimation. Specifically, Scott et al. measure prevalence based only on the Exon 8 Splice Junction Mutation (E8SJM) in samples from the New York metropolitan area and the Dallas Heart Study.

To reach the [redacted] per million prevalence rate used in the budget-impact analysis, Scott et al.'s 1:130,000 estimate is first adjusted to reflect differences in England's ethnicity mix, yielding an estimate of [redacted] per million (or [redacted]). However, as noted in Section 13, while reflecting the ethnicity mix of England, this estimate (1) only reflects prevalence of the E8SJM and (2) is based on a relatively small sample. Three other adjustments are therefore made:

- **Step 1: Improve E8SJM Carrier Frequency Estimate**: Include a larger number of E8SJM carriers in the analysis, adding data from Stitziel et al. (2013) and the Exome Aggregation Consortium (ExAC) Broad database (ExAC, 2015), which increases the sample size and reduces the estimate to [redacted] cases per million.
- **Step 2: Add Causal Mutations**: Consider all causal mutation combinations which contribute to LAL Deficiency beyond E8SJM. Combining mutations from Reiner et al. (2014), Alexion's clinical studies, and analysis of the ExAC database, this increases the estimate to [redacted] cases per million.
- **Step 3: Incorporate Mortality**: Scott et al.'s original analysis did not consider the reduced life-span of patients with LAL Deficiency. Incorporating mortality as it is reported in Burton et al. (2015c), and also observed in Alexion's clinical studies, leads to an estimate of [redacted] cases per million.

These adjustments were made by Alexion's bioinformatics department using a model, which incorporates allelic frequencies from the EXAC database and accounts for novel mutations through in-silico and statistical methods. The [redacted] per million estimate represents Alexion's most accurate estimation of the prevalence of LAL Deficiency in the Age 1+ presentation group.

b. Incidence rate for the Age 0-1 presentation group,

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Alexion Response:
As noted in Section 13 of our initial submission, Meikle et al. (1999) provide a published estimate of incidence of LAL deficiency in the Age 0-1 presentation group of 1.42 per million (or 1:704,000). However, this estimate is (1) dated and (2) does not account for various causal mutations associated with LAL Deficiency. Consequently, Alexion's' bioinformatics department also modelled the incidence of LAL Deficiency in the Age 0-1 presentation group, reaching an estimate of [redacted] per million (or [redacted]). This estimate is based on the frequency analysis from Scott et al. (2013), which is combined with null-allele assessment from Reiner et al. (2014) and allelic frequency data obtained from the EXAC genomic database in order to account for causal mutations of LAL Deficiency other than the E8SJM. Genotype/phenotype linkage based on Scott et al. and Reiner et al. is then applied to the new carrier frequency of LAL Deficiency causal mutations (expanded from Scott et al.'s analysis of E8SJM) to enable an assessment of incidence of presentation of symptoms at birth.

As noted above in question B12.a, the causal-mutation-frequency analysis underlying these estimates was performed by Alexion's bioinformatics department using a biostatistical model, which incorporates allelic frequencies from the EXAC database and accounts for novel mutations through in-silico and statistical methods.

c. Incidence rate for the Age 1 + presentation group.

Alexion Response:
As noted in Section 13 of our initial submission, an incidence rate for Age 1+ presentation group patients is not calculated. Rather, as further described in question B13 below, incident patient estimates are calculated based on (1) the expanded allelic frequency analysis performed by Alexion's bioinformatics department (2) the age dynamic of the English population and (3) the age of onset of symptoms based on Bernstein et al. (2013).

B14. On p. 215 of the company submission, the Manufacturer states that there are *between 5 and 8 incident patients in the Age 1 + presentation group* for each year of the BIM. However, no justification and explanation are provided for the actual number of incident patients in this 5 to 8 range for each year in the BIM (Year 1: 7 incident patients, Year 2: 8, Year 3: 7, Year 4: 5, Year 5: 5).

a. Please justify and explain how the number of incident cases for each year has been determined.

Alexion Response:
In each of the five years modelled, it is estimated that there will be [redacted] incident patients in the Age 1+ presentation group. These incidence estimates are derived from the causal-mutation-frequency analysis described in question B12.a, and take into account the delay in onset of symptoms found in patients with a residual activity phenotype related to the E8SJM mutation as described in Bernstein et al. (2013). Further, year-to-year variation reflects the interaction of the age distribution of the population in England based on the US Census Bureau's International Data Base (IDB)[2] and the distribution of age of onset based on Bernstein et al.

[2] US Census Bureau. International Programs – International Database [Internet]. Available at: https://www.census.gov/population/international/data/idb/informationGateway.php

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

As noted in question B12, the causal-mutation-frequency analysis underlying these estimates was performed by Alexion's bioinformatics department using a biostatistical model which cannot be summarized concisely in the context of this response document. It is unclear whether the ERG's question stems only from methodological curiosity, or from specific concern about the values used in the budget-impact analysis. If the latter, it would be helpful if the ERG could please state its specific concern, and its basis in the published literature.

B15. The company used its experience in ultra-rare diseases to determine the following in its budget impact model (pages 222 to 224 of the company submission):

- The diagnosis rate (from 40 to 80% in the Age 0-1 presentation group and from 20 to 50% in the Age 1+ presentation group)
- treatment rate (from 40 to 60% in the Age 1+ presentation group),
- treatment continuation rate (from 100% to 95% in the Age 0-1 presentation group and from 80 to 70% in the Age 1+ presentation group)
- compliance rate (85% in the Age 1+ presentation group)

Please explain and justify how the company's experience in ultra-rare disease was used to calculate diagnosis, treatment, treatment continuation and compliance rates.

Alexion Response:

Alexion has experience with two other ultra-rare diseases, PNH and aHUS. In PNH, patients are managed through a national service which logs all patients referred, providing a prevalence estimate of around 500 patients in the UK. Of these patients around [redacted] are on eculizumab treatment. All stable patients receive eculizumab through home care provision and compliance rates for patients receiving homecare drug administration are high with [redacted] of patients having compliance rates of [redacted]%.

For aHUS, the number of patients on eculizumab treatment today is [redacted], which is below the 170 estimated by NICE for year 1. This number is close to the total number of patients who have ever been treated with eculizumab ([redacted]) and figures suggest that around [redacted] of patients who start treatment will stay on chronic treatment. Figures suggest that the number of patients diagnosed and treated may not be totally reflective of the true prevalence in the UK as numbers are lower than in other countries with a similar population size to the UK.

B16. In the base case analysis of the BIM, non-drug costs are calculated based on the average baseline age in ARISE (LAL-CL02) (16.6 years) (page 227 of the company submission), while the age distribution of the population at presentation in the BIM is based on Bernstein et al. (2013) (page 217 of the company submission). However, the ARISE and Bernstein et al. (2013) age distributions are different. The ERG thinks this is inconsistent.

a. Please justify this inconsistency.

Alexion Response:

The age distribution from Bernstein et al. (2013) was relied upon in the base case of the BIM, as it is incorporated in the epidemiological calculations underlying the prevalence and incidence rates (please see the description of epidemiological rates in Section 13 of our submission, as well as the response to question B12 above). However, to offer

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

budget-impact estimates more closely aligned with the CCA model's assumption (from Section 12 of our initial submission) of average baseline age based on the trials, a budget-impact sensitivity analysis relying on the age distribution from the ARISE trial was also presented. In this regard, we have sought to avoid inconsistency where it may have meaningful impact.

The inconsistency that the ERG references with regards to the calculation of non-drug direct medical costs was not deemed material, as it results in minimal difference in costs. For reference, the non-drug direct medical costs for the Age 1+ presentation group are £668.06 for sebelipase alfa-treated patients and £1,698.89 for BSC patients when using the average age of 17 years from the ARISE trial (please see question B11 for derivation of these costs). Calculating these values using the average age of 5 years from Bernstein et al. (2013) yields costs for the Age 1+ presentation group are £668.45 for sebelipase alfa-treated patients and £1,699.99 for BSC patients. Non-drug direct medical costs calculated based on the average age in Bernstein et al. (2013) are 0.06% less than those calculated based on the average age in the trials; this difference is due to a minor difference in the background mortality rates over the age ranges 5-9 and 17-21. The difference in costs is minute on an absolute scale, and even more so relative to annual drug costs. As such, the average costs calculated using the average age from the trials were used for simplicity.

b. Please provide a budget impact analysis where both the age distribution used to calculate non-drug costs and the age distribution at presentation are based on Bernstein et al. (2013).

Alexion Response:

As suggested above, the impact of this adjustment is expected to be minimal, and so:

- Budget-impact estimates based on the average age of 17 years from the ARISE trial and the age distribution from Bernstein et al. (2013) (the base case scenario in the BIM) are £4,29M in Year 1 rising to £18,52M in Year 5, and totalling £53,55M across the five-year period.
- Budget-impact estimates based on the average age of 5 years from Bernstein et al. (2013) and the age distribution from Bernstein et al. (2013) are £4,29M in Year 1 rising to £18,52M in Year 5, and totalling £53,55M across the five-year period.
- As reflected in these budget-impact estimates, there is no material difference between using costs calculated based on the Bernstein et al. (2013) average age vs. based on the ARISE trial average age.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Section C: Textual clarifications and additional points

C1. NICE's commitment to transparency in its decision-making means information marked as confidential should be kept to an absolute minimum. We consider that the marking of academic in confidence information is not currently at a minimum, and that release of any further data could jeopardise future publication. Examples of data that we consider to be excessively marked include:

- Page 80 – locations of study centres
- Page 83 – information about dosing used in the study
- Page 84 – information about statistical tests
- Page 90-93 – baseline disease characteristics
- Page 94 – dose
- Page 95 – description of subgroups
- Page 95-98 – patient flow
- Page 98-101 – quality assessment
- Page 123-134 – adverse events
- Page 142 – the percentage and numbers of patients from the UK in the sebelipase alfa trial programme
- Page 152 – conclusion about baseline QOL of patients in LAL-CL02.

Please reduce the amount of confidential marking in your submission to an appropriate level that is aligned with the principles in 'Guide to the process of technology appraisal (2013)', as these are also applicable to the Highly Specialised Technologies programme.

Alexion Response:
We have reviewed the above-mentioned information and agree with NICE on most points. We have updated the information in our initial submission from October 14, 2014, and have noted any changes (in redline/track changes) in the attached version of Appendix H.

Please note, as indicated in an email to NICE on November 10, 2015 related to our asfotase alfa submission, Alexion is willing to share AIC and CIC information with select Consultees and Commentators (C&Cs), if a separate confidentiality agreement is signed by the C&Cs. We are amenable to having the same arrangement with our sebelipase alfa submission.

References:

[1] Mahady SE, Wong G, Craig JC, George J. Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis. *Hepatology* 2012;56(6):2172-9.

[2] Siddiqui MR, Gay N, Edmunds WJ, Ramsay M. Economic evaluation of infant and adolescent hepatitis B vaccination in the UK. *Vaccine* 2011;29(3):466-75.

[3] Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11(14):1-160.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

[redacted] ***representing British Inherited Metabolic Disease Group and Birmingham Children's Hospital***

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ***Yes***
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ***Yes***
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? ***Yes, Consultant Metabolic Physician.***

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

What is the expected place of the technology in current practice?
The following report relates to the early-onset form of LALD [Wolman Disease/ WD], ie age of onset <1 year.

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

The exact number of UK patients is unknown for this condition. This form of LAL deficiency has been quoted to affect between 1 in 500 000 to 1-2 per million live births. A recent historical natural history study identified 35 cases in 45 countries [Jones / 2015].
All affected infants once stabilised would be considered potential candidates for this therapy.

How is the condition currently treated in the NHS?

Children present early in infancy with severe failure to thrive caused by vomiting/ malabsorption /diarrhoea, a spectrum of liver disease, cytopenias, hepatosplenomegaly and possible adrenal dysfunction caused by calcification. It is a rapidly progressive condition leading to death by 1 year of age on the majority of cases. The mainstay of therapy has been supportive of the described symptoms, though a small subset worldwide have been offered haemopoetic stem cell transplantation [HSCT] in an attempt to correct the underlying enzymatic defect.

Is there significant geographical variation in current practice?
No.

Are there differences of opinion between professionals as to what current practice should be?

The decision to pursue HSCT is likely to be an individualised one on a case-by-case basis.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The potential of offering HSCT would be based on the pre transplant morbid state of the child, the age of diagnosis and the availability of a donor source. While HSCT has the potential to offer a long term corrective solution [Tolar / 2009], there is a significant risk of transplant related mortality from conditioning as well as longer term complications of the procedure and the potential for disease progression during the period of engraftment. As we gather more experience of ERT in this population it may well be that this itself proves a better long term solution than HSCT.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

There is a small cohort of affected children who may present under the age of 1 but who go to follow a milder course consistent with the later onset forms of CESD.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Not known. The phase 2/3 study (LAL-CL03) population for early onset disease consisted of 9 subjects with a median age of 5 months. [Jones /2015]

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

Given the likely overall small numbers of active cases identified in the UK, while requiring a high level of support, it is unlikely that this technology will require significant extra requirements to the established paediatric lysosomal centres currently in place and commissioned under the highly-specialised framework.

However while ERT could be provided on an indefinite period, it is possible that it could provide a 'bridge' to a proportion of these children subsequently being assessed for HSCT as the experience in LAL – WD increases and with a relative increase in numbers being referred to transplant services as well as the requirements of increased long term survival.

As with similar diseases, where specific therapies as ERT have become available, increased disease awareness may increase the diagnostic rate, though given the current known phenotype with the majority of cases ultimately presenting to a regional paediatric hepatology unit these numbers maybe small.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

I am not aware of its use outside of the current clinical trial programme.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Guidelines are currently in development. These have been commissioned by NHS England and are being written by Drs Simon Jones, Patrick Deegan, Elaine Murphy, [redacted] and [redacted]. They will be reviewed by other specialists (including hepatology) and by the patient organisation before completion.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The drug was administered by intravenous infusion on a weekly basis during the P2/3 study. Given the medical fragility of subjects this would likely take place in a hospital setting and may require the insertion of a central venous device. Longer term, there could be the potential of home delivery later in childhood. Start/stop criteria will be addressed in the consensus guidelines, but I would anticipate an initial trial of 6 to 12 months would be offered during which time clinical assessments would be undertaken of growth, nutritional status, liver, haematological and adrenal function by standard methods.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.

In the phase 2/3 study (LAL-CL03) in LALD infants with rapidly progressive disease in the first 6 months of life, sebelipase alfa (SA), a recombinant human LAL enzyme, improved survival at 12 months of age (primary endpoint) compared with untreated patients in a historical control group. Secondary endpoints included safety and effects on growth, liver function, and hematological parameters. [Jones/ 2015]

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The study included a UK site

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Beyond survival to 1 year, which was 67% in the study, all subjects demonstrated improved weight gain, improvement of GI symptoms, and

reductions in hepatosplenomegaly. In addition, rapid improvements in biochemical and hematological markers including ALT, AST, hemoglobin, and bilirubin have been observed. [Jones / 2015]

Observed improvements in growth, liver and haematological functions seem to reflect the targeting of the underlying pathogenesis and would thus be suitable surrogate markers. As with similar infantile onset LSD, there is the potential of emerging complications in longer term survivors that have yet to be observed.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

A total of 31 severe adverse events were reported in 8 of 9 patients in the study. All were unrelated with the exception of four severe adverse events in one subject: an infusion reaction of tachycardia, pallor, chills and pyrexia. The majority of infusion associated reactions were pyrexia and vomiting. To date, four subjects tested positive to anti-SA antibodies. [Jones/2015].

This proportion of events / antibody development would not appear dissimilar to the safety profiles in other ERT treated conditions and would be managed according to standard practice.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.
No additional information known.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As described previously, this technology may increase the number of children being considered for HSCT as a more permanent therapeutic option, though the overall numbers will likely be low, notwithstanding a potential for increased diagnostic yield through disease awareness.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

I wouldn't foresee any issues with this specific population of LAL deficiency.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted] [redacted]

Name of your organisation: Children's Liver Disease Foundation

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

The charity exists to support all those affected by childhood liver disease. We take action against the effects of childhood liver disease, providing information, emotional support, research funds and a voice for all affected

Supporting Families

- Following diagnosis CLDF responds immediately to a family's first needs: information, advice and support by phone, e-mail or in person
- CLDF gives families and patients the opportunity to share their experiences and meet together at events and conferences
- CLDF helps families to adjust to life with liver disease with a tailored, one to one service
- Liver disease may affect a child's social and educational development and family relationships - CLDF offers practical advice and emotional support
- Parents may feel lonely and isolated - CLDF provides a feeling of belonging to a supportive family

Supporting Young People

- CLDF has a diverse range of services for young people with liver disease

including a dedicated web site and opportunities to meet and share with others affected and innovative residential programmes

Research

- CLDF is the UK's lead charity supporting medical research into all liver diseases of childhood
- CLDF-funded research has taken knowledge from bench to bedside
- CLDF plays a pivotal role in increasing understanding of the causes and treatments of childhood liver diseases by funding vital research
- CLDF-funded research gives families hope for the future, Almost £9 million invested in research since inception

Education/Information

- CLDF provides a comprehensive information hub on all liver diseases of childhood ranging from medical literature to supporting families and young people living with a liver disease
- CLDF's Yellow Alert campaign assists healthcare professionals and the general public recognise and take action on the signs

Who uses the charity and how is it funded

The charity is in touch with over 4000 young people and their families who use and support our services. These families are affected by a myriad of liver conditions. Currently on our system our families are affected by more than 95 different, very rare liver conditions. In addition we have almost 1,500 young people and families who have been through a liver transplant.

The charity annual turnover is around £950,000 per annum. Our income is derived almost entirely from voluntary donations and fundraising activities made by families affected by childhood liver disease and their networks.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?

X CHIEF EXECUTIVE - an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

- other? (please specify)

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

LAL Deficiency/ Wolman Disease is incredibly, incredibly rare, so rare in fact that we have been unable to put forward an expert patient/ family for the 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. We do however have a lot of experience of working with families affected by liver conditions and those who have to face and go through liver transplants. We work very closely with consultants and medical professionals in the field and know that children affected by LAL Defiency/ Wolmans disease are very hard to diagnose and often the only solution to the condition is for the child to undergo a liver transplant.

At CLDF we do not put ourselves forward to comment on the medical efficacy of this treatment. Our submission is based on our extensive experience of the families and young people facing an uncertain future and liver transplantation.

This treatment offers an alternative to Liver transplantation in children and young people which is a fantastic break-through for this client group. The use of medication that will alleviate the symptoms and mean that a transplant is not needed is a fantastic development. For those families and children where transplant is the only choice between life and death then transplant is a lifeline. Transplant however is a hugely traumatic experience for all the family, with lifelong consequences, psychological impact, NHS costs, ongoing health needs, a lifetime of expensive medication and the possibility that the graft will fail.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

Children with liver conditions can be incredibly unwell, children/ families faced with a Wolmans/ LAL deficiency diagnosis will already have been through a very difficult time in order to even get a diagnosis as the condition is hard to diagnose because of

its rarity. If their child becomes very ill the only current response is a liver transplant we feel that this technology could offer a real alternative, so that the condition is managed with much better outcomes for the children / families. We say this not on the basis of its medical efficacy but on our knowledge of the burden of transplant, from working so closely with 1000's of families affected**.**

Transplants are hugely expensive not only in terms of NHS spending on the actual retrieval, transplant surgery, post op care, rehab and the lifetime of medication needed, but also on the lives of the families and young people. One life threatening condition is swapped for a life with ongoing care needs and costs. The transplant journey is also hugely complex, stressful and all- consuming for the families

Our families tell us of the burden of being told that their child will need a liver transplant 'one day' – there is a real anxiety in all the family, attending hospital appointments and having all the routine tests, not knowing if that's the appointment that the doctor will say it's the time to go for transplant assessment.

The transplant assessment time and then subsequent waiting for a donor liver is overwhelmingly stressful for the family. Not only do they have to have considerable time off work which affects financial family matters, but they face the ongoing uncertainty of whether the 'right' liver will be found in time. Some of our families describe this as ticking time bomb. Dependent on where they live in the country it may be that movement as a family is constricted during this time. We had a family recently who were unable to be more than 15- 20 minutes from the airport for the whole 6 months there child was on the transplant list. Life feels like it's been put on hold. One parent describes the immense anxiety waiting for the phone to ring and when it does hoping and praying it's the call to say the liver has been found. Of course sometimes a liver is found and everyone prepares only for at the 11th hour to find out that it's actually unsuitable after all and the wait starts again. The family can be consumed by the fear of the child dying before a liver becomes available and they live with the knowledge that with our current donor shortage this is a real possibility.

Recovery after transplant is a huge undertaking. It's an intensive experience, requiring huge amounts of skill and care from the multidisciplinary team. It also means long periods away from the family/school and peer groups for the child/ young person. Our families and young people also live with the knowledge that in addition to the lifetime of complex meds that are needed following transplant there is also the possibility that there liver will fail and that further transplants will be needed. We work with one family where the child has had 4 liver transplants and another who has just endured her 4th. The initial transplant may not give a forever result and these families and young people know and live with that knowledge, another ongoing burden.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

The condition is so rare that we are not in touch with any families affected although we know that they do exist and we take part in this process to look after their interests

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

The need for liver transplants in the group will be diminished, if not extinguished, Please see explanation of complex burden of the transplant journey (in previous section)

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

Much better quality of life and diminished need for transplant
Please see explanation of complex burden of the transplant journey (in previous section)

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

We are not aware of any, but our response to the evaluation is based on our work with families who have to go through transplant.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

Not applicable, we are not in touch with numbers of affected families and young people with differing opinions

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Not that we are aware of, but we have no direct medical expertise.

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Liver Transplant

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)

- side effects (for example nature or number of problems, how often, for how long, how severe).

We are unable to answer this question as we don't have the knowledge to do so

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions.

We are unable to answer this question as we don't have the knowledge to do so

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

We are unable to answer this question as we don't have the expertise/ knowledge to do so

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

We are unable to answer this question as we don't have the expertise/ knowledge to do so

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Symptoms would be managed and the need for liver transplants would be diminished/ extinguished Please see explanation of complex burden of the transplant journey (in previous section)

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

They would have to continue as currently, with transplants being needed

(iii) Are there groups of patients that have difficulties using the technology?

We are unable to answer this question as we don't have the expertise/ knowledge to do so

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

We are unable to answer this question as we don't have the expertise/ knowledge to do so; however we do know that the condition is exceptionally rare, with some professionals in the field never coming across a single case in their careers.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues

Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

If this treatment manages symptoms of LAL deficiency and Wolman Disease and limits the need for liver transplants in children and young people from this group then it should be available, paid for by the NHS to children and young people affected. This would improve their quality of life and would be cost effective not only in NHS resources but also for the family's emotional and financial resources and the child's education/ social welfare and development.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Appendix G – NHS England statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Commissioner's perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: E G Jessop

Name of your organisation: NHS England

Please indicate your position in the organisation: Public health adviser, Specialised commissioning team

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Lysosomal acid lipase deficiency presents in a wide spectrum of severity; current treatment is symptomatic and supportive, appropriate to the severity of the patient's condition.
We are not aware of any significant geographical variation in current practice nor differences of opinion between professionals.
There are no direct alternatives to the technology.

Appendix G – NHS England statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

To what extent and in which population(s) is the technology being used in England?

- is there variation in how it is being used across England?
- Not in use

- is it always used within its licensed indications? If not, under what circumstances does this occur? (not applicable)

- what is the current total budget for specialised and highly specialised services? £14bn per annum

- what is the scale of the NHS investment in areas of medicine comparable to lysosomal acid lipase deficiency? It is not possible to answer this question without greater clarity on what is meant by 'areas of medicine comparable to'.
-

- what is the impact of the current use of the technology on resources?
- Not in use

- what is the outcome of any evaluations or audits of the use of the technology?
- None beyond the published information from trials to which English centres recruited.

- what is your opinion on the appropriate use of the technology?

Given the expense of the drug, it is crucial that clear criteria for use of sebelipase alfa are developed, with use restricted to patients who are severely affected.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

Guidance is needed to allow NHS England to develop its commissioning policy for Sebelipase alfa.

In what setting should/could the technology be used – for example, expert centres only, homecare? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

Patients should be managed, and treatment initiated, in expert centres. Patients who are stable on treatment should be transferred to home care.

Appendix G – NHS England statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

It is not possible to estimate the budget impact; this will be driven by patient numbers and hence by eligibility criteria for use of sebelipase.

What considerations relating to the management of the highly specialised commissioning budget should be taken into account when formulating a recommendation?

There are no particular aspects of budget management to consider beyond the total annual cost.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

Would there be any need for education and training of NHS staff?

Minimal training would be required in the use of a new drug. There is already considerable expertise in the management of the condition and in the use of enzyme replacement therapies.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Other Issues

Appendix G – NHS England statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology? The phenotype of liposomal acid lipase deficiency ranges from a lethal condition of infancy to remain asymptomatic in their sixth or seventh decades of life. It is crucial that the guidance defines clearly the patient groups in whom sebelipase is a good use of NHS resources.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]
Consultant in Adult Inherited Metabolic Medicine

Name of your organisation: Salford Royal Hospital NHS Foundation Trust
Are you (tick all that apply):

- √ A specialist in the treatment of people with the condition for which NICE is considering this technology?
- √ A specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- √ An employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Currently there are about 20-30 non-infantile patients known with this condition in England. Taking in to account that there are a few undiagnosed cases I do not expect the number to be greater than 60 and of that by a rough estimate 50% would require or agree to the technology

How the condition is currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

1) The condition in adults is currently being treated by lipid lowering therapy and dietetic advice. In situations where patients have developed advanced liver disease liver transplant is offered. There is no variation across the country the way it is managed currently or difference of opinions.
2) There is infantile form of the disease (Wolman's disease) where the disease is very aggressive and fatal and is being addressed by the paediatrics colleagues. Being an adult clinician I cannot comment on that.

3) Current alternative treatments in non-infantile disease are liver transplant in advanced cases and for other patients; management of lipid profile (lipid lowing therapy and dietetic intervention)

The ideal scenario is where patients can avoid the need for a liver transplant. Liver transplant is the last chance for these patients and should not to be seen as an alternative therapy.

Advantages and disadvantages of liver transplant

Advantage: Once successfully received can be a permanent solution

Disadvantage:

a) Patients to have advanced liver disease or certain criteria to qualify
b) Scarcity of available organs and death while waiting for transplant or decline in condition becoming unsuitable for procedure and removal from list. (*http://www.odt.nhs.uk/pdf/organ_specific_report_liver_2014.pdf*)*
c) Quality of life very poor for a significant duration due to advanced liver disease and requiring multiple admissions to the hospital while on waiting list
d) Mortality and morbidity due to the procedure (*http://www.odt.nhs.uk/pdf/organ_specific_report_liver_2014.pdf*)*
e) Organ rejection
f) Long term need of immunosuppressants and monitoring.

**please refer to the data published on this*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Lipid management (lipid lowing therapy and diet modification)

Advantage: This helps to normalise lipid profile
Medications easier to use and are well tolerated

Disadvantage: Has got no beneficial effects of liver
Diet compliance can be poor

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In the non-infantile form of the disease some patient may have received liver transplant and in such patients the technology may not be of any benefit.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

The technology in discussion is delivered by biweekly intravenous infusion. The specialist centres in England are equipped for similar technology to be delivered for other conditions. I do not expect that any additional staffing or training will be required to deliver this.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

It is not available at the moment except for the patients who are participating in clinical trials for this technology.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no available guidelines at the moment however the specialist centres across England are currently working towards writing guidelines. I am part of the group writing these guidelines. These guidelines will take into consideration available information on the efficacy of technology, safety and the natural history of the disease, evidence of effectiveness of existing therapy and technology in discussion. This will take into consideration all the published and unpublished data.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Compare with current alternatives used in the UK**:**

(I have already provided this information in earlier section)
Current alternative treatments in non-infantile disease are liver transplant in advanced cases and for other patients; management of lipid profile (lipid lowing therapy and dietetic intervention)
The ideal scenario is where patients can avoid the need for a liver transplant. Liver transplant is the last chance for these patients and should not be seen as an alternative therapy.

Advantages and disadvantages of liver transplant

Advantage: Once successfully received can be a permanent solution

Disadvantage:
Patients to have advanced liver disease or fit the criteria to qualify
Scarcity of available organs and death while waiting for transplant (*http://www.odt.nhs.uk/pdf/organ_specific_report_liver_2014.pdf*)
Quality of life very poor for a significant duration due to advanced liver disease and patients' needs multiple admissions to the hospital while on waiting list
Mortality and morbidity due to the procedure
Organ rejection
Long term need of immunosuppressants and monitoring.

Lipid management (lipid lowing therapy and diet modification)

Advantage: this helps to normalise lipid profile
Medications easier to use and are well tolerated

Disadvantage: Has got no beneficial effects of liver
Diet and medication compliance can be poor

Practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

1) Having a bi weekly intravenous infusion is significant commitment from the patients and with our experience with similar technologies already in use patients comply reasonable well.

2) Once initiated in the hospital it can be delivered at home with the help of home infusion nurses.

3) Initiation of technology will mean that additional monitoring will be required to assess the benefits of the technology. The monitoring tests will be as per agreement in the guidelines for NHS England. This may require need of liver biopsy at the initiation and repeat at certain intervals and interval scans and additional blood tests.

4) Occasionally patients may have difficult access to veins and have been in the need of permanent central line (port-a-Cath). Need for this permanent central line means patients have to go for a procedure. These lines are also at risk of infection and blockage.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The guidelines which are currently being prepared by the specialist centres will address this. In a very informal way for non-infantile patients my views are:

Patients with LALD/CESD (non-infantile) disease not eligible for treatment:

1. Advanced liver disease awaiting liver transplant
2. Other life limiting illness
3. Patients who have received liver transplant

Starting criteria in patients with confirmed LALD/CESD (non-infantile)

1. Abnormal LFTs
2. Evidence LALD in liver by histology
3. Abnormal lipid profile

Stopping criteria:

1. Progressing to advanced decompensated liver disease during therapy and on the list for liver transplant
2. Patients who do not want offered technology
3. Significant adverse reaction to the technology
4. Transaminases (LFT): no significant improvement (published data on this technology to be taken in to consideration)
5. Lipid profile: no significant improvement (published data on this technology to be taken in to consideration)

6. Continue to show progression of liver disease by radiological monitoring (yearly fiberscan and MR liver ideal),
7. No improvement on liver histology (biopsy) ideally at baseline and after 12 months of receiving this technology

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

1) The trials do reflect clinical practice in the UK.
2) In my view the most important outcome is slowing the progression of the liver disease and avoid liver transplant. The duration of trial data has not been long enough to look at this outcome. However the trials have looked at some surrogate markers to reflect improvement in lipid profile and fat deposits in the liver. One can hypothesize that if fat content of liver is reduced then it will lead to reduced liver damage and in effect progression to end stage liver disease.
3) If the technology is approved then it will be useful to measure additional markers of liver fibrosis like fiberscan and biochemical marker (P3NP) in the clinical practice and also perform liver biopsy at base line and to be repeated later.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The reported side effects due to the technology have been reported and published. Recently an abstract has been submitted to the 'World symposium 2016' on the safety of this technology. The main side effect is allergic reaction to the technology. I do not have any reason to believe that there are any other adverse effects related to the technology in addition to what is already published.
Some patients may have to stop the treatment if they have significant technology related adverse reactions.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

This is the reference to the natural history publication about this condition which can get missed in the routine search:

- Burton et al. Clinical Features of Lysosomal Acid Lipase Deficiency – a Longitudinal Assessment of 48 Children and Adults. J Pediatr Gastroenterol Nutr. 2015 August 6, doi: 10.1097/MPG.0000000000000935 Link to article on Pubmed

There was a poster presented at recent SSIEM 2015 conference about successful pregnancies in female patients with non-infantile form of the condition.

In my cohort of 5 adult patients with this condition all except one were diagnosed below the age of 16y and this is in accordance with the published data that majority of non-infantile patients are diagnosed in early years of life.

Of this cohort of 5, one patient required liver transplant prior to age 10 and had been keeping well. All others have varying degree of liver involvement and abnormal lipid profile. Two patients are reluctant to take lipid lowering therapy.
The remaining two patients have participated in clinical trial for this technology. They have shown good tolerance to the technology and have shown benefits in the form of improvement in liver functions and improved lipid profile.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Implementation should not require any additional staff training. Current specialist centres will be in a position to absorb the additional work from the implementation of this technology. Additional monitoring investigations will be required (as per guidelines once finalised) to see the benefits if it is being implemented.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

This technology in unlikely to affect equality rights of the patients

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: Sophie Thomas

Name of your organisation: The Society for Mucopolysaccharide and Related Diseases (MPS Society)

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

The Society for Mucopolysaccharide and Related Diseases (known as the MPS Society) is the only patient organisation in the UK providing patient information, advice, advocacy and support to affected individuals and families in areas such as health, social care and education. Founded in 1982, we now support over 1,250 individuals and families, specialising in 25 mucopolysaccharide and related lysosomal storage diseases. Other key aims of the MPS Society are to promote awareness across both health and social care sectors and to promote research into the development of treatments for these conditions.

The MPS Society has been providing support to LAL D patients since January 2015. Support and information is still in the development stage and our contact with patients is increasing.

The MPS Society supports over 95% of diagnosed MPS patients living across the UK.

The MPS Society does not receive any statutory funding in England and is reliant on funding from Grants, Trusts and Foundations together with monies raised by members and the public through fundraising activities.

The MPS Society receives restricted educational grants from six pharmaceutical companies not exceeding 18% of its total income.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology? **NO**
- a carer of a patient with the condition for which NICE is considering this technology? **NO**
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) **YES ; Advocacy Support Team Manager**
- other? (please specify

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis.
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Due to the rarity of this condition, delays in diagnosis are common. It is not unusual for an adult to first present with symptoms and be tested years before a confirmed diagnosis is made. In one case it took over 20 years for a diagnosis to be made. We would estimate that there are a number of undiagnosed children and adults under the care of gastroenterology departments.

Even in the infant form, many parents reported that their babies from birth were poor feeders, had distended abdomens and suffered from severe vomiting. Many parents were told in the beginning that distended stomachs were due to a build-up of gas /air and that their babies were suffering from colic and reflux. Diagnosis is usually made after a child is admitted into hospital with severe vomiting and diarrhoea.

Unfortunately due to the rarity and lack of awareness of LAL D, many cases of LAL D in infants are picked up too late. LAL D in infants is a rapidly progressive disease with death likely in the first 6 months of life. The transition from diagnosis to treatment needs to be instant to afford the child the best chance of survival.

Information about the condition is scarce but is improving with the gathering of clinical data, better understanding of the disease prevalence and pathway, patient stories and journey profiling. As a patient organisation, we have only taken on the support of LAL D since January 2015 and are currently improving patient contact and the development of patient literature.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

Infants

Physical health

Children with the infantile form of LAL D, present with poor physical health usually within the first few weeks / months of life. They have poor growth, failure to thrive due to malabsorption, distended abdomens, hernias due to hepatomegaly and suffer sever vomiting and diarrhoea. Hepatic fibrosis leading to cirrhosis of the liver develops rapidly.

Children decline quickly and death usually occurs within the first 6 months of life. Children are admitted into hospital and are under the care of NICU.

Parents are usually coming to terms with having a new baby or recovering themselves from the birth when a diagnosis is made. From this point many children never leave hospital and parents have to deal with the diagnosis while dealing with their own physical health post childbirth.

Emotional wellbeing

Parents have reported that delays in diagnosis were unbearable. Parents stated that days after birth, symptoms such as failing to feed, swollen abdomens, extreme vomiting were reported to health visitors and doctors but no action was taken, stating that it was normal for babies to have trapped wind, suffer from reflux or colic and it should settle. Seeing your baby failing to thrive, refusing feeds, crying in pain and vomiting all the time and being told it will pass, gives you a little hope but when it doesn't subside and then professionals start questioning whether it is normal or your child is admitted as an emergency, is an awful burden on families. This is especially hard at a time when your own physical health and wellbeing is recovering and getting used to be a parent whether for the first or subsequent times.

Delays in diagnosis usually results in a child needing critical care and admittance to hospital. It is not unusual for this care to be provided by NICU. At this stage it is very rare that a child would be discharged or moved before death occurs.

Everyday life

From diagnosis, everyday life for many stops. Faced with the prognosis of your new baby only having weeks or months to live is devastating.

It is likely that at least one parent would be on maternity leave but the other is likely to have just returned to work and is faced with having to take time off and support the family household at a time where there is potential for reduced income to already be present.

Work is affected, with many having to take large amounts of time off to be with their critically ill child.

Family life is affected, especially given the rarity of the condition the child is likely to be transferred to a specialist hospital which may be many miles away from home. Hospital admission can be for prolonged periods of time. Siblings can experience long separation from one of both parents along with the prospect of losing their sibling. This could impact them socially as well as effect schooling etc.

Late onset

Physical health

Some of the physical symptoms reported have been chronic pain across the abdomen and back. At times this has been disabling preventing individuals from doing everyday things and feeling exhausted if they exert themselves or do too much. Mobility in many cases was reduced and feelings of extreme fatigue were experienced.

"*The pain I experienced before treatment was extreme. I had to watch what I did; I couldn't lift anything or exert myself".*

Extreme nausea after eating and feeling bloated constantly reducing appetite.

Emotional wellbeing

Patients were questioned about their lifestyles and felt there was an assumption on the type of lifestyle choice, excessive drinking and generally not taking care of themselves.

Having a progressive disease and experiencing delays in diagnosis can have a negative impact on a person's wellbeing.

One patient reported that *"I have always been active, I was part of a cycle group who went out regularly, looked after myself, drank very little and infrequently, but because my ALT levels were raised and I was in my 20's these were the questions I was asked. Apart from bloods and an ultrasound, no further follow up or intervention was offered. Twenty years later I finally got a diagnosis".*

Patients found their emotional wellbeing had been impaired by the constant pain and nausea which at times was disabling and caused moods to become low at times especially when the symptoms impacted on the ability to function and carry out every day tasks.

Everyday life
Reports on everyday life indicate that work and family life can be affected, due to ill health, pain and fatigue

"Even before diagnosis, I became very spatially aware of people around me. I would avoid crowded places or engaging in any contact sports to reduce the risk of anyone bumping into my torso area as any knocks would cause excruciating pain that could last for days".

"The constant pain I experienced ended up impacting on my work and I had to take early retirement as I could no longer carry on with the manual job I had".

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Infants
The main advantage for infants is the chance to live beyond the predicted 6 months. Results so far have shown that disease severity is rapidly reduced in infants and that lipid levels and liver function is much improved and near to normal. In the UK, the oldest child is 3.5 years and their lipid levels and liver function is reported to be near normal and they are meeting all their developmental milestones.

To have near normal development with improved physically and cognitive development. -Parents aspirations are that their child is able to live as near normal life as possible. Parents have reported that in the most part, their children are able to do this. Development is delayed only slightly in some children and could be attributed to the fact that they were critically ill for a long periods of time.

To reduce levels of lipids in the body to near normal - Parents are reporting that in the most part results are showing positive reductions and in some areas, levels appear to have normalised. Parents are hopeful that these will remain stable and their levels will continue to normalise.

Prevent storage of lipids in the liver and spleen, bringing them to near normal levels - Preventing storage in the liver and spleen helps prevent fibrosis and further deterioration and these are considered a high priority for parents of affected children.

To lessen pain caused by gastrointestinal complications, being able to tolerate feeds better, reduce vomiting with a view to moving on to oral feeding -Gastrointestinal problems continue to affect children but with better understanding of their nutritional needs, Parents report that the frequency and duration of symptoms is reduced.

Late onset
Patients are keen to hear that overall storage in the body is reduced and that their bloods are indicating that their levels are near normal. Reports from many patients are that these levels have reduced and are within or near normal range.

Reduced liver and spleen size is important as well as improved function or stabilisation. Patients are keen for liver disease to be halted to prevent the need for a liver transplant.

Reduced pain, nausea and fatigue are important to allow patients to maintain some normalisation in their lives and give them aspirations of continuing with work /getting a job and becoming active again.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

Infants
The course and outcome of the condition
To extend and improve life for children enabling them to live as near normal life as possible. Clinical trials have shown that life for these patients is extended and their quality of life is much improved with continued development.

Physical symptoms
To reduce storage in the liver and spleen reducing abdomen size to near normal, enabling normal development and growth.

Pain
To reduce gastrointestinal pain and pressure by reducing storage and improving nutritional intake and delivery.

Level of disability
Parents hope the technology will prevent any long term disabilities. Reports from parents are that their children are developing well.

Mental *health*
To sustain improved mental health of parents and carers

Quality of life (lifestyle, work, social functioning etc.)
To allow families to get back to as near normal life as possible, accessing everyday life choices, work social opportunities.

Late onset

The course and outcome of the condition

General health and wellbeing to improve and for the condition to remain stable and not decline.

Physical symptoms

To feel physically better, fit and in less pain.

"Before starting on treatment I had to give up cycling as the pain was unbearable. I have now started back cycling without experiencing any pain".

Pain

"Abdominal pain can be intense, indescribable and exhausting. Since being on treatment the pain is reduced to a niggling pain, it's always there but does not impact on my everyday life".

Level of disability

"My general wellbeing is much improved since being on treatment. At diagnosis my condition was extremely disabling, I had to give up my job, stop cycling and socialised less. I am now able to get out more, I have more energy, I am back cycling and I'm looking to get back into work".

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

Cannulation and access can be a disadvantage for the infants or those who are needle phobic or have poor access. However for the infants and children the use of portacaths, play therapist and experienced nurses can overcome these problems.

Parents have reported that sickness and pain can develop halfway through the infusion. This is managed through pre meds and reduced infusion and feeding rates.

It is anticipated that once a patient is stable on treatment homecare could be considered. This will lessen the impact on personal and family life and for those in employment should offer some flexibility in fitting treatment around work.

If home treatment or treatment nearer to home is available the financial impact will hopefully be reduced.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

Not to our understanding.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

All patients clinically assessed and meeting the indications for treatment should be considered for treatment.

Due to the severity of the disease for infants, treatment should be made immediately available without delay.

It is unclear whether patients who have already received a liver transplant should be eligible for treatment. In our view this should be a clinical decision based on clinical investigation and presentation.

6. Comparing the technology with alternative available treatments or technologies
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Infants
HSCT has been used in the past but has shown to have poor outcomes for patients with early death reported in the majority of patients.

Late onset
Liver transplant has been used in some patients; however reported outcomes have been limited with some patients showing signs of success with others continuing to show disease progression. Transplant complications can also be present. It should be noted however, that liver transplants may not address the underlying cause of LAL D as it does not replace the missing enzymes which causes the condition.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Infants
As described above; this is a fatal and rapidly progressive disease with death likely within the first few months of life. Parents report that their children are developing within the normal range, with the oldest child being 3 ½ years old.

Nearly all aspects of the condition have either stabilised or improved and in many instances parents report no further regression of disease being present in major organs and bloods. Nutritional difficulties and tolerance is still present in varying degrees, dependent on the level of damage to the gut. Parents are happy to manage this and follow the advice of the dieticians in relation to management and moving towards normalisation of feeds, transitioning to oral feeds.

Parents have reported that the side effects are minimal with children experiencing abdominal pain and vomiting half way through their infusions. This is managed by anti-sickness medication, anti-inflammatory medication, slowing down of infusion rate and feeding regime and releasing of air via gastrostomy tube.

Late onset
Patients have reported improved outcomes both clinically and in terms of their general wellbeing. Pain is rarely noticed or has become a more tolerated / manageable pain. They have more energy and are able to participate in exercise and are able to think about their future and “getting back to normal”.

Minimal side effects have been reported. Symptoms such as headaches or feeling queezy at the beginning were reported by one patient but this disappeared and they attributed it more to being anxious about starting treatment.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

No disadvantages have been identified compared with the alternative of disease progression and early death.

It is anticipated that patients will be able to move to home care when clinically stable.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

7. Research evidence on patient, family or carer views of the technology
(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions.

From the patients perspective, their experience of being on Sebelipase alfa through the clinical trial as part of the care, reflects that observed under clinical trial conditions

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

Not that we are aware

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

A quality of life study has recently been undertaken. The results of which are still under evaluation but will be submitted as part of the companies submission.

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Infants
Reduced mortality, a better quality of life, improved life expectancy and the chance to grow and develop within normal childhood ranges.

Late onset
Delayed mortality, increased stamina, reduced pain, better quality of life with a hope of re-establishing a level of normalisation in everyday life.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

If the treatment was not available for patients, the disease would progress resulting in death before the age of 6 months for infants. For late onset patients, disease progression would continue, quality of life would be impaired and early death or serious health complications could occur.

(iii) Are there groups of patients that have difficulties using the technology?

Not that we are aware

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

It is estimated that approximately 3-4 infants could be diagnosed a year. It would be expected that all of these if clinically assessed as able to received treatment should be treated. There are currently 3 patients receiving treatment in England.

It is estimated that there are approximately 20 late onset patients, who may expect to be treated. Not all patients are currently receiving treatment. It is estimated however, that there is a population of patients under gastroenterology or liver specialists who have no confirmed diagnosis of LAL D. Therefore the above estimated number could increase.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

The clinical evidence considered by the European Medical Agency has led to marketing approval for Sebelipase alfa.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Our members look forward to the positive reimbursement of Sebelipase alfa and that consideration is given to the fact that LAL D is an ultra orphan disease which has in most cases life threatening outcomes for patients.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name: Amjad Akhtar

Name of your organisation: N/A

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

N/A

Are you (tick all that apply):

- √a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

How does the condition impact on patients, their families or carers?

Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Our son was diagnosed at 2 days old and started treatment when he was only 1 week old. This was an exceptional case and only possible due to the previous loss of one of our children to the same condition.

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.

It wasn't until his first immunisations, that a health visitor with 25 years' experience checked him over and made a referral for further investigations.

At 2 months he underwent some blood tests, which indicated that there were abnormalities. We were referred again as it was suspected that he had damage to his liver and further tests confirmed it was suspected LAL D. We were then referred to Manchester as the hospital we were under had not heard of this condition and a liver biopsy was performed. 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.

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.

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

He was our first child, we had prepared his room, brought new clothes and family and friends had brought gifts. Many of these remained un-opened.

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.

Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

Having one child die from this condition, is beyond words but we have been given hope that our other child will have some chance of a future. The diagnosis has had a huge impact on all areas of our lives and our family's.

As parents you will do anything. We would have accessed treatment anywhere if it meant giving our son a chance to live.

Everyday life has to adapt and your life revolves around the needs of the child but for us, our child's needs is becoming similar to the needs of our other children since being on treatment and life is becoming more balanced.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages
Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Our son, has been given a chance to live. He is now 9 months old and his development is comparable to any other child of a similar age. Having been on treatment since he was one week old has been positive and comparing him against some of the other children we have met has shown that he tolerates feeds better than others, even taking milk feeds orally, his admissions to hospital have been less and for shorter periods of time, he is maintaining a good weight and is above average. The dieticians were actually thinking that he would have to go on a diet if his weight continued to increase at the rate it was.

His liver was enlarged by 5cm's and has reduced down to 2cm's. His cholesterol levels are fine.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

His latest blood results show that all his levels are down to a normal range.

He has started saying a few words such as dad and grandad.

He is in our view meeting his developmental milestones.

He has defied all expectations of clinicians in how well he has responded to treatment and the positive outcomes that he is showing.

Please list any short-term and/or long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition **the treatment has given him a chance to live. We understand that his future is uncertain but we are glad that we have been given the opportunity to find out.**
- physical symptoms-**His symptoms are a lot less severe than those diagnosed and treated later. However, in all cases treatment has offered improved gastrointestinal outcomes and reduced organ damage. With help of treatment and dietician he's now over the 75th centile, more than his cousin who does not have any condition.**
- pain – **pain from abdominal gases, colic, reflux are still a consideration but have not been present since being on treatment.**
- level of disability **It is unclear what level of disability could present itself in the future but our son is currently developing well and within the normal range for his age.**
- mental health – **This has improved for the whole family**
- quality of life (lifestyle, work, social functioning etc.) **we are beginning to have a family life again. Even with the weekly trips to hospital, I am able to still work and our other children get to see both parents and spend time with their brother.**
- other quality of life issues not listed above
- other people (for example friends, employers)
- other issues not listed above.

Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

The alternative option to treatment is not worth thinking of so it is difficult to look at the treatment as a disadvantage. As a parent you will do anything for your child. For us, there would be no disadvantage to starting treatment.

The treatment can cause problems with reflux and trapped wind which presents half way through the infusions. This is lessened by the giving of pre meds, releasing of air from the gastric tube and giving acid indigestion medication.

Our family are supportive and help out with our other children and travel to and from the hospital. This is something that is offered willingly to allow our son to have the best chance. We appreciate that this may not be the case for all and could cause difficulties.

Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

I do not believe that anyone would dispute the usefulness of this technology for infants.

Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

All infants should have access to this treatment without delay

I am not aware of the benefits for older patients, although have seen a child of 12 years who at the start of treatment had a very large stomach approximately 9 months ago and now it has gone down considerably since being on treatment.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

Please list any current standard practice (alternatives if any) used in the UK.

Palliative care is the only alternative without treatment.

Transplants. This isn't possible for everyone and is usually viewed as a last option but survival rate is not good.

If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

The treatment improves all aspects of the condition. Although for us it is a day in hospital once a week, the rest of the time our son is at home with his family, with few hospital admissions and no long stays in ICU.

GP's refuse to see him

If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

There are only improvements.

Although it is a treatment once a week, delivered in hospital this could in time be delivered more locally and possibly at home.

Side effects are mainly attributed to gastrointestinal problems but these are managed.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

A chance to live and live as normal a life as possible.

What implications would it have for patients, their families and/or carers if the technology was **not** made available?

The loss of a child's life and for a parent to look on helpless, as their child starves to death, while knowing that there could have been a treatment available.

Are there groups of patients that have difficulties using the technology?

Some infants may have difficulty if their disease is too far progressed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name: Stuart Lancaster

Name of your organisation: N/A

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

N/A

Are you (tick all that apply):

- √a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

How does the condition impact on patients, their families or carers?

Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

I was diagnosed in March 2009 at the age of 43 but had experienced symptoms since my mid twenties.

During my teenage years I had suffered from bad acne and because of the medication I was on, I had to have periodic blood tests. One of these tests showed raised ALT levels but no follow up was provided.

In my mid twenties, I had a continuous ache on my right side that would travel across my abdomen. I was asked questions about my alcohol intake (approximately 3-4 pints over the course of a week) and was sent for a basic scan (not ultrasound). No follow up was given and as the pain subsided, I did not follow it up myself.

In my thirties, the pain came back but I did not seek any medical advice as I wanted to see if it would go like before. The pain came and went but was bearable.

In my forties the pain was worse and constant. I felt nauseas nearly all of the time, which affected my eating and my physical health was impacting on my work and everyday life. I again presented at my GP surgery and saw a locum Doctor who took a full history of symptoms, felt my abdomen and suspected an enlarged liver. I was booked in for more blood tests and an ultrasound of my Liver. A referral to a gastroenterologist was also made who carried out various tests, CT Scan, MRI Scan, Endoscopy, Needle Liver Biopsy.

After early tests initial suspicions were that I had a tropical disease but as nothing could be grown from my biopsy samples taken during a second Endoscopy to obtain these this was discredited. An Open Liver biopsy was taken to remove a bigger portion of my Liver for analysis after which I was referred to a Metabolic Specialist who again did a blood test and gave me a diagnosis of LAL D which was confirmed on my birthday.

The diagnosis came as a huge shock to me and my family, given the genetics and inheritance. My parents harboured a huge amount of guilt that they had passed the condition to me. At the time of diagnosis, I was informed that although the level of liver damage at diagnosis could not be confirmed, its function and presentation was very poor. The prognosis for the future was not looking very good.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Although I was glad to finally have an answer and a reason as to why I had felt so awful for so long, I also felt a little angered that I was obviously showing symptoms back in my teenage years but that the signs were not picked up or investigated thoroughly enough.

Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

This disease has had an impact on all areas of everyday life and my physical and emotional wellbeing. It is only now, after being on treatment that I am able to participate and enjoy taking part in activities and getting some resemblance of my life back. However, reflecting back on my childhood, I was always really sensitive when getting bumped around my abdomen area and refrained from participating in contact sports, in case I got knocked in my side.

Since leaving school, I worked full time in maintenance for a local NHS trust, taking little time off due to sickness and was able to undertake all duties of my job role. It wasn't until my forties that certain aspects of my job became difficult or would cause me considerable pain which at times was disabling and resulted in me having to have reduced duties and time off. The role was of a mainly manual nature that aggravated my condition & it was agreed for me to take early retirement. This was a huge blow to me as I have always worked and independence was important to me.

Physical Impact.

Before treatment, I suffered from severe nausea and sickness. I had to eat a reduced diet and could only eat little and often. Some days I was not able to eat anything or I would feel hungry and after one or two mouthfuls the nausea would return.

I have always been an active person who had a physical job and a can do attitude. Not being able to do simple things like bend, getting dressed, walking to the shop or changing a light bulb without being doubled up in pain for hours or days was extremely debilitating. I also enjoyed cycling and was part of a cycling club who went out and took part in regular cycling events. Due to the severe pain, lack of stamina and energy I had to give this up.

Emotional wellbeing

Going from a person who was physically active to someone who struggled to participate in anything including everyday tasks was hugely burdensome. The

worry of what was happening internally continues to be a concern as well as the prognosis for the future.

Everyday life

My life changed in all aspects. The constant pain, lack of stamina, low energy levels, constant nausea, inability to carry out simple tasks like cleaning and general upkeep meant I went from being an independent person with a social life and group of friends to someone who rarely went out and if I did it would only be for a short period of time before I had to return home due to exhaustion.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages
Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Having been enrolled on the clinical trial for the past 6 years has been a lifeline for me. Without treatment my life could be very different and potentially fatal.

Please list any short-term and/or long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends, employers)
- other issues not listed above.

Not only do I feel physically better; increased energy & I now only experience discomfort & mild to moderate pain. I have no or infrequent nausea but I understand that my clinical outcomes have shown considerable improvements. Reported outcomes indicate that my LFT's are now normal and my lipids have improved. My liver size is improving and scans show that it is stable with no further deterioration. This is a significant change from my presentation at diagnosis where I was informed that the damage to my liver was significant and due to the level of fibrosis the first biopsy failed as the liver could not be penetrated through standard key hold surgery and I had to undergo an open biopsy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Since being on treatment, my life is getting back to near normal. I am able to go about my day to day business although if I do too much I suffer the following day but not to the extent that I did. I am doing some cycle riding and enjoying getting outdoors walking & meeting up with friends. I am also looking at getting into some part time voluntary work since taking ill health retirement from my full time employment.

My friends and family see the treatment as giving me a lifeline and the chance to participate in all the things I enjoyed before the condition took a hold and removed everything I worked for, valued and enjoyed.

Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

I view the technology as positive and if your disease is significant enough to meet the requirements of treatment, I would encourage anyone to have it. There are no negatives from my perspective.

I have tolerated the technology well with few side effects. Mild headaches at the start of my treatment but not at all now. I have not had any infusion related reactions.

I drive myself to and from the treatment centre and as I am no longer working making this possible. At the start of the treatment I was still working and had to change my pattern of work but this was accepted by my workplace.

There are some financial implications in receiving treatment and accessing the treatment site, however these can be lessened in the longer term by either receiving treatment in a local hospital or having home treatment.

Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

It is my experience that all those receiving treatment have a positive view on the effects and usefulness of the treatment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

Everyone should be clinically assessed and an individual recommendation for treatment made if their presenting symptoms meet the criteria for treatment. I understand that some patients may not require treatment but should be monitored closely and treatment reviewed if symptoms deteriorate. I am also aware that infants with this condition are critical and require immediate access to treatment.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

Please list any current standard practice (alternatives if any) used in the UK.

There are various other medications such as statins.

Liver transplant

Palliative care for infants

Transplants

If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

The technology brings levels down to near normal and stabilises and may improve organ function. Other medications available may not reduce or help individuals to this extent.

The technology may prevent the need for a liver transplant a risky procedure in itself with a high level of medical intervention and follow up required.

For the infants the technology will give them a chance to live.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Having to receive intravenous infusions may be viewed as a disadvantage by some people.

Accessing a specialist centre may be a burden if you live far away or work. However, alternatives could be explored such as local hospitals or home care.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

Patient Quality of Life Survey.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

Having access to treatment has made a huge impact and difference to my life.

I only experience discomfort & mild to moderate pain.

My bloods, lipids and LFT'S are back to normal or near normal.

I have a better quality of life, improved stamina and wellbeing

I have a chance of life again

What implications would it have for patients, their families and/or carers if the technology was **not** made available?

Patients would continue to be affected by their condition and risk deteriorating health, poor quality of life, severe pain, liver failure, cardiac complications and premature death.

For the infants there would be no chance of life

Are there groups of patients that have difficulties using the technology?

-

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Lal D is a hidden disease and just because someone may outwardly present as being fine the inside could be a different story.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: N/A

Brief description of the organisation: N/A
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology? Yes
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

How does the condition impact on patients, their families or carers?

Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

and the impact these difficulties have on patients and their families or carers.

From birth, my son suffered with serious vomiting and diarrhoea, when he was a couple of weeks old he was taken to a local doctor, at this time we were advised that he could be lactose intolerant, 3 alternative lactose free milks were tried with no change to his symptoms. In fact, within 2 weeks his milk intake dropped from 3oz to 30ml, even this tiny amount would be vomited up also (at this time, we spent several days in a local hospital). He spent 2 weeks on lactose free milk, during this time we were at home, his symptoms worsened, he was lethargic, hungry and I suspected that he had a hernia. Following a visit to the local doctor, he was referred to hospital as a day case for a hernia in his groin, during this we were told that he may have an issue with his heart, which proved to be inaccurate. He also had bloods taken and a doctor asked us to recount everything that had happened all symptoms throughout his short life. During this time, we were visiting the same hospital for regular weight checks with a health visitor; a cystic fibrosis test was carried out, which gave a borderline result.

Following this we were asked to return to a previously visited local hospital, we had attended a couple of outpatient appointments where his enlarged liver and spleen were not detected by the children's gastroenterologist. We ended up staying here for 3 weeks, the medical staff believed that there was something seriously wrong, but we had no indication as to what. During this time my son undertook countless tests, including blood tests and eye tests. He was given a nasal gastric tube to help to keep milk feeds down and prevent vomiting. With his health unimproved we asked for an outpatient appointment at a children's specialist hospital in London, an additional cystic fibrosis test was undertaken at Kings hospital. Subsequently we visited Evelina, where [redacted] detected his very enlarged liver and spleen. Further tests were carried out to find a suspected metabolic condition, including taking a small sample of his arm.

We stayed at Evelina for a week, continuing with the lactose free milk and nasal tube as before. We then received a semi diagnosis, that our son had a child form of CESD, and that there was no cure. We asked for any help possible, and thankfully we received it. A blood film had been sent to Manchester, and finally just a day later, it was confirmed that our son had Wolmans disease, at this time he was 3 months old. Just a day later he was offered a place on a clinical trial for enzyme replacement and we were provided with all information we needed. We then travelled to Manchester hospital, and attended the meeting to confirm our sons place.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

-The life expectancy for a patient with Wolmans is anything under a year with no treatment

-Feeding difficulties due to vomiting and diarrhoea from birth, effects of this in necessity of constant and intensive care by parents, current feeding difficulties were also caused by the necessity of nasal tube feeding

-Tires easily, has less stamina and is smaller than the average child of the same age, concern as parent that 3 initial months following birth with no enzyme has affected him long term

-Currently still entrally fed a specialised diet every 3 hours (including throughout the night) by gastric peg, restricted independence for both patient and carers

-Struggles with eating an unrestricted diet means inability to join peers in activities such as snack time at playschool

-Minor illnesses such as colds and coughs will affect him more than a child without the condition, he cannot fight it off as well as others as his immune system was suppressed, although this has improved over time.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages
Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Please list any short-term and/or long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends, employers)
- other issues not listed above.

In short, our son would not be alive today without this clinical trial; it has extended his life expectancy, amongst other children too. It is almost unexplainable how much this means to him, and to all of our family and friends.

He no longer has the main medical issues which was he born with: enlarged liver and spleen, abnormal bloods are now in normal range including liver function, lipids, albumin, and chemistry bloods. He has no pain, which the condition could likely have caused.

He would never have had such a great quality of life without the drug, milestones in his life, like being able to attend a playschool would never have happened. On his first day I didn't cry because I had to leave him there like the other Mums did, I cried because he was even there in the first place.

The enzyme replacement treatment has done more than given [redacted] an improved quality of life, it has given him the chance at one.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

Considering the huge impact the technology has had on our sons life, it is difficult to talk about any disadvantages at all. However we are aware that as he has been a patient in a clinical trial there is an unknown element to the drug, there is no evidence base that there won't be unwanted side effects in the future, or that it will continue to be successful, particularly considering that his diet is specialised to ensure that the drug works with milk feeds. We worry about providing him with an unrestricted diet in the future.

The nature of Wolmans at this level means that providing his body with the enzyme means providing it with something completely foreign, he was born with none at all. We were always aware that he could have an allergic reaction, which he did after 3 months of treatment, as a result he had to have pre meds, which allow his immune system to accept the treatment; which is now being reduced to ensure his body can be receptive to treatment on its own.

The infusion treatment currently has to be administered at weekly hospital visits. For 6 months we travelled to Manchester for this, we now travel the shorter distance to London.

Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

As far as we are aware, all carers are unanimous in their opinion on the usefulness of the technology in the extension of the life expectancy of their children.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

All patients have lived longer than predicted at birth, despite varying degrees of receptiveness to the technology in their individual cases.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

Please list any current standard practice (alternatives if any) used in the UK.

There are currently no alternatives other than a bone marrow transplant, which is unproven in its success.

If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

As a carer of the patient receiving the technology, it has worked as proposed, despite being aware that as one of the clinical trial patients, there would be unknown hurdles during the clinical trial period.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

Quite simply, it would be life changing. As a family we have accepted that Wolmans is lifelong condition, controlled with his treatment, but making this available would mean making [redacted]'s life as regular as possible. It would give both him, and his parents as primary carers more independence from the disease and allow him to not have to take days out of school, for example.

What implications would it have for patients, their families and/or carers if the technology was **not** made available?

[redacted] is currently receiving the drug weekly under a clinical trial, if it is not made available and he can no longer receive it, due to the huge financial cost to make it privately available, it is highly likely that he would be unable to continue to receive enzyme replacement treatment. The result of this is not one that myself, my partner, family or friends, would like to entertain; this drug has saved lives.

Are there groups of patients that have difficulties using the technology?

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Dr Simon Jones

Name of your organisation:
Are you (tick all that apply):

Yes a specialist in the treatment of people with the condition for which NICE is considering this technology?

Yes a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

LAL deficiency is a lysosomal storage disorder associated with an accumulation of cholesteryl esters and triglycerides. There exists a spectrum, from a rapidly fatal form in infancy to a much more slowly progressive form affecting children and adults.
In this response I will deal exclusively with the infantile form of LAL deficiency, historically known as Wolman disease. Infants with this disease present in the first 6 months of life with hepatosplenomegaly, profound malabsorption of feed and failure to thrive. This presentation is universally fatal in the first 6 months of life (Jones et al, 2015). Infantile LALD is ultra orphan, with an incidence between 1:500,000 and 1:1,000,000. There may be around 1 to 3 new babies born with this condition every year in the UK, and before Sebelipase most were managed with palliative care and died a few weeks after diagnosis. The only previous treatment that has been offered to a small number of babies was bone marrow (or haematopoietic stem cell) transplantation. While this is a very rational treatment option for this disease the reported (and unreported) mortality was extremely high with only 2 reported survivors of the procedure anywhere. In our unit (nor in other UK units) this is not a standard indication for HSCT, unlike in other LSDs. Infants with LALD are much too ill to tolerate conditioning necessary for HSCT, and the delivery of enzyme by this method is not rapid enough for the natural history of the disease.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Sebelipase alfa has dramatically changed the prognosis for infantile LALD. In the original clinical trial 6 out of 9 infants survived to the primary endpoint of 12 months, with 5/9 long term survivors. We have subsequently treated a further 5 infants in the CL08 study in Manchester, with similar outcomes. Those infants not surviving have died of complications of therapy (central line/ abdominal catheter complications) or because they were very ill (multi-organ failure) at diagnosis and treatment initiation. Long term survivors show normal developmental profiles and have only residual disease manifestations in the GI tract e.g. need for modified feeds. In the first few months of treatment these children are extremely ill and often require prolonged inpatient stays. They may need blood transfusions, parenteral nutrition and MDT care. Multiple infections and even overactivity of the immune system can be seen.

Guidelines for treating infants with LALD have been drawn up and are attached to this submission. They have been drawn up by consensus between the 3 children's LSD centres, the patient organisation, and both Alexion and NHS England have been shown the documents. They are draft guidelines and drawn up in the light of the experience in the clinical trials –over 50% of all infants treated globally were based at a UK site. It is not yet clear which subgroups may respond better than others, although early treatment is likely to be better than later treatment. The guidelines attempt to deal with the uncertainties as best they can given our limited evidence with this very rare disease. They are based on expert consensus and the result of the 2 clinical trials in infants (CL03 and CL08). The manuscript from the CL03 trial is submitted but not published and there is as yet no data officially presented from the CL08 trial. The guidelines specifically deal with the issues of dose. Since the regulatory submissions it has become clear that a number of infants need a dose of 5mg/kg to stabilise. At this stage it is not clear which infants require this and doses have been escalated following discussions around inadequate response. While the licensed dose in the SmPC is from 1-3mg/kg, currently of the surviving patients we have managed in Manchester, 3 out of 5 are requiring 5mg/kg of Sebelipase alfa weekly to maintain stability. We strongly feel that the initial starting dose should be 3mg/kg weekly, with escalation to 5mg/kg if there is an inadequate response.

The care of infants with LALD should remain within the designated LSD service. While some of these infants present to liver units this is a multi-system disease, and the diagnosis is almost always made by an LSD laboratory. While the delivery of the ERT itself is easily manageable by the existing services, the management of the multi-disciplinary care would put significant pressure on the resources of these units. There is little current funding for dietetic support within the LSD services, and these infants require long term intensive management. They may often spend their first 6 months of treatment as inpatients, and these factors would need to be considered with regards to staffing of the designated services.

The advantages and disadvantages of the technology

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Over 50% of the trial patients were treated in the UK, with most from the UK originally, and so the patients reflect well the UK experience of the disease. Starting and stopping criteria are discussed further in the guidelines attached. The benefit to the patients is clear. Without this therapy all will die by 6 months, on the CL03 study 6 out of 9 children survive to the primary endpoint of 12 months. 5 out of 9 are long term survivors.
Side effects of Sebelipase appear to be restricted to infusion associated reactions (seen in almost all enzyme replacement therapies) and which are managed by standard approaches (see attached guidelines). No infants have stopped ERT secondary to these reactions.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must

include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

All the currently relevant evidence is unpublished but much of this will be given in the submission by Alexion. Aside however from the trial reports themselves, there exists considerable clinical experience in the UK with this disease and this therapy, greater than in most other countries. The guidelines attached attempt to reflect that experience. International guidelines are planned to be published but are not yet in any form that can be shared. The UK guidelines are likely to represent the first document of its kind.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Extra staffing resources may be required in the longer term, especially if new patients are identified. It is expected that if new infants are diagnosed they would require treatment rapidly (within days) and Sebelipase should be made available.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

No such impacts are known.

Standard Operating Procedures for the Investigation and Management of Infantile Onset Lysosomal Acid Lipase Deficiency (LALD)
(October 2015)

These guidelines are aimed at improving the diagnosis, clinical management and quality of life of those affected by LALD. They will assist commissioning of services for LALD and have been prepared by a multidisciplinary group consisting of:

Dr Simon Jones	Consultant in Paediatric Metabolic Medicine, CMFT
[redacted]	Consultant in Paediatric Metabolic Medicine, CMFT
[redacted]	Clinical Nurse Specialist, CMFT
[redacted]	Clinical Research Fellow, CMFT
[redacted]	Lead Specialist Metabolic Dietitian, CMFT
Mrs Sophie Thomas	Advocacy Support Team Manager, The Society for Mucopolysaccharide Diseases
[redacted]	Specialist Registrar in Clinical Genetics, CMFT
[redacted]	Senior Research Nurse, CMFT
[redacted]	Clinical Scientist, Genomic Diagnostics Laboratory, CMFT
[redacted]	Consultant in Paediatric Metabolic Medicine, GOSH
[redacted]	Consultant in Paediatric Metabolic Medicine, BCH

Document controller: [redacted]
Version: 1.0
Date: 14/10/2015

Table of contents

1 Disease overview 3
1.1 Presentation 3
1.2 Wolman Disease 3
1.2.1 Associations 3
2 Diagnosis 4
2.1 Laboratory diagnosis of LALD 4
2.2 Carrier testing and prenatal diagnosis 4
3 Clinical management 4
3.1 Multidisciplinary management 4
3.2 Initial management and stabilisation 4
3.3 Central venous access 5
3.4 Infections and immunity 5
3.5 Nutrition 5
3.6 Enzyme Replacement Therapy (ERT) 7
3.6.1 Clinical Trials of ERT 7
3.6.2 Dosing 7
3.6.3 Criteria for ERT 7
3.6.4 Expected outcomes of treatment 8
3.6.5 Administration of ERT 8
3.6.6 Infusion associated reactions (IARs) 11
3.7 Recommended assessments 11
3.8 Home care 12
3.9 Cognitive ability, development and special educational needs 12
3.10 Other treatments 12
4 Audit 13
References 14

1 Disease overview

1.1 Presentation

Lysosomal acid lipase deficiency (LALD) is a very rare inherited autosomal recessive lysosomal storage disease (LSD), characterized by a failure to break down cholesteryl esters and triglycerides in the lysosomes. It is a multi-system disease and common manifestations are liver, gastrointestinal and cardiovascular complications resulting in significant mortality and morbidity. LALD results in massive accumulation of lipid material in the lysosomes in a number of tissues and profound dysregulation of lipid metabolism. It remains a relatively under recognized condition with many individuals receiving no diagnosis or an incorrect diagnosis of non-alcoholic fatty liver disease. LALD is due to mutations in the *LIPA* gene located on chromosome 10q23.2-q23.3. In late onset LALD which presents in children and adults, many cases are associated with a common mutation which may result in some residual enzyme activity (Aslanidis et al. 1996). However, in LALD which presents in infants there are a variety of private mutations that may result in a complete loss of enzyme function (Assmann and Seedorf 2001). It has also been hypothesized that there may be a correlation between enzyme activity and disease severity.

1.2 Wolman Disease

Although LALD is a single disease it presents as a continuum with two major phenotypes, historically termed Wolman Disease and Cholesteryl Ester Storage Disease.

Wolman disease was first described by Abramov in 1956 and it is estimated to affect 1 in 350,000 births. It is the most aggressive form of LALD and the phenotype is progressive and rapidly fatal in the first 6 months of life (Jones et al. 2015). It is characterized by gastrointestinal and hepatic manifestations, including malabsorption, growth failure, profound weight loss, steatorrhoea and hepatomegaly. Fibrosis and cirrhosis develop rapidly and have been described in affected infants within the first 6 months of life. Clinical signs may arise during pregnancy with reports of polyhydramnios, hepatomegaly and fetal ascites detected on ultrasound.

Diagnosis is usually made within the first few weeks of life, when infants have often required hospitalisation due to vomiting and diarrhoea. Physical findings include abdominal distension with hepatomegaly and splenomegaly plus calcification of the adrenal glands on radiologic examination. Mesenteric lymphadenopathy is also common. Investigations typically reveal elevated levels of serum transaminases, raised bilirubin, low albumin, low haemoglobin levels, raised ferritin and often minor changes in CRP, evidence of macrophage activation and low LAL enzyme activity. Due to the rapidity and aggressive form of this disease there is a need for enhanced awareness of LALD so that early diagnosis can help limit disease-associated mortality and morbidity and help to provide appropriate treatment.

1.2.1 Associations

A small number of infants with LALD have been reported to have an inflammatory phenotype and in clinical trials patients have developed severe viral and bacterial infections (section 3.4).

A number of infants in clinical trials have been noted to have hypertension and have been commenced on antihypertensive medications. Consultation with a paediatric nephrologist is advised.

Despite the calcification of adrenal glands seen on radiographic examination, adrenal failure has not been a reported finding, even in long term follow up of treated affected infants.

Small numbers of patients in clinical trials have been found to have patchy calcification of the liver, confined to a single lobe.

2 Diagnosis

Although LALD presenting in infants is rare this is a rapidly life threatening disease which now has an effective therapy. Evidence from clinical trials suggests that children who have more advanced disease manifestations at initiation of therapy have a higher mortality. Infants presenting with severe growth problems and hepatosplenomegaly, liver disease or even isolated hepatosplenomegaly should be investigated early for LALD.

2.1 Laboratory diagnosis of LALD

Biochemical diagnosis of LALD is achieved by direct measurement of LAL activity by using either a dried blood spot (DBS) (Hamilton et al. 2012), or isolated leucocytes as the sample source (Guy and Butterworth 1978). There are a number of key centres of excellence for the diagnoses of LSDs in the UK, with significant experience is diagnosis of LALD. These are the Biochemical Genetics services based in Glasgow, Birmingham, Manchester and London (Great Ormond Street Hospital and Guy's Hospital). Each laboratory will have an established reference range for normal and affected individuals within their validated laboratory protocol, and reference should be made to laboratory expertise. It is essential that when there is strong clinical suspicion of infantile onset LALD, the referral laboratory is contacted by the clinical team to clarify sample requirements and request that analysis of the sample is prioritised. When reviewing patient results, reference should be made to the normal range specific to each laboratory and their experience of deficient individuals. DBS testing should include use of an inhibitor to avoid detection of other lipases. When an abnormal biochemical result is found, indicating a diagnosis of LALD, confirmation on a second sample (which should be leucocytes) is recommended. Confirmation of the enzyme deficiency by DNA analysis and sequencing of the *LIPA* gene is recommended, but the diagnosis is usually established by the clinical findings and enzyme levels, Initiation of therapy should not wait for DNA confirmation. Finding of the common mutation c.894G>A would suggest a late onset phenotype but other genotype-phenotype correlations have not been made.

2.2 Carrier testing and prenatal diagnosis

Once the molecular diagnosis is established, carrier testing can be offered to the parents to establish recurrence risk. Referral to the regional Clinical Genetics service should be considered for discussion of carrier status and prenatal testing. Prenatal testing is available either for known mutations or LAL activity (via an enzyme test), and should be discussed with the appropriate laboratory in advance of any samples being taken.

3 Clinical management

3.1 Multidisciplinary management

Infantile onset LALD is a fatal and rapidly progressive disease. In a retrospective natural history study (Jones et al. 2015) the median age at diagnosis was 2.5 months and the median age at death was 3.5 months. Because infantile onset LALD is multisystem and rapidly progressive, affected individuals should be managed by a multidisciplinary team of health care providers, based in a designated paediatric LSD centre. This team should include metabolic paediatricians as well as specialist paediatric metabolic dietitians and clinical nurse specialists. Other specialists who may be involved are immunology, hepatology, gastroenterology, haematology and surgical specialties (for central venous access).

3.2 Initial management and stabilisation

These infants are generally very ill at diagnosis and require hospitalisation. Rapid transfer to a specialist centre is essential as infants have the potential to deteriorate quickly, even if apparently relatively well at presentation. Inpatient stays are often prolonged.

Infants with LALD tend to be malnourished at diagnosis often with features of hepatic failure, including ascites and coagulopathy. They may have anaemia and some have an inflammatory phenotype resembling macrophage activation syndrome (MAS). Once diagnosed they should be rapidly transferred to a centre experienced in the management of these patients for stabilisation, confirmation of diagnosis and evaluation for ERT. These infants may need to be nursed in a critical care environment initially. There should not be delays in diagnostic tests or transfer as initiation of treatment must be rapid if a good outcome is to be achieved. Supportive care includes aggressive treatment for infections, fluid resuscitation for dehydration and blood product administration where appropriate. Diuretics and albumin infusions may be required if ascites is present. Supplementation of fat soluble vitamins should be assumed until it is proven they are replete.

3.3 Central venous access

Most infants with LALD will be poorly nourished at diagnosis and have symptomatic liver disease. Managing their nutrition, supportive care and weekly ERT will require central venous access. These infants seem at higher risk from complications, and may have an elevated bleeding risk related to liver disease, poor absorption of fat soluble vitamins and splenomegaly.

3.4 Infections and immunity

In clinical trials a number of infants receiving treatment for LALD developed significant and recurrent bacterial and viral infections, including central venous catheter (CVC) infections. The incidence of CVC infections appeared to be higher than expected in infants. It is possible that infantile onset LALD is associated with an increased risk of CVC infections, but the low number of patients treated thus far and other factors including poor nutrition must be taken into account. Nonetheless, as a number of infants have developed CVC infections, prophylactic antibiotic cover with teicoplanin is suggested at the time of CVC insertion.

A small number of infants with LALD have had inflammatory processes which resemble either macrophage activation syndrome or even haemophagocytic lymphohistiocytosis (Taurisano et al. 2014). This has been reported often enough and also seen in clinical trial patients to be likely to represent a true disease manifestation. Therefore fevers, persistently raised ferritin and a poor response to therapy (see section 3.6.4) should prompt evaluation for this and consideration of additional therapies. This risk appears to be associated with severity of disease and longer term patients doing well on ERT have not demonstrated the same problems.

We recommend that patients receive a full standard schedule of immunisations, however in the event of recurrent infections assessment of functional antibody status is recommended.

3.5 Nutrition

All infants with LALD will require some form of nutritional intervention to support growth in conjunction with ERT.

Accumulation of cholesteryl esters and triglycerides within lysosomes in the gut has a profound effect on the absorption of nutrients. This not only affects fat absorption but depending upon the degree of damage to the gut also the digestion of whole protein, into peptides and amino acids, and of disaccharides for their subsequent absorption. In addition and related to fat malabsorption there are usually fat soluble vitamin and essential fatty acid deficiencies.

The ability to achieve adequate nutrition enterally will vary depending upon the severity of malnutrition and degree of gut failure at diagnosis. It is likely that parenteral nutrition will initially be required in the majority of cases. When there is malnutrition or failure to tolerate feeds, it is important to respond quickly, modifying feeds appropriately (as detailed below)

and using parenteral nutrition if required. However, changes towards normalisation of feeds are not always well tolerated and must be made slowly and cautiously. Whilst all surviving children treated thus far have improved with regards to growth and tolerance of feeds, this process has been slow and often complex.

Feed composition

1. Fat

- Feeds must be extremely limited in long chain fat, both to avoid further accumulation of cholesteryl esters & triglycerides in lysosomes and to aid feed absorption. Some MCT appears to be tolerated as this is absorbed directly to the liver where it undergoes β oxidation. The most suitable formula currently available is Monogen (1.9% fat, 80% MCT)

- It is likely that only a minority of less severe infants will tolerate minimal fat, whole protein feeds (Monogen) initially.

2. Protein

- Protein requirements will usually be higher than normal due to poor digestion and malabsorption.

- Where there is failure to tolerate a whole protein feed due to diarrhoea or significant vomiting, an amino acid, modified low fat formula is required. There are no such commercially available ready to use formulas and a modular feed must be designed composed of amino acids, glucose polymer, MCT fat, micronutrients and essential fatty acids.

3. Carbohydrate

- Additional carbohydrate, as glucose polymer, can be used to provide additional calories. The carbohydrate concentration of feeds will usually need to be in excess of the standard concentrations for age. In practice concentrations of up to 20% under the age of one and up to 25% over one year have been tolerated.

4. Parenteral nutrition

- Where the infant is severely malnourished it is likely that total parenteral nutrition (TPN) will be required initially to allow both growth and gut recovery. Bespoke TPN with restriction of total fat and modification of lipid source will be required along with higher than standard amino acid content and glucose concentration. SMOF lipid should be used preferentially due to its lower LCT content (fat composition 30%MCT, 55%LCT, 15% omega 3 fatty acids) to both modify the form of lipid intake and to try and prevent further liver damage while on TPN.

5. Other nutritional considerations

- Fat soluble vitamins – additional supplements of these should be given at least until blood levels and coagulation normalise

- Essential fatty acids – whilst there is severe restriction of long chain fat these should be supplemented and plasma red cell levels monitored

6. Gut motility issues

- Most infants will have a degree of gastro-oesophageal reflux disease requiring anti-reflux medications and feed thickeners. Some infants also demonstrate intermittent abdominal bloating which can be uncomfortable.

- Vomiting can be present from a very early age, even seen in a patient diagnosed at birth and on fat restricted feeds, and leads to poor weight gain. This may respond to an amino acid, modified low fat formula.

3.6 Enzyme Replacement Therapy (ERT)

3.6.1 Clinical Trials of ERT

Sebelipase alfa is a recombinant human lysosomal acid lipase licensed for the treatment of LALD. Clinical trials in infants showed safety and efficacy at doses from 0.35 – 5mg/Kg (UK SmPC plus unpublished data). Infants treated in the CL03 and CL08 studies were selected for LAL deficiency and early growth failure, a group found in the natural history study (Jones et al. 2015) to not survive beyond 6 months of age. In the pivotal CL03 study 9 infants were treated and 6 reached the primary endpoint of survival at 12 months. Further follow up showed longer term survival in 5/9 children, the longest currently surviving beyond 4 years.

A number of infants developed infusion associated reactions but all were able to continue on therapy (see section 3.6.6).

Hepatosplenomegaly improved as did markers of liver function and growth, although all children required intensive nutritional support. Dosing in the CL03 study started at 0.35mg/kg and escalated if response was less than complete. The protocol was amended to include doses up to 5mg/kg. The more recent CL08 study used a starting dose of 1mg/kg, and again allowed dosing up to 5mg/kg. All long term survivors on both studies are receiving doses between 3 and 5mg/kg weekly. No increasing toxicity was noted at higher starting doses.

3.6.2 Dosing

Sebelipase alfa is administered as a weekly IV infusion, over 2-4 hours. While the starting dose outlined in the SmPC is 1mg/kg with escalation to 3mg/kg at the discretion of the physician, it is our view that infants presenting with symptomatic LAL deficiency in the first few months of life should commence therapy at 3mg/kg unless there are specific reasons for prescribing less than this. Mortality in the CL03 and CL08 trials appeared to be related to severity of disease at onset, and some infants deteriorated very rapidly following diagnosis. It is appropriate in this context to dose quickly and aggressively following diagnosis, to ensure the best outcome possible. There were no increase in adverse events noted when doses were increased and the finding of a transient increase in plasma lipids following initial doses of Sebelipase Alfa in adults with LALD has not been replicated in the infants. Dose escalation to 5mg/kg should be considered in the context of an inadequate response (see section 3.6.4). While the clinical trials did allow for reduction of dosing frequency to alternate weekly, this was not well tolerated in 2 infants and is not therefore recommended.

3.6.3 Criteria for ERT

<u>Start criteria</u>

1. 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 Deficiency.

2. Likely phenotype of rapidly progressive/infantile onset disease either by clinical signs and symptoms in the first year of life or a history of a sibling with a rapidly progressive course of LAL Deficiency.

<u>Exclusion criteria</u>

1. Clinically important concurrent disease or co-morbidities which, in the opinion of the specialist team, would not benefit from treatment of the underlying LALD.

2. End stage manifestations of LALD that mean the patient would be unlikely to benefit from therapy, including but not limited to multi-organ failure. In the event that the status of the child is considered to be borderline, there should be discussion with the parents, within the wider MDT and with other LSD centres if appropriate. Treatment decisions should however be concluded rapidly due to the severity of this phenotype.

Criteria for discontinuation of treatment

1. The patient develops a life threatening complication unlikely to benefit from further ERT.

2. Evidence of disease progression (see section 3.6.4) despite regular ERT at an optimised dose (at least 5mg/kg weekly) and other supportive management strategies (especially nutritional).

3.6.4 Expected outcomes of treatment

In addition to increased survival as described previously, treated infants have shown improvements in the signs and symptoms of LALD. These include improved growth, improvement or resolution of organomegaly and less vomiting and diarrhoea.

LALD is a multisystem disorder and multiple parameters must be taken into account when assessing the response to ERT in order to make decisions about dose escalation or discontinuation of treatment. These include:

- poor growth
- deteriorating liver function tests
- persistence or worsening of organomegaly
- increased frequency of intercurrent infections
- persistence or worsening of other symptoms of LALD (vomiting, diarrhoea)

In addition, plasma oxysterols (Cholestane-3β,5α,6β-triol) appear to be a potentially useful biomarker of disease and an increase in plasma oxysterols or a failure to decline to normal levels should be considered in decisions regarding dose escalation.

Given the rapidly progressive nature of the disease, decisions regarding dose escalation should be made in the context of the response to therapy over a period of 4-6 weeks, and these decisions should be discussed within the wider MDT and other LSD centres if required.

3.6.5 Administration of ERT

Steps for infusion of sebelipase alfa are summarised in Table 2.

Venous access

Venous access must be established before the infusion is made up. Infants with LALD tend to have poor or difficult access and require a permanent line inserted.

The choice of line is either a Hickman line (especially in very young infants) or a totally implantable venous access device (TIVAD).

Prevention of line infections

When accessing a line strict aseptic non-touch technique (ANTT) should be followed.

Due to the risk of infection routine bleeding back of TIVADs to check gripper needle position is not recommended. The TIVAD should only be accessed twice and then the LSD centre should be contacted for further advice.

Preparation of ERT

The infusion bag (or syringe) containing Sebelipase Alfa should be prepared just prior to the start of infusion administration once IV access is secured and the child is deemed clinically well.

Prior to preparation of the infusion, drug vials should be visually inspected. The solution should not be used if it contains foreign particulate matter or is discoloured. The solution may be used if a small number of visible translucent to opalescent or white amorphous or threadlike particles are present in the vial.

The contents should NOT be warmed using a microwave or other heat source but should be allowed to equilibrate to room temperature for at least 30 minutes.

Sebelipase alfa is a protein and must be handled and mixed carefully to minimise foaming.

If the child's weight cannot reliably be obtained on the morning of the infusion then the most recent weight measurement within 7 days, rounded to the nearest 0.1 kg, will be used for calculating the volume of drug to be withdrawn from the vial(s) to prepare the infusion.

Sebelipase alfa should be diluted to an appropriate volume for infusion, with a final concentration of 0.1 to 1.5 mg/ml. Suggested volumes based on weight ranges are given in Table 1 (based on a 3mg/kg dose) but will vary depending on the actual dose prescribed.

Table 1: Recommended infusion volumes (3mg/kg dose)

Weight range (kg)	**Total infusion volume (ml)**
1-10	20
11-24	50
25-49	100

Risk Factors for Infusion Associated Reactions (IARs)

As with any intravenous protein product, there is always a risk of an infusion reaction. IARs are more common if ERT is administered when there is evidence of active infection. The infusion should be given with caution in individuals with asthma and/or eczema, if the patient has had an immediate hypersensitivity reaction previously to another drug, and in individuals with known egg allergy. The patient is at more risk of an IAR if they have had an interrupted course of ERT.

Postponement of ERT

While other enzyme replacement therapies are not routinely administered in the context of infection, this has been done in the context of infantile onset LALD. In the case of active infection, patients should either be infused under close observation, or the infusion should be postponed to later in the same week if the patient is stable. Missing the weekly dose is not recommended.

Pre-medications

To reduce the risk of some of the more common infusion reactions occurring, patients may be pre-medicated with an antihistamine, an antipyretic and/or a low dose corticosteroid prior to infusion. These should be given PO/IV 30-60 minutes prior to infusion. There does not seem to be a need for routine pre-medication but if previous reactions have occurred or there is concern about the clinical condition (e.g. fever) then this should be considered.

Administration of infusion

Sebelipase alfa should not be infused with other products in the same infusion tubing as the compatibility of Sebelipase alfa in solution with other products has not been evaluated.
To prevent occlusion it is required that all infusions of Sebelipase alfa be administered using in-line filtration with a low-protein binding 0.2µm filter to prevent occlusion. The infusion will be administered at an infusion rate depending on the subject's weight (Table 3), and must be administered under close clinical supervision. Sebelipase alfa should not be administered at an infusion rate exceeding 4 ml/kg/hr.

Table 2: Administration of Sebelipase alfa using a syringe driver

Step 1	Establish venous access prior to making up the infusion. Obtain all necessary supplies prior to making up the infusion
Step 2	Visually inspect vial Vials can be used if a small number of visible translucent to opalescent or threadlike particles are present in the vial or seen over time. Do not use if the solution is discoloured or foreign particles are present
Step 3	Using ANTT slowly withdraw the calculated volume of Sebelipase alfa from the vials, rounded to the nearest 0.1ml DO NOT use filter needles during the dilution of the drug
Step 4	Using the same syringe draw up enough 0.9% Sodium Chloride to make up the correct total infusion volume
Step 4	Inspect the prepared solution and do not use if the infusion is discoloured or foreign particles are present
Step 5	Mix the solution by gentle inversion - DO NOT SHAKE. Label the syringe
Step 6	Initiate administration of the infusion as soon as possible after preparation.
Step 7	Though it is stated in the SmPC that the infusion should be given over 120 minutes at a constant rate, clinical practice at LSD centres has changed to using a series of increasing infusion rates as this has been a useful approach to the prevention of infusion associated reactions (Table 3), and consistent with the administration of other ERTs. NB line occlusion can occur during infusion.
Step 8	At the end of infusion the line should be flushed with 0.9% Sodium Chloride running at the same rate to ensure full dose of drug is delivered.

Table 3: Suggested rates for infusion of Sebelipase alfa

Rate (mg/kg/hour)	**Duration**
0.5	30 minutes, if no IAR proceed to next rate
1.0	30 minutes, if no IAR proceed to next rate
1.5	Remainder of infusion (if no IAR)

It is anticipated that infusions will take approximately 2-4 hours to complete. Following an IAR infusion rates for subsequent doses may be reduced at the discretion of the specialist team at the treating LSD centre.

Patient monitoring during infusion

Pre-infusion observations must be performed to ensure patient is well for the infusion.

Vital signs should include: temperature, pulse, BP, respirations, SaO_2. Vital signs should be frequently monitored throughout the infusion and for one hour post infusion. Patients are free to go home after one hour unless there are contraindications when they should stay for further observations until clinically stable.

It is important that the families have up-to-date contact details of the LSD centre in case of emergencies.

3.6.6 Infusion associated reactions (IARs)

At least half of infantile onset patients have had events that may be considered IARs although all have continued therapy with Sebelipase alfa.

Two types of reactions have been observed with enzyme replacement therapy. The reactions that occur during the infusion are usually minor and respond quickly to oral therapy and/or reduction of the infusion rate. The patients can develop symptoms at any time after starting the infusion.

Delayed or biphasic reactions can occur and these tend to present as a rash, pyrexia, and occasional respiratory symptoms. The second wave of symptoms usually occurs 1-8 hours after initial symptoms but this delay can be longer.

Serious reactions are extremely unlikely but can occur and should be managed appropriately and reported immediately to the prescribing LSD Centre.

Management of infusion reactions

Infusion associated reactions to Sebelipase alfa are similar in nature to those seen with other ERTs and may be managed in a similar manner.

In the case of a severe life-threatening reaction, current medical standards for emergency treatment are to be followed.

Mild to moderate IARs should be managed by LSD centres according to standard practice.

3.7 Recommended assessments

Once diagnosed, patients should undergo regular comprehensive assessments to evaluate the outcomes of therapy. Recommended assessments are summarised in Table 4. During the first six months, infants are likely to be inpatients and will need intensive daily review by the multidisciplinary team.

Oxysterols appear to be a provisionally useful biomarker and should be included in the assessment of patients with apparently worsening clinical condition.

Table 4: Recommended schedule of assessments

Assessment	Frequency
Clinical assessment	At diagnosis, weekly for first 6 months, monthly until 2 years, then 3 monthly
Dietetic assessment	At diagnosis, weekly for first 6 months, fortnightly until 2 years, then 3 monthly, or more frequently depending on clinical progress
Height (length), weight, head circumference, mid upper arm circumference	At diagnosis, weekly for first 6 months, monthly until 2 years, then 3 monthly
DNA for *LIPA* mutation analysis (patient) DNA for *LIPA* mutation analysis (parents)	At diagnosis At diagnosis
Full blood count & film, urea & electrolytes, liver profile (including AST, GGT and albumin), lipid profile, ferritin, CRP, LDH, oxysterols	At diagnosis, weekly for first 6 months, monthly until 2 years, then 3 monthly

Coagulation profile	At diagnosis, then 3 monthly (more frequently if abnormal)
Vitamin A/D/E, essential fatty acids	At diagnosis, then 3 monthly if unstable or fat intake being adjusted
Alpha-fetoprotein	At diagnosis, then 3 monthly
Anti-drug antibodies	At diagnosis, then 3 monthly
Immunoglobulins, B/T lymphocyte subsets	At diagnosis, may require repeat if abnormal
Abdominal ultrasound (volumetric for liver and spleen)	At diagnosis, then 3 monthly
Abdominal MRI* (when possible and if appropriate)	Annually

*If concerns regarding suspicious lesions are raised on imaging, liver biopsy may be indicated.

3.8 Home care

Due to the young age and the on-going complex needs of these infants home care should be carefully considered on an individual basis. Patients seem to become more stable between the ages of 12-24 months and may well be suitable for home care at this stage.

3.9 Cognitive ability, development and special educational needs

Treated infants with LALD do appear to have a degree of early motor delay which may be related to nutritional status and general illness. Other aspects of development do not appear to be affected, but treatment for infantile onset LALD is still in its early stages and developmental progress will need to be monitored carefully in the long term.

Support is a very important aspect of any rare, progressive disease and the help and on-going support of the MPS society is useful (www.mpssociety.org.uk)
Such children may develop some social care needs and may be eligible for Disability Living Allowance. The MPS society can help assist with the completion of applications.

3.10 Other treatments

Haematopoietic stem cell transplantation (HSCT)

HSCT has been performed in a small number of infants with limited success due to the high toxicity of the conditioning regimen in such sick infants. Long term outcomes from survivors remain unclear. Given treatment outcomes for ERT so far HSCT should only be considered in those infants not responding to ERT or who have other complications (e.g. HLH) which may be amenable to HSCT. Consideration of HSCT in LAL deficient infants should be discussed with other teams at one of the national HSCT in IEM MDT videoconferences.

Palliative care
Infants who satisfy exclusion criteria for starting ERT (see section 3.6.3) should be offered palliative care. This approach may also be suitable for families of infants with advanced disease who do not wish to start ERT.

4 Audit

It is a requirement that each treatment centre will perform audit of their service including patient/parent satisfaction surveys. Other audit activity will be national and based on input into the national registry when developed.

After taking informed consent patient data should be entered into the disease specific registry as this is a component of the drug's licensing approval.

References

Sebelipase alfa (Kanuma) – UK SmPC

Aslanidis, C., S. Ries, P. Fehringer, C. Büchler, H. Klima and G. Schmitz (1996). "Genetic and Biochemical Evidence That CESD and Wolman Disease Are Distinguished by Residual Lysosomal Acid Lipase Activity." Genomics **33**(1): 85-93.

Assmann, G. and U. Seedorf (2001). Acid lipase deficiency: Wolman disease and cholesteryl ester storage disease Metabolic and Molecular Bases of Inherited Diseases. C. R. Scriver, A. L. Beaudet, D. Valle and W. S. Sly. New York, McGraw-Hill**:** 3551–3572.

Guy, G. J. and J. Butterworth (1978). "Acid esterase activity in cultured skin fibroblasts and amniotic fluid cells using 4-methylumbelliferyl palmitate." Clin Chim Acta **84**(3): 361-371.
Hamilton, J., I. Jones, R. Srivastava and P. Galloway (2012). "A new method for the measurement of lysosomal acid lipase in dried blood spots using the inhibitor Lalistat 2." Clinica Chimica Acta **413**(15–16): 1207-1210.

Jones, S. A., V. Valayannopoulos, E. Schneider, S. Eckert, M. Banikazemi, M. Bialer, S. Cederbaum, A. Chan, A. Dhawan, M. Di Rocco, J. Domm, G. M. Enns, D. Finegold, J. J. Gargus, O. Guardamagna, C. Hendriksz, I. G. Mahmoud, J. Raiman, L. A. Selim, C. B. Whitley, O. Zaki and A. G. Quinn (2015). "Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants." Genet Med.

Taurisano, R., A. Maiorana, F. De Benedetti, C. Dionisi-Vici, R. Boldrini and F. Deodato (2014). "Wolman disease associated with hemophagocytic lymphohistiocytosis: attempts for an explanation." Eur J Pediatr **173**(10): 1391-1394.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

Dr Elaine Murphy, representing British Inherited Metabolic Disease Group and University College London Hospitals
and
Dr Patrick Deegan, representing the Royal College of Pathologists and Cambridge University Hospitals

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ***Yes***

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ***Yes***

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? ***Yes, Consultant Metabolic Physicians.***

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

What is the expected place of the technology in current practice?
The following report relates to the late-onset forms of LALD, ie age of onset >1 year.

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?
Less than 20 patients are known in the UK at present. A recent literature search (2013, Bernstein) identified 135 patients worldwide. Estimates based on the frequency of the common E8SJM mutation give a prevalence of between 1 in 40,000 and 1 in 300,000 depending on ethnicity and geographical location (2014, Reiner). It is likely that the current known caseload in the UK is underestimated.

There is a spectrum of disease severity. Not all patients are severely affected. The natural history, particularly of atherosclerotic complications in late onset LALD is unknown.

How is the condition currently treated in the NHS?
The disease is often misdiagnosed as familial hypercholesterolaemia or non-alcoholic fatty liver disease and treated as such. Correctly diagnosed patients are followed by hepatologists or metabolic specialists. There is no current disease-modifying treatment and general supportive care is offered. Statins are used to ameliorate the dyslipidaemia but do not slow progression of liver disease. There is limited experience with other lipid-lowering agents in the condition. Liver transplant is indicated for patients who have progressed to end-stage liver disease, who meet the usual criteria for transplantation.

Is there significant geographical variation in current practice?
No.

Are there differences of opinion between professionals as to what current practice should be?
Few physicians are experienced in treating this condition. We have been in contact with most of them and believe we are representing their views.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Lipid lowering therapy does not impact upon the liver disease. Liver transplantation is a life-saving rescue procedure for those with end-stage liver failure and is not a suitable comparator.

Enzyme replacement therapy therefore represents the first and only disease-modifying therapy. The principal disadvantage is that the treatment is in the form of a biweekly intravenous infusion. Infusion related reactions and other adverse reactions are however uncommon (2015, Burton).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Yes, homozygotes for the common E8SJM mutation have a uniformly early presentation with inevitable progression of disease in childhood or adult life. Otherwise, there is little evidence that genotype predicts outcome.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
Unknown. Clinical trials evaluated surrogate endpoints in patients with clinically stable disease, who nevertheless had evidence of fibrotic liver disease. No subgroups were evaluated.

There is variation in the natural history and age at presentation. Broadly speaking those with LALD can be categorised into three groups:
A. Those who present in childhood with failure to thrive, malabsorption and hepatomegaly. In this group the disease may progress relentlessly (A1), but in a subgroup there is apparent spontaneous improvement with residual lipid and liver enzyme abnormalities in adulthood (A2). Some of these individuals progress to liver failure and need to transplant later in adulthood (A3).
B. Those who are picked up incidentally on the basis of their abnormal laboratory tests or imaging results, but who are otherwise ostensibly well. A number of these patients will not be identified until they present with a clinical event such as decompensated cirrhosis or a cardiovascular event.
C. Patients with additional, often modifiable risk factors for cirrhosis, such as heavy alcohol intake and obesity. Every attempt will be made to modify such risk factors, but where this fails clinical judgement, if necessary with a second opinion, will be needed to determine if such individuals are likely to benefit from ERT.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?
There is already a well-established system for assessment and treatment of patients with lysosomal diseases like LALD. There are three paediatric and five adult centres In England commissioned under the highly-specialised framework. These centres are accustomed to providing multidisciplinary and multisystem care for rare inherited disorders. We recognise that some patients may currently be under the sole care of hepatologists, metabolic and/or lipid specialists. We anticipate that enzyme replacement therapy will be provided via the lysosomal centres in close collaboration with hepatology and other specialties.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
The technology has received marketing authorisation. There are already several patients receiving the therapy as part of the clinical trial programme.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Guidelines are currently in development. These have been commissioned by NHS England and are being written by Drs Simon Jones, Patrick Deegan, Elaine Murphy, [redacted] and [redacted]. They will be reviewed by other specialists (including hepatology) and by the patient organisation before completion.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

- ***This will take the form of a biweekly intravenous infusion; some patients may require implanted central venous access devices.***
- ***We anticipate that patients will be able to receive this at home as part of existing homecare arrangements.***
- ***Diagnostic services, including enzyme activity testing and genetic testing will be required as part of commissioned services.***
- ***Once stable, regular monitoring (six monthly to annually) will include***
    - ***Weight, height and blood pressure***
    - ***Clinical examination***
    - ***Laboratory tests (liver enzymes, clotting, lipid levels)***
    - ***Imaging: magnetic resonance imaging for fat content and volume, liver ultrasound for portal flow and fibrosis assessment, echocardiogram, ECG, and vascular imaging as indicated***
    - ***Liver biopsy at treatment baseline, with further liver biopsies as clinically indicated***

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Genetic testing to identify homozygotes for the E8SJM mutation will be required to highlight this important subgroup at greater risk. Consensus guidelines in development will address starting and stopping criteria. We anticipate that, in relation to liver involvement, treatment would be initiated

based on evidence of progressive or fibrotic liver disease. At present the role of ERT in treating cardiovascular disease is unknown.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.
Broadly speaking, patients in the clinical trial represented a subgroup toward the middle of the disease spectrum (2015, Burton). Patients with only mild liver enzyme abnormalities and patients with decompensated liver disease (Child-Pugh class C) were excluded.

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?
The trials were conducted in the UK.

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
Surrogate outcomes were employed, indicating a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. These outcomes, on well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition. To date, despite these encouraging results, there is no evidence to address long-term and key clinical endpoints (progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death). We recommend that treating clinicians therefore collaborate with planned registry studies to establish long-term impact in clinical practice.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
The frequency and distribution of adverse events were similar in placebo- and sebelipase-treated patients. Infusion reactions were uncommon (2015, Burton).

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.
No additional information known.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
Please refer to our comments on service delivery above. We anticipate that, with availability of disease-modifying treatment, more patients may be identified. This will increase the need for NHS resources, including staff. Awareness among clinical specialists and pathologists remains low. Treating physicians will continue to collaborate with professional organisations (eg BIMDG, RCPath, ACB, BSG, RCP etc) and industry to educate and raise awareness.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

There will be patients with other significant well-recognised risk factors for cirrhosis and liver failure, such as heavy alcohol intake and obesity. Every attempt will be made to modify such risk factors, but where this fails clinical judgement, if necessary with a second opinion, will be needed to determine if such individuals are likely to benefit from ERT.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Sebelipase alfa for treating lysosomal acid lipase deficiency

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

Authors
Rob Riemsma, Review Manager, Kleijnen Systematic Reviews Ltd, UK
Manuela Joore, Health Economist, Maastricht UMC, The Netherlands
Bram Ramaekers, Health Economist, Maastricht UMC
Anoukh van Giessen, Health Economist, Maastricht UMC
Marie Westwood, Systematic Reviewer, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Xavier Pouwels, Health Economist, Maastricht UMC
Gill Worthy, Statistician, KSR Ltd
Lisa Stirk, Information Specialist, KSR Ltd
Johan L. Severens, Professor of Evaluation in Health Care, EUR
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Rob Riemsma, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

Date completed 09/12/2015

Source of funding: This report was commissioned by the NIHR HTA Programme as project number HST 15/07/01.

Declared competing interests of the authors

None.

Acknowledgements
None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Riemsma R, Joore MA, Ramaekers BLT, Van Giessen A, Westwood M, Armstrong N, Pouwels X, Worthy G, Stirk L, Severens JL, Kleijnen J. Sebelipase alfa for treating lysosomal acid lipase deficiency: a Highly Specialised Technology Evaluation. York: Kleijnen Systematic Reviews Ltd, 2015.

Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Manuela Joore acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Anoukh van Giessen, Xavier Pouwels and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Marie Westwood acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Johan L Severens critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACAT	Acyl-Cholesterol Acyltransferase
ADA	Anti-drug antibody
AE	Adverse Events
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ApoB	Apolipoprotein B
APRI	Aspartate aminotransferase to Platelet Ratio Index
ARISE	Acid Lipase Replacement Investigating Safety and Efficacy
AST	Aspartate transaminase
BIC	Bayesian information criterion
BIM	Budget impact model
BNF	British National Formulary
BSC	Best supportive care
CAD	Coronary artery disease
CC	Compensated cirrhosis
CDF	Cancer Drugs Fund
CV	Cardiovascular
CE	Cholesteryl Esters
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company Submission
CSR	Clinical study report
CVD	Coronary vascular disease
DBS test	Dried blood spot test
DCC	Decompensated cirrhosis
EMA	European Medicines Agency
ECG	Electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
EU	European Union
EUR	Erasmus University Rotterdam
FA	Fatty Acid
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FC	Free Cholesterol
FCH	Familial combined hyperlipidaemia
FFA	Free Fatty Acid
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
H&E stain	Haematoxylin and eosin stain

HBV	Hepatitus B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitus C virus
HDL/HDL-c	High density lipoprotein/ High density lipoprotein cholesterol
HELLP	Haemolysis; elevated liver enzymes; low platelet count
HeFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
HMG-CoAr	Hydroxymethylglutaryl-coenzyme A reductase
HR	Hazard ratio
HRG	Health resource group
HRQoL	Health related quality of life
HSCT	Haematopoietic stem cell transplantation
HST	Highly Specialised Technologies
HTA	Health Technology Assessment
IAR	Infusion associated reaction
IC	Indirect Comparison
ICER	Incremental Cost-effectiveness Ratio
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LAL/ LAL Deficiency	Lysosomal acid lipase/ Lysosomal acid lipase deficiency
LDH	Lactate dehydrogenase
LDL/ LDL-c	Low density lipoprotein/ Low density lipoprotein cholesterol
LDLR	Low-Density lipoprotein receptor
LIPA	Lysosomal acid lipase gene
LLM	Lipid lowering medication
LOCF	Last observation carried forward
LSD	Lysosomal storage disorder
LYG	Life year gained
LYS	Life Year Saved
MedDRA	Medical Dictionary for Regulatory Activities
MEGE-MRI	Multiecho gradient echo sequence-magnetic resonance imaging
MHRA	Medicines and Healthcare Products Regulatory Agency
MPS	Mucopolysaccharide
MRI	Magnetic resonance imaging
MRU	Medical resource utilisation
MSE	Mean squared error
MTC	Mixed Treatment Comparison
NA	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNT	Number needed to treat
NR	Not Reported
ONS	Office of National Statistics

OS	Overall survival
PAS	Patient access scheme
PDFF	Proton density fat fraction
PedsQL™	Paediatric quality of life inventory questionnaire
PES	Primary efficacy set
PFS	Progression-free survival
PH	Proportional hazards
PLT	Platelet test
PNH	Paroxysmal nocturnal haemoglobinuria
PP /PPS	Per protocol/ per protocol set
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
QOW	Every other week
QW	Weekly
RCT	Randomised Controlled Trial
rhLAL	Recombinant human lysosomal acid lipase
RR	Relative Risk
SAE	Serious adverse event
ScHARR	School of Health and Related Research
SD	Standard deviation
SF-36	Short form 36
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SRBEP	Sterol regulatory element binding proteins
SRT	Substrate reduction therapy
STA	Single Technology Appraisal
SVR	Sustained viral response
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TFHN	Transfusion-free haemoglobin normalisation
TG	Triglyceride
TTF	Time to failure
TTO	Time trade-off
TTP	Time to progression
UDCA	Ursodeoxycholic acid
U/L	Units per litre
UMC	University Medical Centre
WFA	Weight for age
WHO	World Health Organisation
VLDL-C	Very Low Density Lipoprotein Cholesterol

Table of Contents

Abbreviations **3**
Table of Tables **9**
Table of Figures **10**
1. SUMMARY **11**
1.1 Background 11
1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology 11
1.3 Critique of the decision problem in the company's submission 11
1.4 Summary of clinical effectiveness evidence submitted by the company 12
1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted 13
1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS 14
1.7 Summary of the ERG's critique of the value for money evidence and cost to the NHS and PSS submitted 15
1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services 16
1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health related benefits 17
1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty 17
1.11 Summary of exploratory sensitivity analyses undertaken by the ERG 18
1.11.1 Summary of exploratory analyses for the cost consequences analysis 18
1.11.2 Summary of exploratory analyses for the budget impact analysis 19
1.11.3 ERG exploratory analysis for the wider societal benefits 19
2. BACKGROUND **20**
2.1 Introduction 20
2.2 Description of health problem 20
2.2.1 Lysosomal acid lipase deficiency 20
2.2.2 Epidemiology 20
2.2.3 Aetiology 20
2.2.4 Pathogenesis 21
2.2.5 Clinical features 21
2.2.6 Diagnosis 22
2.2.7 Prognosis 22
2.2.8 Impact on patients' health-related quality of life (HRQoL) 22
2.3 Current service provision 23
2.4 Description of the technology under assessment 23
2.4.1 Sebelipase alfa 23
2.5 Current usage in the NHS 24
3. CRITIQUE OF THE COMPANY'S INTERPRETATION OF THE DECISION PROBLEM **25**
3.1 Introduction 25
3.2 Adherence to the decision problem 25

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope 28
3.3.1 Population 28
3.3.2 Interventions 28
3.3.3 Comparators 28
3.3.4 Outcomes 28
3.3.5 Cost to the NHS and PSS, and value for money 29
4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS 30
4.1 Critique of the methods of review(s) 30
4.1.1 Searches 30
4.1.2 Inclusion criteria 30
4.1.3 Critique of data extraction 31
4.1.4 Quality assessment 31
4.1.5 Evidence synthesis 32
4.2 Critique of trials of the technology of interest, their analysis and interpretation 32
4.2.1 Studies included in/excluded from the submission 32
4.2.2 Details of relevant studies not included in the submission 34
4.2.3 Summary and critique of company's analysis of validity assessment 34
4.3 Summary and critique of results 35
4.3.1 Efficacy in paediatric (≤ 2 years) patients with LAL Deficiency 37
4.3.2 Efficacy in Paediatric / adult (≥ 4 years) patients with LAL Deficiency 39
4.3.3 Efficacy in adults (≥ 18 years) with LAL Deficiency 42
4.3.4 Health related quality of life 43
4.3.5 Safety and tolerability 47
4.4 Summary of evidence presented in other submissions 51
4.5 Additional work on clinical effectiveness undertaken by the ERG 51
4.6 Conclusions of the clinical effectiveness section 51
4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies 51
4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes 52
4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness 52
5. VALUE FOR MONEY FOR THE NHS AND PSS 54
5.1 Introduction 54
5.2 Review of existing economic analyses 54
5.3 Exposition of the company's model 55
5.3.1 Economic evaluation scope 55
5.3.2 Model structure 58
5.3.3 Evidence used to inform the company's model parameters 63
5.3.4 Model evaluation 77
5.4 Headline results reported within the company's submission 79
5.4.1 Headline total QALYs and total costs for sebelipase alfa versus standard care 79
5.4.2 Sensitivity analyses presented within the company's submission 81
5.4.3 Validation 85
5.5 Discussion of available evidence relating to value for money for the NHS and PSS 86

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG 88
6.1 Introduction 88
6.2 Re-analysis of the company's economic analysis following the correction of technical programming errors 89
6.3 Development of the exploratory ERG model 89
6.4 Cost-consequence results produced using the ERG model 90
6.4.1 Headline cost-consequence results produced using the ERG model 90
6.4.2 Exploratory analyses produced by the ERG model 92
6.5 Discussion 92
7. COST TO THE NHS AND PSS AND OTHER SECTORS 94
7.1 Summary of submitted evidence relating to the costs to the NHS and PSS 94
7.1.1 Model approach 94
7.1.2 Prevalence and incidence 94
7.1.3 Uptake of sebelipase alfa 96
7.1.4 Technology costs 98
7.1.5 Results 100
7.1.6 ERG additional analyses 102
8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE 108
8.1 Summary of cost savings estimated within the CS 108
8.1.1 Nature of estimates presented 108
8.1.2 Societal costs 108
8.1.3 Costs borne by patients 109
8.1.4 Other carer costs 109
8.1.5 ERG discussion of wider societal (non-health) benefits 109
8.2 Staffing and infrastructure requirements associated with the use of the technology 110
9. DISCUSSION 112
9.1 Statement of principal findings – clinical effectiveness 112
9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis 113
9.2.1 Cost-consequence analysis 113
9.2.2 Cost to the NHS and PSS 115
9.2.3 Non-health benefits 116
9.3 Strengths and limitations 117
9.3.1 Strengths of the CS 117
9.3.2 Weaknesses of the CS 117
9.4 Uncertainties 117
10. REFERENCES 119
Appendix 1: Further Search Critique and ERG Search Strategies 126
Appendix 2: Sensitivity analyses on budget impact model (based on ERG corrected model; 5 mg vials available from the second year of the model onwards) 130

Table of Tables

Table 3.1: Adherence of the CS to the agreed decision problem....26
Table 4.1: Eligibility criteria....31
Table 4.2: Studies included in the CS....33
Table 4.3: Studies not included in the CS....34
Table 4.4: Baseline demographic and disease characteristics....36
Table 4.5: Summary of results for paediatric (≤ 2 years) patients with LAL Deficiency....39
Table 4.6: Summary of primary and secondary efficacy endpoints (Study LAL-CL02)....41
Table 4.7: Summary of secondary efficacy endpoints (Study LAL-CL02)....42
Table 4.8: Health related quality of life outcomes from LAL-CL02....46
Table 4.9: Adverse reactions reported in infants[c] receiving sebelipase alfa....47
Table 4.10: Adverse reactions reported in children and adults[d] receiving sebelipase alfa....48
Table 4.11: Summary of treatment-emergent adverse events, regardless of causality, occurring in three or more patients (Study LAL-CL03, safety population)....49
Table 4.12: Summary of treatment-emergent adverse events, regardless of causality, occurring in three or more sebelipase alfa-treated patients, by treatment group (Study LAL-CL02, FAS, double-blind treatment period)....50
Table 5.1: Adherence to the reference case principles relevant to highly specialised technologies....57
Table 5.2: Transition probabilities between the "LALD without CC, DCC or HCC" and "CC" health states for sebelipase alfa (based on Table D12.6 from the CS)....65
Table 5.3: Overview of annual transition probabilities (retrieved from the submitted model)[a]....66
Table 5.4: Compensated cirrhosis based on the FIB-4 scores (based on Table D12.6 of the CS and the response to clarification question B5....68
Table 5.5: Overview of annual transition probabilities (ERG base case)[a]....70
Table 5.6: Overview of health state utilities....71
Table 5.7: Overview of health state utilities used in the ERG base case....73
Table 5.8: Health state costs, variation in health state costs, population used to obtain health state costs and source of these costs, as used in the cost-consequence analysis (based on CS, table D12.13)....75
Table 5.9: Summary results of the company's model....80
Table 5.10: QALY gain by health state for the base case analysis....80
Table 5.11: Costs associated with sebelipase alfa and BSC per health state for the base case analysis....81
Table 5.12: Multi-way scenario-based sensitivity analysis of patient scenarios....83
Table 5.13: Multi-way scenario-based sensitivity analysis of transition probabilities....85
Table 6.1: Scenario analyses performed by the ERG....90
Table 6.2: Results of explorative analyses (conditional on ERG base case)....92
Table 7.1: Diagnosis rate of LAL Deficiency (CS, table D13.10)....96
Table 7.2: Treatment rate of LAL Deficiency (CS, table D13.11)....96
Table 7.3: Treatment continuation rate amongst treated patients, by years from start of treatment (CS, table D13.13)....97
Table 7.4: Compliance rate of LAL Deficiency (CS, table D13.14)....97
Table 7.5: Comparison of the number of sebelipase alfa treated patients versus total number of patients after applying diagnosis, treatment and treatment continuation rates to the LAL Deficiency patient population (CS, budget impact model)....97

Table 7.6: Non-drug direct medical costs, by treatment option and age of presentation group (adapted from CS, table D13.16) 99
Table 7.7: Net budget impact: company's base case scenario (CS, table D13.19) 100
Table 7.8: Net budget impact: base case analysis (ERG correction) 101
Table 7.9: Five year net budget impact resulting from sensitivity analyses on prevalence and incidence rates (based on ERG corrected model) 102
Table 7.10: Five year net budget impact resulting from sensitivity analyses on diagnosis and treatment rates of the Age 1+ presentation group (based on ERG corrected model)[1,2] 103
Table 7.11: Five year net budget impact resulting from sensitivity analyses on treatment continuation and compliance rates of the Age 1+ presentation group (based on ERG corrected model)[1,2] 106
Table 8.1: Changes in hours of work and professions for carers (n=8) (CS, Table E14.1) ... 109
Table 8.2: Exploratory scenario analysis of productivity loss in patients/carers (discounted at 1.5%) 110

Table of Figures

Figure 4.1: Monthly weight gain by date of first chart review 38
Figure 5.1: Model structure as provided by the company 59
Figure 5.2: Model structure as provided by the ERG for the base case scenario 60
Figure 5.3: Model structure as provided by the ERG for the infant scenario 60
Figure 5.4: Base case: sebelipase alfa Markov trace 79
Figure 5.5: Base case: BSC Markov trace 79
Figure 5.6: Tornado diagram of incremental QALYs 82
Figure 5.7: Tornado diagram of incremental life years (undiscounted) 82
Figure 5.8: [redacted] 82

1. SUMMARY

1.1 Background

Lysosomal acid lipase deficiency is an ultra-rare inherited autosomal recessive lysosomal storage disease (LSD). It is characterised by a failure to break down cholesteryl esters and triglycerides in the lysosomes, resulting in a build-up of cholesteryl esters (CEs) and triglycerides (TGs) in vital organs, blood vessels, and other tissues with multi-system manifestations. Lysosomal acid lipase Deficiency (LALD) results in cirrhosis with portal hypertension, liver failure, and early atherosclerosis. The age at onset varies, but LALD is primarily a childhood condition with serious complications frequently occurring at an early age.

1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology

There are no published data on HRQoL in people with LALD. The CS reports the findings of an on-line survey of patients and their families. The survey was conducted by Alexion and distributed through three patient organisations from the UK, Spain and the USA. In addition, HRQoL data from the LAL-CL02 (ARISE) trial were reported, and HRQoL data relating to the effects of chronic liver were presented for diseases considered to be comparable.

Eleven participants took part in the survey (median age 11 years, range 3 to 49 years). Eight (73%) of the participants were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa. The mean age at diagnosis was 5.6 years for children and 33.5 years for adults; for infantile-onset LALD HRQoL is likely to be a secondary consideration to improving survival. The most commonly reported symptom was abdominal pain (91%) of LALD patients; other symptoms mentioned by more than half of the survey sample were fatigue, diarrhoea, nausea, loss of appetite, itchy skin and having a swollen abdomen. Five of the six school age children who participated in the survey were reported as being "able to follow full-time education"; four of these five children were being treated with sebelipase alpha, but it was not clear whether treatment had any effect on their schooling. The mean EQ-5D scores, before treatment with sebelipase alpha, were 0.76 for children (N=8) and 0.34 for adults (N=2); the CS reported small increases in score after treatment (0.84 for children (N=6) and 0.76 for adults (N=1)).

Quality of life data were collected in the sebelipase alfa study LAL-CL02 (ARISE), which included both children and adults (minimum age five years). Study inclusion criteria meant that the HRQoL of participants, at baseline was similar to that expected for an unaffected population. The study included people with substantial pathological liver damage at baseline, [redacted]

1.3 Critique of the decision problem in the company's submission

The remit of the appraisal, as specified in the final NICE scope, is to evaluate the benefits and costs of sebelipase alfa within its marketing authorisation for treating lysosomal acid lipase

deficiency for national commissioning by NHS England. The ERG notes some deviations from the final agreed NICE scope. Briefly, these include:

- The company notes that data are not available for the following four efficacy outcomes for any of the ongoing sebelipase alfa clinical trials: liver synthetic function, liver disease progression, liver transplant, and cardiovascular events.
- The company submission did not include subgroup analyses for infants with very rapidly progressing lysosomal acid lipase deficiency and for people who have had a liver transplant as requested in the scope.

1.4 Summary of clinical effectiveness evidence submitted by the company

The CS presents results from four intervention studies and one historical control study. One of the intervention studies was a placebo controlled randomised trial.

Paediatric (≤ 2 years) patients with LAL Deficiency:

Two studies were included for this population: study LAL-CL03 was a single arm dose escalation study of sebelipase alfa (from 0.35 to 1 mg/kg once weekly IV; up to 3 or 5 mg/kg once weekly IV) including nine patients with follow-up up to 208 weeks; and study LAL-1-NH01 was a retrospective historical control study including 35 patients diagnosed between 1985 and 2012.

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients who survived past 12 months of age in LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics. In LAL-CL03, six of nine sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, one additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival, 95% CI: 0% to 16%).

No other comparative data were presented for this population.

Paediatric/adult (≥ 4 years) patients with LAL Deficiency:

Study LAL-CL02 (ARISE) was a 20-week placebo controlled randomized trial including 36 sebelipase alfa-treated patients (1 mg/kg) and 30 placebo patients.

A statistically significant improvement in multiple endpoints was observed in the sebelipase alfa-treated group as compared to the placebo group at the completion of the 20-week double-blind period of the study. The absolute reduction in mean alanine transaminase (ALT) level was -57.9 U/l [redacted] in the sebelipase alfa-treated group and -6.7 U/l (-6%) in the placebo group.

Sixty-five of 66 patients entered the open-label period (up to 130 weeks) at a sebelipase alfa dose of 1 mg/kg once every other week. In patients who had received sebelipase alfa during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels. [redacted] Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period. Consistent with what was observed in sebelipase alfa-treated patients during the

double-blind period, initiation of treatment with sebelipase alfa during the open-label period produced rapid improvements in ALT levels and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Adults (≥ 18 years) with LAL Deficiency:

Study LAL-CL01 was a four week single arm sebelipase alfa study including nine patients divided over three cohorts: 0.35, 1, and 3 mg/kg once weekly IV. Study LAL-CL04 was a 156-week extension including eight adult patients who had completed LAL-CL01.

Changes in serum transaminase levels observed in adults in study LAL-CL01 were consistent with those reported in study LAL-CL02 and were maintained during the extension study LAL-CL04. Initiation of treatment with sebelipase alfa in study LAL-CL01 produced a rapid decline in ALT and aspartate aminotransferase (AST). When patients went off treatment at the end of study LAL-CL01 (interval between dosing of 9 to 28 weeks), both ALT and AST increased. Normalisation of transaminase levels continued during long-term treatment (through Week 104) in the extension study LAL-CL04.

Safety and tolerability

According to the European Medicines Agency (EMA) European Public Assessment Report (EPAR) the most serious adverse reactions experienced by 3% of patients taking sebelipase alfa in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

In addition, three deaths were reported in the sebelipase alfa clinical programme as of the data cut-off across the four primary studies evaluating safety; all patients who died were enrolled in study LAL-CL03. All fatal events were assessed as unrelated to sebelipase alfa treatment by the investigators.

Serious adverse events (SAEs) were reported in 12 (14.3%) of the 84 patients in the pooled safety set. SAEs were more frequent among infants in study LAL-CL03 with the most rapidly progressive form of LAL Deficiency (eight of nine patients, 89%) and were relatively infrequent among children and adults (four of 75 patients, 5%). The most commonly reported types of SAEs were infections (five of 84 patients, 6%). One patient in study LAL-CL02 reported a serious infection (gastroenteritis). The only other SAE reported in more than one patient in the pooled safety set was pyrexia, reported in two patients in study LAL-CL03.

1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted

The main uncertainty regarding the effectiveness evidence is the comparability of baseline characteristics from treated patients and historical control patients, the use of surrogate outcomes and the lack of long-term follow-up.

[redacted]. Given the likely improvements in supportive care over time, results from comparisons between treated patients (LAL-CL03) and historical control patients (LAL-1-NH01) may be biased in favour of sebelipase alfa.

Surrogate outcomes showed a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. These outcomes, on well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition. However, there is no evidence to address long-term and key clinical endpoints (progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death). One of the most important outcomes is slowing the progression of the liver disease and hence delaying or avoiding liver transplant. The duration of the trials providing data presented in the submission was not long enough to look at this outcome. In addition, the long-term safety and efficacy profile of sebelipase alfa is uncertain.

1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on quality of life, cost effectiveness and resource use data for patients with LAL Deficiency or provide utilities, resource use or cost data for the economic model. The company did not identify any economic studies, health state utility data, resource use data nor cost data for LAL Deficiency patients.

A model-based cost-consequence analysis (CCA) is presented to compare the costs, life years and QALYs of sebelipase alfa and best supportive care (BSC) for the treatment of LAL Deficiency from an NHS perspective. Costs and consequences are estimated for a population of 11 years-old over a lifetime horizon. For patients with infant disease onset, a scenario analysis is presented. The Markov model is an adaptation of a model for non-alcoholic fatty liver disease (NAFLD) published by Mahady et al.[2] The model consists of four health states representing different stages of liver disease progression; compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and "LAL Deficiency without CC, DCC, or HCC". Furthermore, it includes a liver transplant tunnel state and an absorbing death state. Adverse events were not included in the cost-consequence analysis. Health outcomes and costs are both discounted at a rate of 1.5%. Patients receiving sebelipase alfa will remain on treatment for their entire lives. In the BSC group, the only treatment option is a liver transplant, which is offered to patients that have progressed to HCC. Health state utilities were retrieved from the economic model by Mahady.[2] Costs were based on literature.[3] The costs of sebelipase alfa depend on dosing scheme (different for infant onset and later onset) and patient weight. The transition probabilities for sebelipase alfa are mostly based on the LAL-CL02[4] data, whereas for BSC transition probabilities retrieved from Mahady et al[2] and Hartwell et al[5] are used. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient compared to BSC and the incremental costs would be [redacted] per patient compared the BSC. In the company's sensitivity analyses this result was most sensitive to discount rate and the transition probabilities to and from the "LAL Deficiency without CC, DCC" and "HCC" health states. In the infants scenario analysis the LAL-1-NH01 study[6] and LAL-CL03 study[7] were used to inform the transition probabilities for the first year. Health state utilities and costs were mostly based on assumptions. This scenario results in 28.6 QALYs gained and incremental costs of [redacted]

A budget impact model submitted by the company estimates the total costs to the NHS of adopting sebelipase alfa in the UK for a period of five years. Two hypothetical scenarios are presented: one where a proportion of patients would receive sebelipase alfa with the remainder receiving BSC, and a second scenario in which all patients would receive BSC. The budget impact model includes two groups of patients. The first group contains patients diagnosed with LAL Deficiency in their first year of life (Age 0-1 presentation group) and the second group includes patients with presentation of symptoms after one year of age (Age 1+ presentation group). Prevalence and incidence are based on various sources of literature and internal modelling by the company. The uptake of sebelipase alfa is determined by diagnosis and treatment rates. Furthermore, the model assumes that several patients will not continue sebelipase alfa treatment or will not comply with prescribed dosing, by using treatment continuation and compliance rates. These rates are based on the company's experiences with other treatments for rare diseases. Applying these rates result in [redacted] of LAL Deficiency patients treated with sebelipase alfa in the first year, to [redacted] of patients treated in the fifth year. The costs of sebelipase alfa are conditional on the availability of a 5 mg vial of sebelipase alfa one year after market access. The net five year budget impact amounts to £53,548,573.

1.7 Summary of the ERG's critique of the value for money evidence and cost to the NHS and PSS submitted

The ERG's critique of the CCA entails the following main points: the health economic search, model structure and estimates for transition probabilities, costs of sebelipase alfa, health state utility estimates, and the handling of uncertainty.

The ERG notes that one limitation of the health economic search is that all Ovid databases were searched in one single strategy. Moreover, the company focused the search strategy on LAL Deficiency only, while it aimed to identify all economic studies that could be used to inform the design of the economic model or provide utilities, resource use or cost data for the economic model. The model structure used in the CCA differs between the comparators as a result of using different sources for transition probabilities (LAL-CL02[4] data for sebelipase alfa and Mahady et al[2] and Hartwell et al[5] for BSC). For sebelipase alfa it is assumed that, based on surrogate endpoints in LAL-CL02, patients cannot progress to the "CC", "DCC", "HCC" health states, and, as a result, cannot receive a liver transplant. In absence of comparative evidence on the clinical endpoints underlying these health states, the ERG questions this model structure. After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market. Furthermore, drug costs were influenced by the foreseen introduction of 5 mg vials of sebelipase alfa one year after market access. This reduces waste and costs associated with sebelipase alfa. The ERG thinks the 5 mg vials of sebelipase alfa should not be incorporated in the cost-consequences analysis because these are not yet available.

The health state utility used in the CCA exceeded the UK general population utility scores.[8] In addition, it was unclear whether the health state utility scores selected by the company were the most appropriate ones for the UK context.

In the probabilistic sensitivity analysis, multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges. In addition, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect.

The ERG's critique on the budget impact model entails three main points. Firstly, the estimation of incidence and prevalence was not transparently reported. As a result, the ERG was not able to assess the quality and the validity of the adjustments made by the company on Scott et al's prevalence rate.[9] Secondly, the estimation of diagnosis, treatment, treatment continuation and compliance rates seem to result in an underestimation of patients receiving sebelipase alfa, when compared to the company's experiences with other treatments for rare diseases. Thirdly, the costs of sebelipase alfa are conditional upon the availability of a 5 mg vial one year after market access.

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

The CS includes estimates of impacts of sebelipase alfa for LAL Deficiency in (i) lost productivity in patients due to premature death and morbidity, (ii) lost productivity in carers, (iii) respite care and other welfare payments, (iv) out of pocket costs associated with transportation and dietary requirement, and (v) carer's time. The main source of information was the EU-LAL-D Survey.(Appendix 5 CS[1])

The company gives an overview of qualitative accounts of patients and carers on productivity. In addition, quantitative accounts of changes in work hours are provided. The impact of sebelipase alfa on these accounts is unclear. It is mentioned that some LAL Deficiency patients are required to follow a low fat diet, which may be more costly than a regular diet. Furthermore, it is mentioned that family members who accompany patients to the hospital will have travel expenses and may be required to take time off work. Treatment with sebelipase alfa may be also associated with travel expenses to receive treatment as long as administration is not transitioned to home care.

Sebelipase alfa treatment should be supervised by an experienced healthcare professional experienced in the management of patients with LAL Deficiency, other metabolic disorders, or chronic liver diseases.[10] Sebelipase alfa is administered by intravenous infusion with an administration time of approximately two hours. The company states that in England, it is expected that initiation of the infusions and stabilisation of the patient will occur at specialist LSD centres followed by transition to local hospital outpatient clinics or homecare arrangements, as is the case for currently available enzyme replacement therapies. It is anticipated that besides this, no additional infrastructure is necessary. The company also notes that the management of infants is more complex than in older children and adults. Managing infants may require prolonged hospital stay and multi-disciplinary treatment approaches which may impact on resource requirements for the expert centres managing these infants.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health related benefits

A major source of information on the impact of sebelipase alfa on wider societal non-health benefits provided in the MS is the EU-LAL-D Survey.(Appendix 5 CS[1]) The ERG agrees with the company that due to the very low sample size and missing values, the results of this survey must be interpreted with caution. In addition, the survey was performed in various European countries, so does not only reflect the situation in the UK. This adds to the uncertainty of the information from this survey.

In addition to information from the survey, information from the literature is presented. It is unclear to the ERG how the studies mentioned in the MS have been retrieved. As a result, the ERG is unable to assess whether the information is complete, and provides an unbiased reflection of the evidence available in the literature.

The information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is descriptive in nature. No attempt has been made to value the impact in terms of costs. The ERG thinks that, using literature and assumptions, some quantification of wider societal benefits is possible. Presumably, the impact on productivity loss would be highest in terms of costs. Therefore, the ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency.

The ERG thinks it is reasonable to assume that the specialist LSD centres present in the UK will provide the necessary infrastructure to use sebelipase alfa in LAL deficiency patients. The costs of administration of sebelipase alfa in both infants and children older than one year and adults are incorporated in the CCA and the budget impact model.

1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

Strengths: Despite LAL Deficiency being a rare disease, the company presented an impressive series of studies in treated patients and historical controls, including a randomised placebo-controlled trial in 66 patients.

The CS contains details of a recent on-line survey of patients and their families from the USA and Europe which provides relevant information concerning the impact of the disease on patients and their families as well as information on resource use.

Despite the limited evidence available, particularly regarding the long-term consequences of the disease and treatments, the company presented a CCA with a lifetime time horizon along with several sensitivity and scenario analyses.

Weaknesses: Comparative data from treated patients and historical controls may be biased in favour of sebelipase alfa, [redacted] and supportive care will most likely have improved over time. Results from the randomised controlled trial show effects on surrogate endpoints, but no evidence is presented to address long-term and key clinical endpoints, such as progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death. The duration of trials providing data presented in the submission was not long enough to look at

key outcomes such as: progression of the liver disease, avoidance of liver transplant and adverse events.

The CCA and the budget impact model lacked transparency, which made it difficult for the ERG to assess whether the results are complete and valid.

In absence of comparative evidence on long-term and key clinical endpoints, the modelling of the long-term impact of the technology is extremely uncertain.

The calculation of the incidence and prevalence of LAL Deficiency in the UK for the budget impact model lacked transparency. As a result, the ERG was unable to assess the validity of these estimates.

Areas of uncertainty: There is no mention in the CS of possible stopping rules for sebelipase alfa. In fact the company assumes treatment will be administrated for the full lifetime of the patient (CS, Section 2.3, page 31). However, given the many differences between patients it cannot be assumed that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

Although, there is considerable follow-up in some of the sebelipase alfa studies, with nine patients having received sebelipase alfa treatment for up to 208 weeks and eight patients receiving up to 156 weeks of treatment, this is only a fraction of the expected lifetime treatment with sebelipase alfa. Therefore, the long-term safety and efficacy profile of sebelipase alfa remains uncertain.

The availability of a 5 mg vial after one year of market access is considered uncertain. Also, after 10 years of market access, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market.

1.11 Summary of exploratory sensitivity analyses undertaken by the ERG

1.11.1 Summary of exploratory analyses for the cost consequences analysis

The ERG preferred base case resulted in a substantial decrease of the incremental QALYs; from 19.2 QALYs in the company base case to 0.0 QALYs in the ERG base case, indicating no additional benefit for sebelipase alfa. This decrease was mainly due to the use of alternative transition probabilities; removing inconsistent assumptions regarding the model structure and use of sources for model input estimation. In addition, the use of alternative utilities had a substantial impact on the incremental QALYs. The incremental costs estimated by the company [redacted] were lower than the incremental costs estimated in the ERG base case ([redacted]). This could mainly be explained by removing the 30% cost reduction after 10 year. Moreover, there was substantial uncertainty regarding the incremental costs (95% confidence interval showed a range of approximately [redacted].

The infant scenario presented by the company showed incremental costs and QALYs of [redacted] and 28.6, respectively. In the infant scenarios performed by the ERG using the

1.5% discount rate, the incremental costs were relatively similar while the incremental QALYs were approximately halved.

1.11.2 Summary of exploratory analyses for the budget impact analysis

The ERG performed additional analyses on (1) incidence and prevalence rates, (2) diagnosis and treatment rates and (3) treatment continuation and compliance rates due to the uncertainty surrounding these estimates in the company's budget impact model

The ERG performed analyses on incidence and prevalence rates in the Age 1+ presentation group. The results show that a 50% increase of the prevalent population will increase the five year net budget impact to £90,541,337. The incidence rate does not strongly influence the five year budget impact.

The ERG performed sensitivity analyses on diagnosis and treatment rates in the Age 1+ presentation group by increasing and decreasing these rates with 10% or 20% in the sebelipase alfa with market access scenario. In these analyses the five year net budget impact ranged from £23,439,245 to £126,845,898 and the number of treated patients in the fifth year of the budget impact model varied from [redacted] to [redacted].

The ERG performed sensitivity analyses on treatment continuation and compliance rates. These rates were increased and decreased with 10% or 20% in the sebelipase alfa with market access scenario. In these analyses the five year net budget impact ranged from £36,137,359 to £206,367,686 and the number of treated patients in the fifth year of the budget impact model varied from [redacted] to [redacted].

The company stated that approximately [redacted] of the PNH patients are on eculizumab treatment.[11] Based on this information, the ERG thinks that the scenario where treatment rates are increased by 10%, diagnosis rates increased by 20% and both treatment continuation and compliance rates are set on 100% may be the most plausible because it provides [redacted] of treated patients with sebelipase alfa. This scenario results in a five year net budget impact of £178,527,667 which is more than three times higher than the company's base case five year net budget impact.

1.11.3 ERG exploratory analysis for the wider societal benefits

The ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency. In the searches the ERG conducted to retrieve additional information for the CCA, the study by Scalone[12] was identified. This study reports on productivity loss due to chronic hepatic diseases. Productivity loss corresponded to on average 6.8 days/patient-month by patients and caregivers, and 14.4 days/patient-month for transplant patients. The ERG performed the productivity loss calculations in two ways: based on the human capital approach (HCA) and the friction costs method (FCM). The ERG used a friction period of three months, hence time horizon does not impact these calculations. The lifetime HCA calculation resulted in productivity loss of £268,856, and the FCM resulted in £2,226.

2. BACKGROUND

2.1 Introduction

This chapter presents an overview of lysosomal acid lipase deficiency (LALD) and its management. The content of this chapter is based on relevant literature, information provided by clinical advisors to the Evidence Review Group (ERG) and information presented in the background sections of the company's submission (CS).[1 13] For additional information on the aetiology, epidemiology, health impact, prognosis and management of LALD, please see the CS (pages 39-73).

2.2 Description of health problem

2.2.1 Lysosomal acid lipase deficiency

Lysosomal acid lipase deficiency is an ultra-rare inherited autosomal recessive lysosomal storage disease (LSD). It is characterised by a failure to break down cholesteryl esters and triglycerides in the lysosomes, resulting in a build-up of cholesteryl esters (CEs) and triglycerides (TGs) in vital organs, blood vessels, and other tissues with multi-system manifestations.[1, 13] LALD results in cirrhosis with portal hypertension, liver failure, and early atherosclerosis.[1] The age at onset varies, but LALD is primarily a childhood condition with serious complications frequently occurring at an early age. In a review of 135 childhood and adult cases, the median age at first onset was five years, with 83% presenting at 12 years of age or younger.[14] In this study, 87% of people with LALD experienced manifestations in more than one organ and 79% of these were 19 years of age or younger.[14] A further observational study reported that the median age at the first report of disease related abnormalities was 5.8 years, with 81% of cases (n=48) being younger than 18 years.[15] Infants presenting with LALD experience rapid disease progression, characterised by malabsorption, growth failure, and liver failure with a reported median age of death of 3.7 months.[16]

2.2.2 Epidemiology

The CS reports published estimates of the prevalence of LALD ranging from 1:40,000 to 1:300,000 or 1:400,000.[9, 17, 18] Infantile presentation of LALD is rarer with a reported incidence estimate of approximately 1:704,000 births.[19] The CS estimated the prevalence of LALD in England to be 1:99,000.[1]

2.2.3 Aetiology

LALD 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. In late onset LALD, presenting in children and adults, many cases are associated with a common mutation and patients may have some residual enzyme activity.[20] The most commonly occurring mutation is the exon 8 splice site mutation, c.894G > A (E8SJM), which is found in more than 50% of children and adults with LAL Deficiency.[21] In LALD which presents in infants, there are many different mutations that can result in complete loss of enzyme function.[22]

2.2.4 Pathogenesis

Lysosomal acid lipase (LAL) is a critical component of lipid metabolism, which breaks down 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 LALD, absent or reduced 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 up-regulation 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).[1, 21]

2.2.5 Clinical features

As noted above, infantile onset is the most severe form of LALD, with early and severe symptom onset observed at a median age of one month. Infantile onset disease is characterised by rapid progression with a median age at death of 3.7 months[16] and almost 100% mortality within six months.[1] Accumulation of cholesteryl esters and triglycerides in the liver, intestines and adrenal glands results in hepatosplenomegaly, liver dysfunction, diarrhoea, vomiting, anaemia, failure to thrive, adrenal calcifications and liver fibrosis and cirrhosis.[23-27] Early death in infants with LALD is largely attributable to severe failure to thrive and/or rapidly progressing liver disease.[21]

Childhood and adult LALD is also associated with a significant morbidity burden and early mortality. Liver pathology is the dominant presentation, with 86% of LALD patients having liver manifestations.[14] The CS reports study data indicating that approximately 50% of paediatric and adult LALD patients progresses to fibrosis, cirrhosis or liver transplant within three years of presentation.[28] This is supported by baseline data from a phase 3 trial in which 44% of LALD patients (n=66) had a history or evidence of medically important chronic liver disease at baseline, including cirrhosis, portal hypertension, and/or coagulopathy.[29] Histologically confirmed cirrhosis has been described in children as young as four years of age, (range 4 to 21 years), with death due to liver failure occurring as early as seven years of age and 50% of deaths occurring in patients under 21 years.[14] Hepatobilliary malignancies have also been reported in young LALD patients.

Dyslipidaemia in childhood and adult LALD has also been associated with a risk of accelerated atherosclerosis. Adverse cardiovascular outcomes such as stroke and myocardial infarction have been reported in patients with LALD, however, the cardiovascular risk profile of these patients remains poorly understood. The CS reports study data showing baseline dyslipidaemia (mean LDL-cholesterol 207.9 ± 65.9 mg/dL) in 40% of participants, despite lipid lowering medication, [30] and the Bernstein review reported that 87% of 135 LALD patients had cardiovascular manifestations.[14]

In addition to severe failure to thrive in infants, LALD can have an effect on growth in older children. The CS reports study data showing that 12% of 50 patients under 18 years of age were at less than the fifth centile on population growth charts. [30] Similarly, a published review estimated failure to thrive, vomiting, diarrhoea, and gastrointestinal symptoms in approximately 30% of children with LALD.[31]

Other, less common clinical presentations and complications of childhood and adult LALD include pulmonary hypertension, severe splenomegaly and splenic infarcts leading to splenectomies in children, mesenteric lymphadenopathy, anaemia, and thrombocytopenia.[14, 21]

2.2.6 Diagnosis

LALD can be diagnosed on the basis of deficient enzyme activity, using either a dried blood spot (DBS)[32] or isolated leukocytes.[33] LAL activity can be measured, from a DBS, using the fluorimetric substrate 4-methylumbelliferyl palmitate. Because the assay is considered developmental and validation is performed within individual laboratories, it has been recommended that the results of LAL activity testing should be interpreted with respect to the normal reference ranges of the individual laboratory performing the test.[16] The CS states that, for the majority of laboratories using a DBS testing method, the effective diagnostic cut-off is "non-detectable".[1]

A diagnosis of LALD can also be established using genetic testing (complete sequencing of the coding regions of LIPA). The CS states that genetic testing is not considered necessary to establish a diagnosis, but can be useful in pre-natal and carrier testing.[1]

Liver biopsy specimens cannot be used to make a diagnosis of LALD.[21] Liver biopsy is considered to be the most reliable method of evaluating liver abnormalities, such as the development of fibrosis and cirrhosis, however, it is an invasive procedure with associated risks and costs.[34] The CS states that blood tests should be used for initial assessment prior to biopsy.[34, 35] The CS also notes that hepatic magnetic resonance imaging (MRI) is being developed as an assessment technique for patients with LALD. MRI is not considered to be diagnostic, but may be a useful technique for monitoring progression (in preference to multiple repeated biopsies.[36]

2.2.7 Prognosis

As previously noted, LALD in infants is characterised by early and severe symptom onset with a median age of death 3.7 months[16] and almost 100% mortality within six months.

There are limited data on the life expectancy of LALD patients who present in childhood and adulthood, however, the Bernstein review of 135 LALD patients reported that 50% of deaths due to liver failure occurred before the age of 21 years and less than 10% of patients were older than 40 years of age.[14] In addition, a recent observational study of patients with LALD reported that the proportion of patients over 40 years of age identified was substantially lower (18.7%) than would be expected for the normal population (46.7%).[15]

2.2.8 Impact on patients' health-related quality of life (HRQoL)

There are no published data on HRQoL in people with LALD. The CS reports the findings of an on-line survey of patients and their families in the USA and Europe. The survey was conducted by Alexion and distributed through the UK Society for Mucopolysaccharide Diseases (MPS), AE LALD (Spanish LAL Deficiency support group) and a US based LAL Deficiency patient organisation, SOLACE (Support Organization for LAL Deficiency - Advocacy, Care and Expertise) which has some European based members. The CS states that the survey was designed in collaboration with clinicians and was approved by patient associations working with people affected by LALD.[1] In addition, HRQoL data from the

LAL-CL02 (ARISE) trial were reported,[37] and HRQoL data relating to the effects of chronic liver were presented for diseases considered to be comparable.[1] The limitations of this approach were acknowledged.

Eleven participants participated in the survey (median age 11 years, range 3 to 49 years). Eight (73%) of participants were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa.[1] The mean age at diagnosis was 5.6 years for children and 33.5 years for adults; for infantile-onset LALD HRQoL is likely to be a secondary consideration to improving survival. The most commonly reported symptom was abdominal pain (91%) of LALD patients; other symptoms mentioned by more than half of the survey sample were fatigue, diarrhoea, nausea, loss of appetite, itchy skin and having a swollen abdomen.[1] Five of the six school age children who participated in the survey were reported as being "able to follow full-time education"; four of these five children were being treated with sebelipase alpha, but it was not clear whether treatment had any effect on their schooling.[1] The mean EQ-5D scores, before treatment with sebelipase alpha, were 0.76 for children (N=8) and 0.34 for adults (N=2); the CS reported small increases in score after treatment (0.84 for children (N=6) and 0.76 for adults (N=1)).[1]

Quality of life data were collected in the sebelipase alfa study LAL-CL02 (ARISE), which included both children and adults (minimum age five years).[30] Study inclusion criteria meant that the HRQoL of participants, at baseline was similar to that expected for an unaffected population.[30] The study included people with substantial pathological liver damage at baseline, but this was not sufficiently severe to result in significant HRQoL detriment relative to the general population. The CS states that significant HRQoL detriment would be expected with progression to more severe liver disease such as decompensated cirrhosis/liver failure, liver cancer and liver transplantation.[1]

2.3 Current service provision

The CS states that Alexion is not aware of any published NICE, NHS England, other national or expert guidelines for the diagnosis, treatment or management of LALD. It is further stated that clinical guideline from the children's LSD centres in England is currently in draft form and will be submitted to NICE for review.[1] There is currently no standard treatment or typical care pathway for people with LALD. Prior to the development of sebelipase alfa, there were no safe and effective, pharmacological options with regulatory approval for the treatment of LALD.[1] Management options are focussed on supportive care and controlling or treating liver complications and include lipid-lowering therapies, vitamin E supplementation, haemaopoietic stem cell transplantation and liver transplantation.[1] Section 8 of the CS, pages 66 to 73 provides a detailed description of various management options.

2.4 Description of the technology under assessment

2.4.1 Sebelipase alfa

Sebelipase alfa is an enzyme replacement therapy (ERT), which is administered by intravenous infusion. It is a recombinant form of the human LAL enzyme and was developed to treat LALD by replacing the deficient enzyme. Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently taken up by lysosomes,

where it catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Sebelipase alfa is the first pharmacological treatment to undergo regulatory approval specifically for the treatment of LALD.

2.5 Current usage in the NHS

In the UK there is one patient being treated with sebelipase alfa under a compassionate use protocol and 11 patients currently being treated within a clinical trial.[1]

3. CRITIQUE OF THE COMPANY'S INTERPRETATION OF THE DECISION PROBLEM

3.1 Introduction

The remit of this appraisal, as defined in the final agreed NICE scope, is to evaluate the benefits and costs of sebelipase alfa within its marketing authorisation for treating lysosomal acid lipase deficiency for national commissioning by NHS England. The final NICE scope outlines the agreed population, intervention, comparators and outcomes for the appraisal. The NICE scope also sets out wider considerations relating to the impact of the technology beyond direct health benefits and on the delivery of the specialised service, the nature of the condition, costs to the NHS and PSS and value for money.

On 25 June 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Kanuma (sebelipase alfa), intended for the treatment of lysosomal acid lipase (LAL) deficiency. The full indication is: "for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency." It is proposed that Kanuma be prescribed by physicians experienced with the treatment of lysosomal acid lipase (LAL) deficiency, other metabolic disorders or chronic liver disease.

3.2 Adherence to the decision problem

Table 3.1 presents a summary of the decision problem as set out in the NICE scope and the company's adherence to this (based on information presented on pages 25-29 of the CS).

Table 3.1: Adherence of the CS to the agreed decision problem

	Final scope issued by NICE	**Deviations of submission from the scope**
Population	People with lysosomal acid lipase deficiency	The population is in line with scope
Intervention	Sebelipase alfa	The intervention is in line with scope
Comparator(s)	Established clinical practice without sebelipase alfa	The comparator is in line with scope The submitted cost-consequence model compares SA to BSC, in line with the scope. BSC included liver transplant, but other treatment options were not included (see 5.3.2).
Outcomes	The outcome measures to be considered include: • mortality • cholesterol level (total, LDL and HDL) • triglycerides level • transaminase level • liver synthetic function • liver disease progression • liver transplant • liver fat content • cardiovascular events • adverse effects of treatment • health-related quality of life (for patients and carers).	The following outcome measures are not reported: • liver synthetic function, • liver disease progression, • liver transplant, and • cardiovascular events.
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	No variation from final scoping document.
Impact of the new technology	• Clinical effectiveness of the technology • Overall magnitude of health benefits to patients and, when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	No variation from final scoping document.

Cost to the NHS and PSS, and Value for Money	• Budget impact in the NHS and PSS, including patient access agreements (if applicable) • Robustness of costing and budget impact information • Technical efficiency (the incremental benefit of the new technology compared to current treatment) • Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)	The company states that the CS shows no variation from the final scoping document. However, costs falling within PSS have not been included or discussed in the CS.
Impact of the technology beyond direct health benefits, and on the delivery of the specialised 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 • Staffing and infrastructure requirements, including training and planning for expertise.	No variation from final scoping document.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows the following subgroups will be considered • infants with very rapidly progressing lysosomal acid lipase deficiency • people who have had a liver transplant	No subgroup analyses have been undertaken. The company added: "Currently, all patients with LAL deficiency are being considered. Subgroup analysis will not be undertaken." And "No data are available on patients with a liver transplant and therefore this subgroup analysis is not possible."

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The population included in the submission relates to people with lysosomal acid lipase (LAL) deficiency. This is in line with the population in the scope

The studies included in the submission focus on the following populations and studies:

- Paediatric (≤ 2 years) patients with LAL Deficiency: LAL-CL03 (single arm sebelipase alfa study) and LAL-1-NH01 (historical control group)
- Paediatric/adult (≥ 4 years) patients with LAL Deficiency: LAL-CL02 (ARISE, 20 weeks placebo controlled RCT)
- Adults (≥ 18 years) with LAL Deficiency: LAL-CL01 (4 weeks single arm sebelipase alfa study) and LAL-CL04 (156 weeks extension of CL01)

3.3.2 Interventions

The intervention included within the CS relates to sebelipase alfa in line with its licensed indication.

In the CS (page 12 and 31) the recommended dosage regimens of sebelipase alfa are described as: The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL Deficiency is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response. The recommended dose in children and adults who do not present with rapidly progressive LAL Deficiency prior to six months of age is 1 mg/kg administered as an intravenous infusion once every other week. The intervention is expected to be a lifetime therapy.

3.3.3 Comparators

The comparator is described in the CS as Best Supportive Care (BSC). This is in line with the NICE scope which defines the comparator as "established clinical practice without sebelipase alfa".

Data for the comparator were taken from a randomised controlled trial (LAL-CL-02 (ARISE)) for patients aged four years and older with LAL deficiency (N=66, 36 sebelipase alfa and 30 placebo) and from a natural history study including 35 paediatric patients (≤ 2 years) with LAL deficiency (study LAL-1-NH01).

3.3.4 Outcomes

As specified in the Table with the Statement of the decision problem (CS, Table A1.1, page 25), the studies do not provide data on the following outcomes:

- liver synthetic function
- liver disease progression
- liver transplant
- cardiovascular events

This is particularly problematic because liver failure is one of the main manifestations of

LAL Deficiency. As specified in the company submission: "Serious liver complications often develop at an early stage of disease and progress at a faster rate than in most other liver diseases" (CS, page 11). In addition, the CS describes the mechanism of action of sebelipase alfa as follows:

> "Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL). Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Replacement of LAL enzyme activity leads to reductions in liver fat content and transaminases, and enables metabolism of cholesteryl esters and triglycerides in the lysosome, leading to reductions in low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (HDL-c), triglycerides, and increases in HDL-c. Improvement in growth occurs as a result of substrate reduction in the intestine (Kanuma SPC, 2015)." (CS, page 12)

Therefore, only the following outcomes have been reported in the CS:

- mortality
- cholesterol level (total, LDL and HDL)
- triglycerides level
- transaminase level
- liver fat content
- adverse effects of treatment
- health-related quality of life (for patients and carers)

Regarding health-related quality of life, only very small populations were included in the assessment of each instrument, making it impossible to draw strong inferences from the data. In addition, patients in the RCT (LAL-CL02), [redacted]

3.3.5 Cost to the NHS and PSS, and value for money

The CS includes a cost-consequence model in which the primary health outcome is valued in terms of incremental QALYs gained. In general the scope was followed when assessing the costs of sebelipase alfa to the NHS and the value for money it provides.

4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[38] The submission was checked against the interim highly specialised technologies specification for manufacturer/sponsor submission of evidence.[39] The ERG has presented only the major limitations of each search strategy in the main report. Further minor criticisms of each search strategy can be found in Appendix 1.

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on the efficacy and safety of sebelipase alfa. The strategy searched for terms in the intervention facet (sebelipase alfa) only, and did not limit to the LAL Deficiency population.

A good range of resources were searched including: Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, NHS Economic Evaluation Database, MEDLINE and MEDLINE Complete.

The company confirmed in their clarification response[11] that grey literature and conference proceedings were identified through database searches (including PubMed in addition to the databases listed above), reference checking and hand-searching journals publishing conference proceedings. The ClinicalTrials.gov website was also searched. The search terms that were used for grey literature and conference proceedings searches were provided by the company.

No language or date limits were applied. There are minor issues relating to the reporting of the strategy (see Appendix 1), however the database name, database date span, host and date searched were provided for all searches. The searches used indexing terms and free text combined with Boolean logic (AND, OR) and were sufficiently broad to capture all relevant publications on sebelipase alfa. The ERG feels that additional terms such as Kanuma, or the CAS Registry number could have been added to the search, but it is unlikely that relevant records have been missed by not including these terms.

4.1.2 Inclusion criteria

The eligibility criteria for the review are described in Table 4.1 (CS, Table C9.1, page 75 (published studies) and Table C9.2, page 77 (unpublished studies)). The inclusion criteria are broad and aim to include all relevant studies relating to sebelipase alfa.

Table 4.1: Eligibility criteria

Inclusion criteria	
Population	Lysosomal Acid Lipase Deficiency Wolman's disease Cholesteryl Ester Storage disease
Interventions	Sebelipase alfa
Outcomes	Clinical efficacy Disease progression Safety
Study design	Randomised controlled studies, Controlled studies, Observational studies
Language restrictions	No restrictions
Search dates	No restrictions
Exclusion criteria	
Population	No restrictions
Interventions	No restrictions
Outcomes	No restrictions
Study design	Animal Individual case study reports Letters Comment articles
Language restrictions	No restrictions
Search dates	No restrictions

ERG comment:

As can be seen from the table, the search was not aimed at comparator studies. As far as the ERG can see, no searches were done to identify relevant natural history studies. Therefore, the only natural history studies included in the submission are those performed by the company (LAL-1-NH01 and LAL-2-NH01). The ERG is not aware of other relevant natural history studies.

4.1.3 Critique of data extraction

Methods for the systematic review process have not been reported. Therefore, there is no information regarding the number of reviewers involved in the study selection process and the data extraction process. It is common practice in systematic reviews that every step in the review is performed by at least two reviewers to minimise bias and to prevent mistakes. In this case there is no guarantee that the data extraction process was correct.

4.1.4 Quality assessment

There is no information regarding the number of reviewers involved in the quality assessment process.

The randomised controlled trial (study LAL-CL02) was assessed using criteria from CRD guidance (2009).[40] The other two intervention studies (LAL-CL03, and LAL-CL01/04) were assessed using and adapted checklist from the Critical Appraisal Skills Programme (CASP): 'Making sense of evidence, 12 questions to help you make sense of a cohort study'. No references were provided for this instrument. The quality of the natural history study (LAL-1-NH01) was not assessed.

4.1.5 Evidence synthesis

As stated in the CS, no meta-analyses or indirect comparisons were presented (CS, page 134):

> "Due to differences in study methodology and patient demographics, a meta-analysis was not considered to be appropriate. LAL-CL03 is a single arm study in which infants were treated with once weekly doses of sebelipase alfa (0.35 mg/kg escalating to 1mg/kg or 3mg/kg) in contrast to LAL-CL02 which is a randomised study that investigated sebelipase alfa administered at a dose of 1mg/kg every other week in paediatric and adult patients compared to placebo. An indirect comparison was not appropriate or possible since there are no other therapies available to treat LAL Deficiency."

ERG comment:

The ERG agrees with this approach.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The company submission includes four sebelipase alfa studies and one historical control study (See Table 4.2). All studies were performed by Alexion.

Two ongoing unpublished studies, LAL-CL06 and LAL-CL08 were reported in the CS. In addition, Alexion states that "no relevant published studies were excluded" (CS, Section 9.3.2, page 80). However, a second historical control study (LAL-2-NH01) was performed by Alexion which is not included in the submission. This study is mentioned below.

Table 4.2: Studies included in the CS

Study Name (Status)	Study Design	Study Objective(s)	Population	Intervention/ Comparator	Treatment Duration	Data source
LAL-CL03 (Primary analysis complete; Follow-up ongoing)	Phase 2/3, single-arm, open-label	Efficacy, Safety, and PK	Paediatric (≤ 2 years) patients with LAL Deficiency, n=9	Sebelipase alfa: Dose escalation from 0.35 to 1 mg/kg once weekly IV; Up to 3 or 5 mg/kg once weekly IV	Up to 208 weeks	CSR LAL-CL03[41]
LAL-1-NH01 (Historical control group for LAL-CL03, Complete)	Observational, non-interventional	Chart review of children with LAL Deficiency	Paediatric (≤ 2 years), n=35	N/A	N/A	Jones, 2015a[16]
LAL-CL02, ARISE (Double-blind period complete; Open-label period ongoing)	Phase 3, randomised, double-blind, placebo-controlled; followed by open-label extension	Efficacy, Safety, and PK	Paediatric / adult (≥ 4 years) patients with LAL Deficiency, n=66 (36 sebelipase alfa / 30 placebo)	Sebelipase alfa 1 mg/kg every other week IV, Placebo	20 weeks double-blind followed by open-label up to 130 weeks	CSR LAL-CL02; Burton 2015a[30, 42]
LAL-CL01 (Complete)	Phase 1/2, single-arm, open-label, dose escalation	Safety, PK, and PD	Adults (≥ 18 years) with LAL Deficiency, n=9 (3/cohort)	3 cohorts: 0.35, 1, and 3 mg/kg once weekly IV	4 weeks	Balwani, 2013a; CSR LAL-CL01[37, 43]
LAL-CL04 (Enrolment; complete; Follow-up ongoing)	Phase 2, single-arm, open-label extension for patients who completed LAL-CL01	Efficacy and Safety	Adults with LAL Deficiency (≥ 18 years), n=8	Sebelipase alfa: 0.35, 1, or 3 mg/kg, once weekly IV for 4 weeks; 1 or 3 mg/kg once every other week IV	Up to 156 weeks	Balwani, 2013a; CSR LAL-CL04[43, 44]

Source: CS, Table C9.3, page 79

4.2.2 Details of relevant studies not included in the submission

As reported above, two ongoing unpublished studies, LAL-CL06 and LAL-CL08 with expected completion dates of June 2017 and December 2018 respectively, were reported in the CS. The efficacy results from these studies are not included in this submission due to lack of availability, however where possible, available safety data has been included in the submission.

Alexion states that "no relevant published studies were excluded" (CS, Section 9.3.2, page 80). However, a second historical control study (LAL-2-NH01) was performed by Alexion which is not included in the submission. According to Alexion: "This study focused on centres with living patients and, as all patients were alive at the time of data collection, this study provided very little insight into end-stage disease and mortality associated with LAL Deficiency". It is unclear how many of these patients were comparable to any of the patients included in the sebelipase alfa studies.

These three studies are described in Table 4.3

Table 4.3: Studies not included in the CS

Study Name (Status)	Study Design	Study Objective(s)	Population	Sebelipase alfa - Dose	Treatment Duration	Data source
LAL-CL06 (Enrolment complete; Follow-up ongoing)	Phase 2, single-arm, open-label	Efficacy, Safety, and PK	Paediatric / adult (> 8 months) (N=31)	1 mg/kg qow IV	Up to 96 weeks	NR Completion date June 2017
LAL-CL08 (Ongoing)	Phase 2, single-arm, open-label	Efficacy, Safety, and PK	Paediatric (< 8 months) (N=Up to 10 planned)	1 mg/kg qw IV; Up to 3 or 5 mg/kg qw IV	Up to 156 weeks	NR Completion date December 2018
LAL-2-NH01 (Historical control group, Complete)	Observational, non-interventional	Chart review of children with LAL Deficiency	Patients with LAL Deficiency, either alive or deceased, who were ≥ 5 years of age at the time of consent and had a documented diagnosis of LAL Deficiency, n=48 (prospective data for 24)	N/A	N/A	CSR LAL-2-NH0[28]

Source: CS, Table A4.1, page 34 and Section 6, page 47

4.2.3 Summary and critique of company's analysis of validity assessment

The following concerns regarding the quality of study LAL-CL02 were reported in the CS:

- Groups were similar in terms of baseline demographics, onset of LAL Deficiency-related abnormality, serum transaminases, liver fat content and volume and history of lipid-

lowering medication. However, levels of Non-HDL-c and cholesterol were significantly lower in the sebelipase group. HDL-c and LDL-c were not significantly different.

- The analyses did not include an ITT analysis. The Full Analysis Set (FAS) comprised patients in the Consented Set who, in addition, were randomised and received at least one dose of sebelipase alfa or placebo.
- The study included a 20-week double-blind period, which was followed by an open-label period of up to 130 weeks.

Studies LAL-CL03 and LAL-CL01/04 were well performed single arm cohort studies. However, the evidence derived from these studies has severe limitations. The main problem with these studies is the lack of a comparable control group. In the case of study LAL-CL03, the company has used data from a historical group as a control group. In the case of studies LAL-CL01/04, no control group has been provided.

4.3 Summary and critique of results

An overview of the baseline disease characteristics for the patients enrolled in studies LAL-CL03, LAL-CL02 and LAL-CL01 is provided in Table C9.9 of the CS and Table 4.4 below.

According to the company, the infants enrolled in study LAL-CL03 presented with an immediately life-threatening disease requiring urgent medical intervention and that the baseline characteristics for this group are consistent with those reported among the patients in the natural history study LAL-1-NH01, supporting the comparison of survival data and outcomes between the patients in these two studies.

However, the target population for study LAL-CL03 was patients presenting with LAL Deficiency in infancy with evidence of rapidly progressive disease based on documented growth failure within the first six months of life. In the natural history study LAL-1-NH01 growth failure within the first six months of life was not an in- or exclusion criterion. Therefore, a subpopulation of 21 infants from study LAL-1-NH01 with growth failure within the first six months of life based on objective criteria similar to those used in study LAL-CL03 and, like patients in study LAL-CL03, who had not received prior HSCT or liver transplant, was used for the primary comparison. In addition, a subpopulation of 25 infants from study LAL-1-NH01 was used, [redacted] This comparison group was added because [redacted]

Table 4.4: Baseline demographic and disease characteristics

Characteristics	LAL-CL03	LAL-1-NH01	LAL-1-NH01	LAL-1-NH01	LAL-CL02			LAL-CL01
	All (N = 9)	All (n=35)	All (n=21)*	All (n=25)**	All (n=66)	Sebelipase alfa (n=36)	Placebo (n=30)	All (N = 9)
Males, n (%)	5 (56)	19 (54.3)	10 (47.6)	[redacted]	33 (50)	18 (50)	15 (50)	6 (67)
White, n (%)	[redacted]	17 (48.6)	[redacted]	[redacted]	55 (83)	27 (75)	28 (93)	9 (100)
Not Hispanic or Latino, n (%)	[redacted]	26 (74.3)	[redacted]	[redacted]	56 (85)	30 (83)	26 (87)	9 (100)
Age at Onset of LAL Deficiency-related abnormality (years) Mean ± SD (Median)	[redacted]	0.12 ± 0.11 (0.08)	[redacted]	[redacted]	6.5 ± 7.12 (4.0)	7.5 ± 8.36 (5.0)	5.4 ± 5.16 (4.0)	13.1 ± 11.19 (9.8)
Age at Randomisation/First Dose (years) Mean ± SD (Median)	[redacted]	N/A	N/A	N/A	16.1 ± 10.93 (13.0)	16.8 ± 11.52 (13.5)	15.2 ± 10.24 (13.0)	32.2 ± 10.54 (29.9)
Age < 12 years, n (%)	9 (100)	35 (100)	21 (100)	25 (100)	24 (36)	14 (39)	10 (33)	0
Mutation								
Homozygous Common	0	1 (8.3[c])	0 (0)	[redacted]	21 (32)	11 (31)	10 (33)	1 (11)
Heterozygous Common	0	2 (16.7[c])	1 (16.7[c])		35 (53)	17 (47)	18 (60)	8 (89)
Other[b]	6 (100[c])	4 (33.3[c])	0 (0)	[redacted]	10 (15)	8 (22)	2 (7)	0
Baseline transaminases (U/L) Mean ±SD								
ALT	[redacted]	NR	NR	NR	102.4±43.71	105.1±45.31	99.0±42.23	76±29
AST		NR	NR	NR	82.8±34.15	86.6±33.49	78.2±34.93	56±12
Baseline serum lipids (mg/dL) Mean ±SD								
LDLc	[redacted]	NR	NR	NR	207.9±65.85	189.9±57.16	229.5±69.95	144±71
Non-HDL-c	[redacted]	NR	NR	NR	240.2±71.06	220.5±61.48	263.8±75.48	NR
TG	[redacted]	NR	NR	NR	162.6±60.42	174.4±65.90	174.4±65.90	152±79
HDL-c	[redacted]	NR	NR	NR	32.8±7.22	32.4±7.09	33.4±7.46	35±10
Liver fat content (%) at baseline, Mean ±SD	NR	NR	NR	NR	8.50±3.50	8.75±3.95	8.16±2.80	NR
Baseline LLM use, n (%)	NA	NA	NA	NA	26 (39)	15 (42)	11 (37)	7 (78)

Source: CS, Table C9.9, page 93 and Response to Clarification Letter, Question A2

LAL = liposomal acid lipase; SD = standard deviation, NA = not applicable, NR = not reported, U/L = Units per litre

[a] [redacted]; [b] 'Other' mutation: at least one of the alleles has a defined mutation, nether allele has the common mutation; [c] [redacted]) 21 patients from study LAL-1-NH01 (with 'failure to thrive within 1st 6 months based on objective criteria similar to those used in LAL-CL03'); **) 25 patients from study LAL-1-NH01 ('all patients who have not received haematopoietic stem cell transplantation or liver transplant, irrespective of whether these patients met objective criteria for early failure to thrive').

The baseline disease characteristics in children and adults in study LAL-CL02 indicate that LAL Deficiency is a multisystem disease in this population with serious complications, including ongoing liver injury, advanced liver fibrosis and cirrhosis occurring at an early age, and marked disturbances of lipid metabolism.

All studies included patients from the UK. Study LAL-CL03 (N=9) included [redacted] paediatric patients. The natural history study LAL-1-NH01 (N=36) included [redacted]. Study LAL-CL02 (N=66) included [redacted] Study LAL-CL01 (N=9) included [redacted]. A full list of countries in each trial is presented in the Response to the Clarification Letter (Question A5).[11]

4.3.1 Efficacy in paediatric (≤ 2 years) patients with LAL Deficiency

LAL-CL03 was a multicentre, open-label, single-arm study of sebelipase alfa in nine patients with LAL deficiency with growth failure or other evidence of rapidly progressive disease prior to six months of age. Patients also had rapidly progressive liver disease and severe hepatosplenomegaly. The age range at study entry was 1-6 months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first two weeks and then 1 mg/kg once weekly. Based on clinical response, dose escalation to 3 mg/kg once weekly occurred as early as one month and up to 20 months after starting treatment at 1 mg/kg. A further dose escalation to 5 mg/kg once weekly was allowed.

4.3.1.1 Survival

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients in LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics (a subgroup of 21 patients from LAL-1-NH01). In LAL-CL03, 6 of 9 sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, one additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival, 95% CI: 0% to 16%).[10]

[redacted]

ERG comment:

The broader historical control group from study LAL-1-NH01 that included [redacted], seems to be the most comparable control group for the nine patients from study LAL-CL03. However, there is still considerable concern about the comparability of any of the patients in study LAL-1-NH01. Patients in study LAL-CL03 were all born in 2010 or later, while patients enrolled in the historical control study LAL-1-NH01

received a clinical diagnosis of "Wolman disease" between 1985 and 2012.[16] From patients listings provided by the company as part of the Response to Clarification Letter, [redacted]. Of course, it needs to be noted that there are very few data other than weight gain by which the patients in each of these studies can be compared. Nevertheless, on the basis of failure to thrive, the prognosis for patients in study LAL-CL03 appears similar to the prognosis for patients in study LAL-1-NH01 without sebelipase alfa.

Figure 4.1: Monthly weight gain by date of first chart review

[redacted]

4.3.1.2 Liver pathology

Transaminase levels: [redacted]

Liver fat content and liver volume: Liver fat content was not assessed in infants in study LAL-CL03 but liver volume was assessed by ultrasound and/or MRI. [redacted]

Liver histopathology: No liver biopsies were obtained in infants enrolled in study LAL-CL03.

4.3.1.3 Dyslipidaemia

LDL-c levels were shown to [redacted]

A summary of results in paediatric (≤ 2 years) patients with LAL Deficiency is presented in Table 4.5. As can be seen from the results presented above and in the table below, no comparable data were presented for the control group on any of the outcomes other than survival.

Table 4.5: Summary of results for paediatric (≤ 2 years) patients with LAL Deficiency

	Sebelipase Alfa (LAL-CL03, N=9)	Control patients* (LAL-1-NH01, N=21)	Control patients** (LAL-1-NH01, N=25)
Survival beyond 12 months	6 out of 9 (67%, 95% CI: 30% to 93%)	0 out of 21 (0%, 95% CI: 0% to 16%)	[redacted]
Median reduction in ALT levels at 4 weeks	[redacted]	NR	NR
Liver Fat Content	NR	NR	NR
Liver volume	[redacted]	NR	NR
Liver Histopathology	NR	NR	NR

*) 21 patients from study LAL-1-NH01 (with 'failure to thrive within 1st 6 months based on objective criteria similar to those used in LAL-CL03');
**) 25 patients from study LAL-1-NH01 ('all patients who have not received haematopoietic stem cell transplantation or liver transplant, irrespective of whether these patients met objective criteria for early failure to thrive').

4.3.2 Efficacy in Paediatric / adult (≥ 4 years) patients with LAL Deficiency

LAL-CL02 was a multicentre, double-blind, placebo-controlled study in 66 children and adults with LAL deficiency. Patients were randomised to receive sebelipase alfa at a dose of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. The age range at randomisation was 4-58 years old (71% were < 18 years old). For study entry, patients were required to have ALT levels of ≥1.5 X upper limit of normal (ULN). The majority of patients (58%) had LDL-cholesterol > 190 mg/dl at study entry, and 24% of patients with LDL-cholesterol > 190 mg/dl were on lipid lowering medicinal

products. Of the 32 patients who had a liver biopsy at study entry, 100% had fibrosis and 31% had cirrhosis. The age range of patients with biopsy evidence of cirrhosis was 4-21 years old.[10]

The following endpoints were assessed: normalisation of ALT, decrease in LDL-cholesterol, decrease in non-HDL-cholesterol, normalisation of AST, decrease in triglycerides, increase in HDL-cholesterol, decrease in liver fat content assessed by multi-echo gradient echo magnetic resonance imaging (MEGE-MRI), and improvement in hepatic steatosis measured by morphometry.

Transaminase levels: A statistically significant improvement in multiple lipid parameters was observed in the sebelipase alfa-treated group as compared to the placebo group at the completion of the 20-week double-blind period of the study, as shown in Table 4.6. The absolute reduction in mean ALT level was -57.9 U/l [redacted] in the sebelipase alfa-treated group and -6.7 U/l (-6%) in the placebo group.

Open-label period
Sixty-five of 66 patients entered the open-label period (up to 130 weeks) at a sebelipase alfa dose of 1 mg/kg once every other week. In patients who had received sebelipase alfa during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels. [redacted]

Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period. Consistent with what was observed in sebelipase alfa-treated patients during the double-blind period, initiation of treatment with sebelipase alfa during the open-label period produced rapid improvements in ALT levels and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Liver endpoints were provided in the company's response to the clarification letter[11] and have been added to Table 4.6. As explained by the company, meaningful interpretation of the outcomes related to liver disease progression at baseline and subsequent follow-up biopsies is challenging because of the short follow-up, small sample size and sampling variability in liver biopsies.

Table 4.6: Summary of primary and secondary efficacy endpoints (Study LAL-CL02)

Endpoint, Statistic	Population	Seb. alfa (N = 36)	Placebo (N = 30)	Difference (p-value)[a]
PRIMARY ENDPOINT:				
Normalisation of ALT, % (n/N)[c]	All, N = 66	31% (11/36)	7% (2/30)	24% (0.0271)
SECONDARY ENDPOINTS:				
Relative reduction in LDL-c, Mean (SD)[d]	All, N = 66	-28% (22.3)	-6% (13.0)	-22% (<0.0001)
Relative reduction in Non-HDL-c , Mean (SD)[d]	All, N = 66	-28% (18.6)	-7% (10.9)	-21% (<0.0001)
Normalisation of AST, % (n/N)[e]	Abnormal at Baseline, N = 65	42% (15/36)	3% (1/29)	39% (0.0003)
Relative reduction in triglyceride, Mean (SD)[d]	All, N = 66	-25% (29.4)	-11% (28.8)	-14% (0.0375)
Relative increase in HDL-c, Mean (SD)[d]	All, N = 66	20% (16.8)	-0.3% (12.3)	20% (<0.0001)
LIVER ENDPOINTS:				
Number of patients with confirmed cirrhosis at baseline / week 20: - No CC - CC	[redacted]	[redacted]	[redacted]	
Number of patients with Ishak score progression at week 20 compared to baseline (%): - Same - Improved - Worsened	[redacted]	[redacted]	[redacted]	

Source: CS, Table C9.11, page 107 and EMA EPAR[10], Table 3
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CC = confirmed cirrhosis; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; MRI = magnetic resonance imaging; SD = standard deviation; ULN = upper limit of normal
[a] p-value for treatment differences (Fisher's exact test for normalisation and liver histology endpoints and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of patients who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the patient was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of patients who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).

Liver fat content and liver volume: The percent reduction in hepatic fat content from Baseline to the end of the double-blind treatment period as assessed by MEGE-MRI was significantly greater for sebelipase alfa treated patients (32%) compared with those who received placebo (4%) ($p < 0.0001$) (Table 4.7). The percent reduction from Baseline in liver volume based on MRI also was greater in the sebelipase alfa group (10%) compared with placebo (3%) ($p = 0.0068$).

Table 4.7: Summary of secondary efficacy endpoints (Study LAL-CL02)

Endpoint, Statistic	Population	Seb. alfa (N = 36)	Placebo (N = 30)	Difference (p-value)[a]
SECONDARY ENDPOINTS:				
Relative reduction in liver fat content, Mean (SD)[d]	MRI Eligible[f] (N = 57)	-32% (26.8)	-4% (15.6)	-28% (<0.0001)
Improvement in liver histopathology, % (n/N)[g]	Consent to Biopsy[h] (N = 26)	63% (10/16)	40% (4/10)	23% (0.4216)
Relative reduction in liver volume, Mean (SD)	MRI Eligible[f] (N = 60)	-10% (10.5)	-3% (10.1)	-8% (0.0068)

Source: CS, Table C9.11, page 107 and EMA EPAR[10], Table 3
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; MRI = magnetic resonance imaging; SD = standard deviation; ULN = upper limit of normal
[a] p-value for treatment differences (Fisher's exact test for normalisation and liver histology endpoints and Wilcoxon rank sum test for all other endpoints).
[d] Presented as mean percentage change from Baseline.
[f] Abdominal MRI was required for all patients except 1) those with internal or otherwise non-removable metal medical items and 2) children for whom sedation was required but medically contraindicated. Multi-echo gradient echo assessments of liver fat content were not required in children who could not hold their breath for 15-30 seconds.
[g] The primary disease-specific histopathological assessment was steatosis as measured by morphometry. Proportion of patients with improvement of ≥ 5% in steatosis score over Baseline is presented.
[h] For patients ≥ 18 years of age, biopsies were required unless medically contraindicated. Biopsies were optional for patients < 18 years of age

Liver histopathology: Paired liver biopsies at baseline and week 20 were available in a subset of patients (n=26). Of patients with paired liver biopsies, 63% (10/16) of sebelipase alfa-treated patients had improvement in hepatic steatosis (at least ≥ 5% reduction) as measured by morphometry compared to 40% (4/10) of placebo patients. This difference was not statistically significant (Table 4.7).

4.3.3 Efficacy in adults (≥ 18 years) with LAL Deficiency

LAL-CL01 was a multicentre, open-label, dose-escalation study of sebelipase alfa in nine adult patients with LAL deficiency. The study was primarily designed to investigate the safety and tolerability of sebelipase alfa. No active or placebo control was included. The mean age at study entry was 32.2 years (SD: 10.54). Patients were allocated to one of three dose cohorts (three patients per cohort at 0.35, 1.0 and 3.0 mg/kg); all nine patients completed the study receiving four infusions of sebelipase alfa once weekly. Eight patients from LAL-CL01 entered the extension (up to 156 weeks) study LAL-CL04 between nine and 28 weeks after their last dose of sebelipase alfa in study LAL-CL01.

4.3.3.1 Liver pathology

Transaminase levels: Changes in serum transaminase levels observed in adults in study LAL-CL01 were consistent with those reported in study LAL-CL02 and were maintained over long-treatment during the extension study LAL-CL04.

Initiation of treatment with sebelipase alfa in study LAL-CL01 produced a rapid decline in ALT and AST (CS, Figure C9.6, page 110). When patients went off treatment at the end of study LAL-CL01 (interval between dosing of nine to 28 weeks), both ALT and AST

increased. Normalisation of transaminase levels continued during long-term treatment (through Week 104) in the extension study LAL-CL04.

Liver fat content and liver volume: Reduction in hepatic fat and liver volume was observed during long-term treatment with sebelipase alfa in study LAL-CL04. Although data are limited, mean liver fat content at Baseline in study LAL-CL04 was 9.16% (n=5) with a mean reduction in fat fraction of 37% (n=4) at Week 52 and 39% at Week 104 (n=2). Mean Baseline liver volume was 1.05 multiples of normal (MN) (n=8) with mean absolute decreases from Baseline of 0.10 (n=7) and 0.18 (n=5) at Weeks 52 and 104 respectively.

Liver histopathology: In study LAL-CL04, pathology reports of post-treatment liver biopsies as well as historical pre-treatment biopsies were available from two patients. In these cases, pathology reports suggested that histopathological improvements were observed following extended treatment with sebelipase alfa in steatosis and fibrosis, although biopsies were not evaluated in a central laboratory.

4.3.3.2 Dyslipidaemia

In adults in study LAL-CL01, more substantial increases were noted for cholesterol and triglycerides during the initial four week treatment period (CS, Figure C9.9, page 116). This was observed following the initial four weekly infusions in study LAL-CL04 as patients who entered the extension study had been off treatment with sebelipase alfa ranging from nine to 28 weeks. These increases were higher in studies LAL-CL01/LAL-CL04 than those observed in study LAL-CL02; this difference may be due either to the more frequent dosing interval or more frequent assessments conducted in the earlier studies. By Week 104, all seven patients in study LAL-CL04 with data available at the time of the data cut-off showed decreases from their original study LAL-CL01 Baseline values in LDL-c and most had increases in HDL-c and decreases in triglycerides.

4.3.4 Health related quality of life

Patients enrolled in LAL-CL02 reported HRQoL at baseline that suggested [redacted]

Chronic Liver Disease Questionnaire (CLDQ): The CLDQ is a disease-specific instrument designed to assess health-related HRQoL in patients with chronic liver disease.[45] In LAL-CL02, the CLDQ was self -administered to all patients who were ≥17 years of age on the date of informed consent. The CLDQ has 29 items with a range of scores from one (worst possible function) to seven (best possible function); higher values indicate better HRQoL.

[redacted]

[redacted]

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue): The 13-item FACIT-Fatigue scale was developed to measure levels of fatigue in people living with a chronic disease. In this study, the FACIT-Fatigue scale version four was self-administered by all patients who were ≥17 years of age at date of informed consent. The FACIT-Fatigue total score ranges from 0 to 52. A score of <30 indicates severe fatigue. A higher value indicates a better HRQoL. The FACIT-Fatigue total score could only be calculated if more than 50% of the items were answered (a minimum of 7 of 13 items).[46]

[redacted]

Pediatric Quality of Life Inventory (PedsQL): The PedsQL is composed of generic core scales and disease-specific modules. The 23 item PedsQL 4.0 Generic Core Scales was designed to measure the core dimensions of health, as delineated by the World Health Organisation (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). In addition to the total scale score (all 23 items), two summary scores, the Physical Health Summary (eight items) and Psychosocial Health Summary (15 items), were also reported. In this study, the PedsQL 4.0 Generic Core Scales were self-administered by patients who were five to <18 years of age on the date of informed consent, using one of the three self-report forms (ages 5-7, 8-12, or 13-18), as appropriate to the patient's age.[47] Parent proxy reports were not used in this study. The minimal clinically important difference is 4.4.[48]

[redacted]

As full results for health related quality of life (HRQoL) from LAL-CL02 were not reported in the company submission, the ERG asked the company to complete the table below (Table

4.8). Results show that none of the differences between groups were statistically significant, which was expected given the [redacted] baseline scores suggesting [redacted]

Table 4.8: Health related quality of life outcomes from LAL-CL02

	Sebelipase Alfa						**Placebo**						**Difference**	
	Baseline			**Follow-up (20 wks)**			**Baseline**			**Follow-up (20 wks)**				
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	Mean	p-value
CLDQ														
AB														
AC														
EM														
FA														
SY														
WO														
FACIT Fatigue														
PedsQL														
PH														
PSY														
PHY														
ES														
SF														
SCH														

CLDQ Subscales: AB=Abdominal Activity, AC=Activity, EM=Emotional Function, FA=Fatigue, SY=Systemic Symptoms, WO=Worry
PedsQL Subscales: PH=Physical Health, PSY=Psychosocial Health, PHY=Physical Score, ES=Emotional Score, SF=Social Functioning, SCH=School Functioning
Difference: Difference between the mean change of sebelipase alfa – Placebo; p-value: Wilcoxon rank sum test for treatment differences.

4.3.5 Safety and tolerability

According to the EMA EPAR[10] the most serious adverse reactions, experienced by 3% of patients taking sebelipase alfa in clinical studies, were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

In addition, EMA provided data describing adverse reactions reported in infants who received sebelipase alfa in clinical studies at doses up to 3 mg/kg weekly (Table 4.9) and adverse reactions reported in children and adults who received sebelipase alfa in clinical studies at a dose of 1 mg/kg once every other week (Table 4.10). Adverse reactions are listed by System Organ Class and frequency. Frequencies are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4.9: Adverse reactions reported in infants[c] receiving sebelipase alfa

MedDRA System organ class	Frequency[a]	MedDRA preferred term
Immune system disorders	Very common	Eyelid oedema
Psychiatric disorders	Very common	Agitation[b], irritability[b]
Nervous system disorders	Very common	Hypotonia
Cardiac disorders	Very common	Tachycardia[b]
Vascular disorders	Very common	Hypertension, pallor[b]
Respiratory, thoracic and mediastinal disorders	Very common	Respiratory distress, wheezing, cough, rhinitis, nasal congestion, sneezing
Gastrointestinal disorders	Very common	Diarrhoea, gastro-oesophageal reflux disease, retching, vomiting[b]
Skin and subcutaneous tissue disorders	Very common	Urticaria[b], rash[b], eczema[b], pruritis, rash maculo-papular
General disorders and administration site conditions	Very common	Chills, hyperthermia, pyrexia[b], oedema
Investigations	Very common	Body temperature increased, oxygen saturation decreased, blood pressure increased, heart rate increased, respiratory rate increased

Source: EMA EPAR[10]
a Very common = Reported in ≥ 1 patient receiving sebelipase alfa
b Reported in ≥ 2 patients receiving sebelipase alfa
c Age at first dose: 1 to 6 months

Table 4.10: Adverse reactions reported in children and adults[d] receiving sebelipase alfa

MedDRA System organ class	Frequency[a]	MedDRA preferred term
Infections and infestations	Common	Urinary tract infection
Immune system disorders	Common	Anaphylactic reaction, eyelid oedema
Metabolism and nutrition disorders	Common	Transient hypercholesterolaemia, transient hypertriglyceridaemia
Psychiatric disorders	Common	Anxiety[c], insomnia
Nervous system disorders	Common	Dizziness
Cardiac disorders	Common	Tachycardia
Vascular disorders	Common	Hyperaemia[e], hypotension
Respiratory, thoracic and mediastinal disorders	Common	Laryngeal oedema[e], dyspnoea[b,c,e]
Gastrointestinal disorders	Common	Diarrhoea[b,e], abdominal pain[b,e], abdominal distension, nausea[b,e]
Skin and subcutaneous tissue disorders	Common	Urticaria, rash[c,e] (including rash papular and rash pruritic), pruritus, eczema[e]
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Common	Chills, chest discomfort[c,e], oedema, fatigue, infusion site induration, pyrexia
Investigations	Common	Body temperature increased[b,c]
Injury, poisoning and procedural complications	Common	Infusion related reaction[c]

Source: EMA EPAR[10]

a Common = Reported in ≥ 1 patient receiving sebelipase alfa

b Reported at the same frequency in patients receiving sebelipase alfa or placebo or more frequently in patients receiving placebo during the double-blind period of LAL-CL02

c Reported as part of an adverse reaction in a single patient receiving sebelipase alfa in LAL-CL02

d Age at first dose: 4 to 58 years

e Reported in ≥ 2 patients receiving sebelipase alfa

Adverse events as reported in the CS are as follows:

Common adverse events in infants: [redacted] enrolled in study LAL-CL03 reported at least one treatment emergent adverse event (TEAE). Table 4.11 presents the most commonly reported TEAEs during study LAL-CL03, i.e., those events reported in three or more patients. This cut-off point was chosen based on the small sample size for this study (N=9).

[redacted]

Table 4.11: Summary of treatment-emergent adverse events, regardless of causality, occurring in three or more patients (Study LAL-CL03, safety population)

MedDRA System Organ Class Preferred Term	Patients (N=9) n (%)
[redacted]	[redacted]
[redacted]	
Vomiting	6 (67)
Diarrhoea	6 (67)
Skin and subcutaneous tissue disorders	
[redacted]	[redacted]
Urticaria	3 (33)
Infections and infestations	
Rhinitis	5 (56)
Catheter site or Device related infection[a]	3 (33)
Nasopharyngitis	3 (33)
[redacted]	[redacted]
Blood and lymphatic system disorders	
Anaemia	4 (44)
Respiratory, thoracic and mediastinal disorders	
Cough	3 (33)

Source: CS, Table C9.12, page 126

a Combined preferred terms; patients who reported more than 1 event coded to these terms are counted only once.

Common adverse events in children and adults: In study LAL-CL02, 86% (31 of 36) of patients in the sebelipase alfa group and 93% (28 of 30) of patients in the placebo group reported at least one TEAE during the double-blind period. The most common (≥10% incidence) TEAEs reported during the double-blind period in the sebelipase alfa group with corresponding incidence in the placebo group were headache (28% and 20%, respectively), pyrexia/body temperature increased (25% and 23%, respectively), upper respiratory infection (17% and 20%, respectively), diarrhoea (17% in each group), oropharyngeal pain (17% and 3%, respectively), epistaxis (11% and 20%, respectively), and nasopharyngitis (11% and 10%, respectively) (Table 4.12).

In study LAL-CL02, treatment-related AEs were reported in five patients (14%) in the sebelipase alfa group and six patients (20%) in the placebo group during the double-blind

period. All treatment-related TEAEs (by preferred term) in the sebelipase alfa group were reported in only one patient.

Table 4.12: Summary of treatment-emergent adverse events, regardless of causality, occurring in three or more sebelipase alfa-treated patients, by treatment group (Study LAL-CL02, FAS, double-blind treatment period)

MedDRA System Organ Class Preferred Term	**Seb. Alfa (N = 36) n (%)**	**Placebo (N = 30) n (%)**
Any treatment-emergent adverse event	*31 (86)*	*28 (93)*
Nervous system disorders		
Headache	10 (28)	6 (20)
General disorders and administration site conditions		
Pyrexia/Body temperature increased[a]	9 (25)	7 (23)
Asthenia	3 (8)	1 (3)
Gastrointestinal disorders		
Diarrhoea	6 (17)	5 (17)
Abdominal pain, including upper and lower[a]	4 (11)	4 (13)
Constipation	3 (8)	1 (3)
Nausea	3 (8)	2 (7)
Vomiting	3 (8)	3 (10)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	6 (17)	1 (3)
Epistaxis	4 (11)	6 (20)
Cough	3 (8)	3 (10)
Infections and infestations		
Upper respiratory tract infection	6 (17)	6 (20)
Nasopharyngitis	4 (11)	3 (10)

Source: CS, Table C9.13, page 127

a Combined preferred terms; patients who reported more than 1 event coded to these terms are counted only once.

Deaths and serious adverse events: Overall, three deaths were reported in the sebelipase alfa clinical programme as of the data cut-off across the four primary studies evaluating safety; all patients who died were enrolled in study LAL-CL03. All fatal events were assessed as unrelated to sebelipase alfa treatment by the investigators. All deaths occurred after receiving four or fewer doses of sebelipase alfa with a median age at death of 2.9 years.

Since the conduct of the integrated analyses through the cut-off date for late-breaking safety information (08 Sep 2014), [redacted]

Serious AEs were reported in 12 (14.3%) of the 84 patients in the pooled safety set. SAEs were more frequent among infants in study LAL-CL03 with the most rapidly progressive form of LAL Deficiency (eight of nine patients, 89%) and were relatively infrequent among children and adults (4 of 75 patients, 5%). The most commonly reported types of SAEs were

infections (5 of 84 patients, 6%). One patient in study LAL-CL02 reported a serious infection (gastroenteritis). The only other SAE reported in more than one patient in the pooled safety set was pyrexia, reported in two patients in study LAL-CL03.

The majority of SAEs were assessed by the Investigator as unrelated to study treatment; two of 84 patients in the pooled safety set reported treatment-related SAEs, which were also considered potential hypersensitivity reactions, including one patient each in Studies LAL-CL02 and LAL-CL03; in addition, two patients in study LAL-CL08 had treatment-related SAEs which were also considered potential hypersensitivity reactions.

4.4 Summary of evidence presented in other submissions

No other scientific evidence was submitted by other consultees. This ERG report does not include a detailed discussion of non-scientific opinion submitted by other consultees or expert testimony provided by other consultees to the appraisal process; however, some of this information has been used to inform the discussion sections of this report. The following submissions were made to NICE:

- Birmingham Children's Hospital
- The Society for Mucopolysaccharide and Related Diseases (MPS Society)
- British Inherited Metabolic Disease Group and University College London Hospitals
- Royal College of Pathologists and Cambridge University Hospitals
- Salford Royal Hospital NHS Foundation Trust
- Consultant in Paediatric Metabolic Medicine, CMFT – Willink Unit
- NHS England

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work on clinical effectiveness undertaken by the ERG has been included in Section 4.3 of this report. No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The ERG is confident that all relevant studies (published and unpublished) of sebelipase alfa were included in the CS, including data from ongoing extension studies. Regarding historical control patients, two studies were available, but only results from one of these (LAL-1-NH01) were fully included in the submission. However, the clinical study report for the other historical control study (LAL-2-NH01) was part of the additional papers provided by the company. As described in Section 4.1.2, no searches were done to identify relevant LALD studies without the intervention. Therefore, there could be other, possibly better, natural history studies that were not included in the submission.

Several outcomes reported in the NICE final scope have not been assessed in the included studies, i.e. liver synthetic function, liver disease progression, liver transplant, and cardiovascular events. Instead, surrogate outcomes were used in the trials. These surrogate outcomes suggest a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. However, there is no evidence to address key clinical endpoints, such as

progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death. There is also no evidence to address long-term effectiveness of sebelipase alfa. Although, there is considerable follow-up in some of the sebelipase alfa studies, with nine patients having received sebelipase alfa treatment for up to 208 weeks and eight patients receiving up to 156 weeks of treatment, this is only a fraction of the expected lifetime treatment with sebelipase alfa. Therefore, the long-term safety and efficacy profile of sebelipase alfa remains uncertain.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

Evidence is presented for three populations:

- Paediatric (≤ 2 years) patients: a single arm study (N=9) with a historical control group (N=35, although only 25 comparable controls in terms of inclusion criteria). Only survival was reported for the control group; however, results seem biased in favour of sebelipase alfa due to differences in date of first diagnosis between experimental and control patients.
- Paediatric/adult (≥ 4 years) patients: a randomised placebo-controlled trial (N=66, 36SA/30PLA), which shows that "sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in children and adults with lysosomal acid lipase deficiency".[42] However, no comparative evidence was presented showing any improvements in clinical outcomes, including liver function, and quality of life.
- Adult (≥ 18 years) patients: a single arm study (N=9) without any control group.

Overall, there is no reliable comparative evidence showing any improvements in clinical outcomes, including survival, liver function, and quality of life; in addition, the long-term safety and efficacy profile of sebelipase alfa is uncertain.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The main uncertainty regarding the effectiveness evidence is the comparability of baseline characteristics from treated patients and historical control patients, the use of surrogate outcomes and the lack of long-term follow-up.

[redacted], while all nine patients included in LAL-CL03 were diagnosed after 2010. Given the likely improvements in supportive care over time, results from comparisons between treated patients (LAL-CL03) and historical control patients (LAL-1-NH01) may be biased in favour of sebelipase alfa.

Surrogate outcomes showed a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. These outcomes, on well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition. However, there is no evidence to address long-term and key clinical endpoints (progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death).

One of the most important outcomes is slowing the progression of the liver disease and hence delaying or avoiding liver transplant. The duration of trials providing data presented in the submission was not long enough to look at this outcome.

There is no mention in the CS of possible stopping rules for sebelipase alfa. In fact the company assumes treatment will be for the full lifetime of the patient (CS, Section 2.3, page 31). However, given the many differences between patients it cannot be assumed that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

This chapter is aimed to provide an assessment of whether or not sebelipase alfa for LAL Deficiency represents value for money for the NHS in England. The main source of evidence used to inform this assessment is the CS[1] to NICE, which includes a cost-consequence model and description of the methods and results of an economic analysis using the submitted model. This chapter first looks at a review of existing economic analyses for sebelipase alfa. This is followed by a detailed exposition and critique of the submitted model and accompanying economic analysis. Due to the concerns of the ERG with respect to the credibility of the submitted model, Chapter 6 includes exploratory analyses undertaken using an alternative model developed by the ERG. This analysis is in line with the company's choices regarding the use of evidence sources, assumptions and general model structure as much as possible. However inconsistencies and restrictive assumptions within the company's model are adjusted with the intention of providing a more robust basis for informing decision-making.

5.2 Review of existing economic analyses

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on quality of life, cost effectiveness and resource data for patients with LAL Deficiency or provide utilities, resource use or cost data for the economic model. The strategy searched for terms in the population facet (LAL Deficiency, including Wolman disease and cholesterol ester storage disease phenotypes), and did not limit to intervention (sebelipase alfa). The population terms were combined with study design filters for cost effectiveness, resource use and quality of life in a single search each for the Ovid and EBSCO hosts.

A good range of resources were searched including: Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, NHS Economic Evaluation Database, MEDLINE, MEDLINE Complete and EconLit.

The company confirmed in their clarification response[11] that conference proceedings were identified through the database searches and hand-searching conference proceedings.

No language or date limits were applied. The searches were clearly reported and reproducible, and the database name, database date span, host and date searched were provided for all searches. The searches were clearly structured, and used indexing terms and free text combined with Boolean logic (AND, OR).

ERG comment:

The ERG notes that one limitation of the search is that all Ovid databases were searched in one single strategy, and that only indexing terms for the Embase database (EMTREE) appear to have been used for the study design filters. The omission of Medline indexing terms (MeSH) could have resulted in potentially relevant records being omitted from the search results. The ERG also has concerns regarding the sensitivity of the search terms for resource use and HRQoL, and expansion of these elements of the search could have made them more

sensitive, for example with the use of additional indexing terms, and truncation to retrieve spelling variants/pluralisation. Given the small number of records retrieved by the LAL Deficiency facet, an alternative approach would have been to not apply study design filters. Further details are provided in Appendix 1.

The company focused the search strategy on LAL Deficiency only, while it aimed to identify all economic studies that could be used to inform the design of the economic model or provide utilities, resource use or cost data for the economic model. For this purpose the ERG feels a broader definition of the population would have been useful, in particular including non-alcoholic steatohepatitis (NASH), which was mentioned by the company as the appropriate disease analogue for modelling LAL Deficiency. Moreover, the company used an adapted version of the cost-effectiveness analyses by Mahady et al[49] which considered NASH patients (see also Section 5.3.2). Therefore, the ERG performed an additional search strategy to identify any economic studies, health state utility data, resource use data and cost data for NASH patients. The electronic databases MEDLINE and Embase (Ovid host) were searched, and after deduplication a total of 320 records were found and screened by the ERG. Further details are provided in Appendix 1.

In addition to the cost-effectiveness study by Mahady et al[2, 49] used by the company, this search query identified two additional potentially relevant cost-effectiveness studies. The study by Scaglione et al[50] was a conference proceeding only and did not contain sufficient detail to be used as a starting point to build a new model. The study by Zhang et al[51, 52] assessed the cost-effectiveness of screening strategies for NAFLD and could have been used as an alternative starting point to develop a model by the company (removing the screening part of the model).

The additional search did not identify any relevant health state utility data, resource use data nor cost data for LAL Deficiency patients that could have been used in the cost-consequence analysis.

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

The company's submission to NICE presents a model-based cost-consequence analysis for sebelipase alfa versus BSC for the treatment of patients with LAL Deficiency. The analysis is performed using NHS perspective. Potential costs which may fall under PSS are not reported. Costs and consequences are estimated for a population of 11 years-old over a lifetime horizon by extrapolation of health outcomes and costs of the hypothetical model cohort up to age 101, at which 99.9% of the hypothetical population has died. The primary model outcomes are the estimated incremental QALYs and incremental costs obtained by comparing the use sebelipase alfa with BSC. The company's model also estimates survival, which is used to estimate the QALYs for both arms. Adverse events were not included in the cost-consequence analysis. Health outcomes and costs are both discounted at a rate of 1.5%.

Patients receiving sebelipase alfa will remain on sebelipase alfa treatment for their entire lives, since in the sebelipase alfa group it is not possible in the model to progress to a worse health state and possibly receive other treatment. In the BSC group, the only treatment option

is a liver transplant, which is offered to patients that have progressed to "HCC". Hence, within the BSC group, any drug costs for BSC were not incorporated into the model, however other components of BSC, such as hospitalisations, were incorporated as background healthcare resource use costs, and estimated separately for infants.

ERG comment:

A few variations exist from the final scope issued by NICE in the submission. For instance, cardiovascular events and adverse events of sebelipase alfa treatment were in the final NICE scope, but were not included in the cost-consequence analysis. These issues are further discussed in Section 5.3.2. Other issues and adherence of the CS to the reference case principles can be seen in Table 5.1 below.

Table 5.1: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE	The scope of the economic analysis is generally in line with the scope developed by NICE. Adverse events and cardiovascular events, however, have not been incorporated (see 5.3.2).
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	The submitted cost-consequence model compares sebelipase alfa to BSC, in line with the scope. BSC included liver transplant, but other treatment options were not included (see 5.3.2).
Perspective on costs	NHS and PSS	The company states that the CS shows no variation from the final scoping document. However, costs falling within PSS have not been reported in the CS.
Perspective on outcomes	All health effects on individuals	Patient health benefits are included.
Type of economic evaluation	Cost-effectiveness analysis*	Incremental costs and benefits are assessed in the form of a QALY-based cost-consequence analysis.
Synthesis of evidence on outcomes	Based on a systematic review	Unclear whether appropriate sources were used (see 5.2 & 5.3.3).
Measure of health effects	QALYs	Health outcomes are valued in terms of QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Unclear whether appropriate sources were used (see 5.2 & 5.3.3.6).
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	Costs and outcomes were discounted at 1.5%.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to QALY gains.

**Not stated within the current HST methods guide*

5.3.2 Model structure

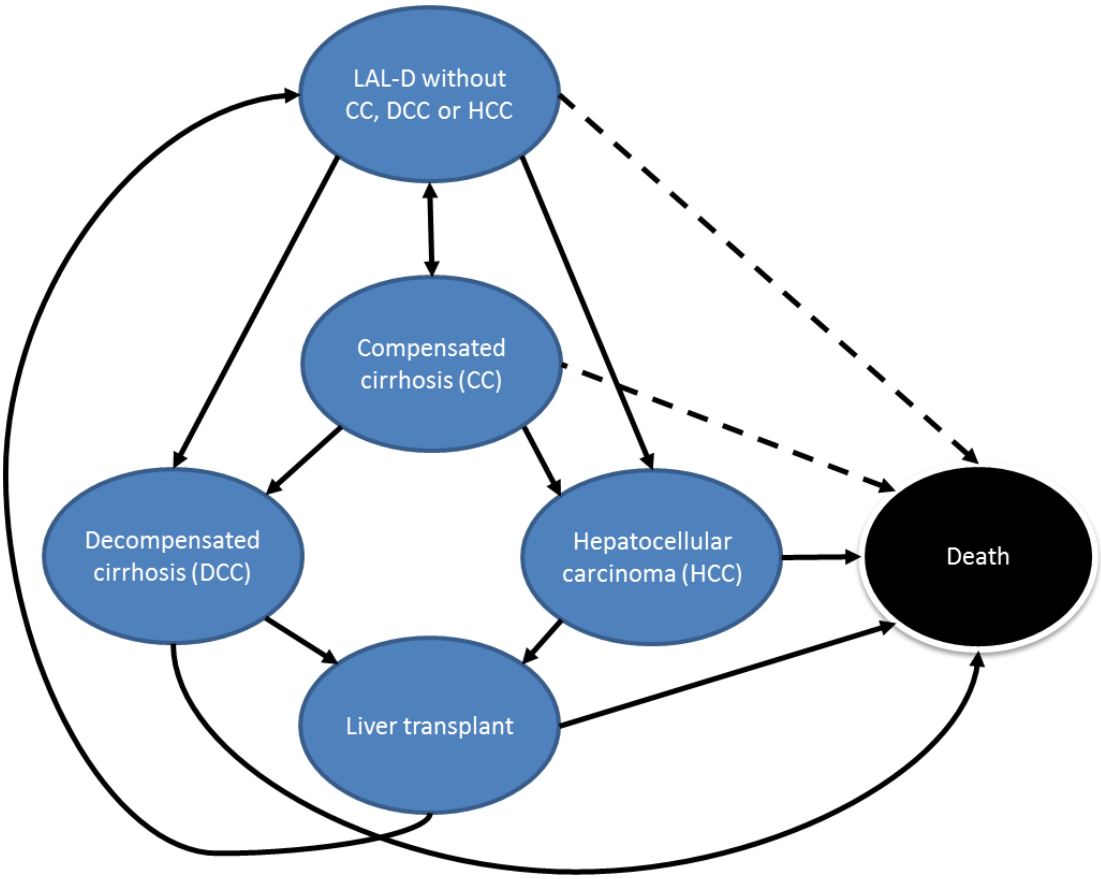
A decision-analytic Markov model was developed in Excel to perform the cost-consequence analyses of sebelipase alfa compared to BSC in LAL Deficiency patients by adapting a model for non-alcoholic fatty liver disease (NAFLD) published by Mahady et al (2012).[2] The CS stated that "NAFLD/NASH (non-alcoholic stepatohepatitis) is the closest disease analogue to LAL-D", which was justified based on clinical opinion of one expert (CS Table D12.1). The model aims to simulate the disease progression of LAL deficiency in both patient groups through liver disease progression, which is the primary manifestation of disease in LAL deficiency patients. Cardiovascular, gastrointestinal and other manifestations that commonly occur in patients with LAL deficiency are not included. Progression of liver disease over time, for patients receiving sebelipase alfa, is calculated based on the LAL-CL02 trial data,[4] whereas for BSC progression is derived from literature.[2] The impact of the disease is translated to costs, survival, and HRQoL via the submitted cost-consequence model.

The model consists of four health states representing different stages of liver disease progression; compensated cirrhosis ("CC"), decompensated cirrhosis ("DCC"), hepatocellular carcinoma ("HCC"), and "LALD without CC, DCC, or HCC". Furthermore, it includes a liver transplant state and a death state. These stages of liver disease are based on the proxy model by Mahady et al,[2] which is consistent with the stages of other liver disease progression models in the literature.[3, 5, 53-55]

Liver transplantation is included as a tunnel state, representing the patients in the "DCC" and "HCC" state that receive a liver transplant and corresponding health utility decrements and additional costs. After liver transplantation these patients automatically transition back to the "LALD without CC, DCC or HCC" health state, with the justification that the underlying disease is not cured and progression can again occur. "Death" is represented by one absorbing state while patients can transfer to this state through background mortality in each health state. Moreover, excess mortality is added for the "DCC", "HCC" and "Liver transplant" states. In the infant scenario, only two health states were used "Alive" and "Death".

Figure 5.1 provides the graphical presentation of the model as reported in the CS (CS Fig D12.1), where the dashed arrows are only possible for infants (age <1 year) and reflect potential for death within first year of diagnosis in patients with infant-onset disease.

Figure 5.1: Model structure as provided by the company



Apart from background mortality, transitions between the health states are not age-dependent. Age-gender specific background death risks are estimated from UK life tables.[56] Liver transplant mortality rates, as well as rates for "DCC" and "HCC" mortality, are obtained from the proxy model by Mahady and other literature.[2, 5] For the sebelipase alfa group, transition probabilities between the liver disease states are estimated from the LAL-CL02 data,[4] whereas for the BSC group they are mostly obtained from the proxy model.[2] Derivation of the "Liver transplant", "DCC", and "HCC" mortality risks and transitions between the "Alive" health states will be further explained in Section 5.3.3.

The model has a lifetime time horizon and adopted NHS perspective. A cycle length of one year was used. The model employs a half-cycle correction. A discount rate of 1.5% per year for health effects and costs was used. In the base case, a starting age of 11 and an initial liver disease distribution of (84%; 16%; 0%; 0%) for ("LALD without CC, DCC, or HCC"; "CC"; "DCC"; "HCC) was used based on the LAL-CL02 data.[4]

In the infant scenario, the starting age is 0 and all infants start in an "Alive" state, based on the LAL-1-NH01 study[6] and the LAL-CL03 study[7].

ERG comment:
Given the differences in assumptions between the comparators (e.g. some transitions are assumed to be absent for sebelipase alfa), the model structure differs largely between the sebelipase alfa and BSC group, as well as between the base case and the infants scenario. This is not clear from Figure 5.1, which is also missing the transition between the "DCC" and

"HCC" state. Therefore, the model structures for the sebelipase alfa and BSC group in the base scenario, as well as the infants scenario, are displayed in Figure 5.2 and Figure 5.3, respectively. Arrows to the "Death" state represent excess mortality. For infants in the sebelipase alfa group, the dashed arrow represents the transition for those surviving the first year to the "LALD without CC, DCC, or HCC" state, in which they then remain according to the base case scenario.

Figure 5.2: Model structure as provided by the ERG for the base case scenario

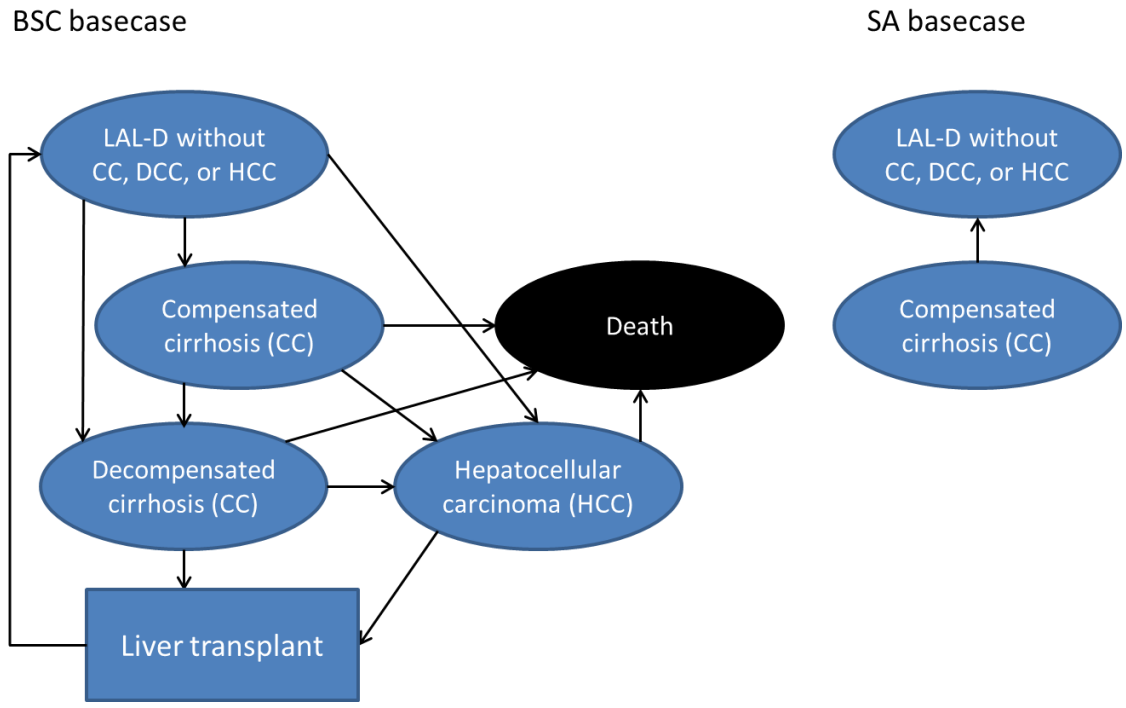
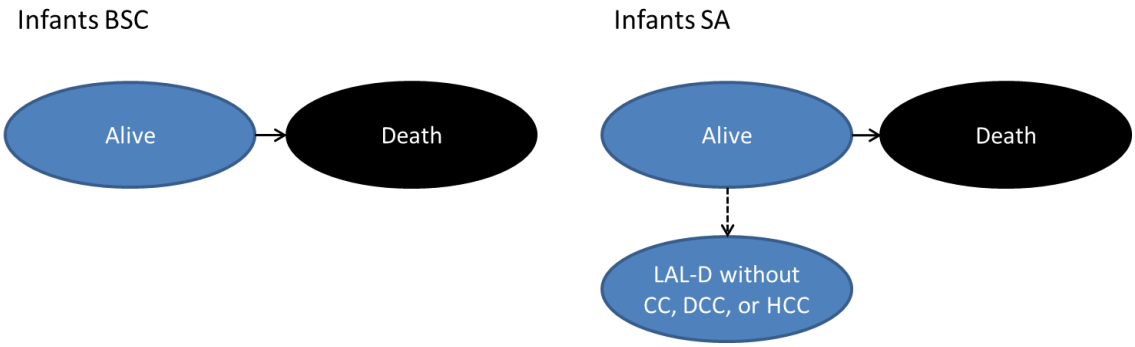


Figure 5.3: Model structure as provided by the ERG for the infant scenario



The model structure for BSC was mainly based on the economic model by Mahady et al.[2] It was assumed based on Mahady et al[2] that for the BSC group it was not possible to transit from "CC" to "LALD without CC, DCC or HCC", whereas this was possible for sebelipase alfa group, based on the LAL-CL02 trial.[4] For the sebelipase alfa group it was assumed that it was not possible to transit to the "DCC", "HCC" and "Liver transplant" health states. As can be seen in Figure 5.3, and alternative model structure was used for the first year in the infant scenario (afterwards the same model structure as for the base case, Figure 5.2, is used). During the first year in the infant scenario, only two health states were used "Alive" and

"Death".[6, 7] An overview of probabilities corresponding to the transitions between the health states is provided in Table 5.2.

Various issues concerning the model structure were identified by the ERG. The main issues are first summarised in Box 5.1 and elaborated afterwards.

Box 5.1: Main issues identified within the model structure in company's economic analysis

1. Appropriateness of use and adaptations of Mahady model as a proxy for LAL Deficiency
   1.1.1. Lack of any treatment related adverse events
   1.1.2. Effect on other organ systems not modelled
   1.1.3. Post-liver transplant state excluded
   1.1.4. Exclusion of treatment options for HCC
2. Appropriateness of discount factor

1. Appropriateness of use and adaptations of Mahady model as a proxy for LAL Deficiency

As there is very little evidence available on LAL Deficiency, the company chose to use evidence from other liver disease models to model the long-term progression of LAL Deficiency. It was unclear why the model (structure, cycle time, transition probabilities etc.) by Mahady et al, which was developed for a population with a much older starting age of 50 years, was selected from the available literature (see Section 5.2).[2] When the ERG requested more information on this choice the company explained that "clinical experts identified NAFLD as the most appropriate analogue to LAL deficiency so Mahady et al was used". As no formal expert elicitation has been performed and this was based on the opinion of only one expert, it remains unclear why NAFLD would be the best proxy disease.

The company also explained that "Mahady et al, which was used in our model, was the only NAFLD model identified in a literature review published in 2015 sponsored by NICE[2]". However, this literature review was not a review of NAFLD models, but aimed to identify "papers comparing the diagnostic accuracy of different non-invasive tests in the diagnosis and monitoring of liver fibrosis and cirrhosis with liver biopsy". Hence, if NAFLD would be the best proxy for LAL deficiency then this review may not have found the best available model as this was not the intention of their search strategy. Following the additional search and screening by the ERG (see Section 5.2) the study by Zhang et al,[51, 52] assessing the cost-effectiveness of screening strategies for NAFLD, could have been used as an alternative starting point to develop a model by the company (removing the screening part of the model). However, because of the differences in disease progression and population, compared to LAL deficiency, it might have been better to develop a de novo model that allows better capturing of the characteristics of the LAL deficiency population and LAL deficiency disease progression.

1.1 Lack of any treatment related adverse events

Treatment related adverse events, such as allergic reactions (including anaphylaxis), which were identified as important risks of sebelipase alfa by the EMA,[57] were not incorporated in

the cost-consequence analysis. In the clinical studies 21 of 106 patients (20%) experienced signs and symptoms either consistent with or that may be related to an allergic reaction (nine out of 14 infants (64%) and 12 out of 92 children and adults (13%)). The CS reports that "A total of 16 (19%) of the 84 subjects who received sebelipase alfa during Studies LAL-CL02, LAL-CL03 and LAL-CL01/LAL-CL04, including 5 (56%) of 9 infants and 11 (15%) of 75 children and adults, were reported to have experienced signs and symptoms either consistent with or potentially related to a hypersensitivity reaction". The majority of these events were mild to moderate in severity. The most serious adverse reactions experienced by 3% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. No subject permanently discontinued sebelipase alfa treatment due to a hypersensitivity reaction. Treatment with sebelipase alfa (or placebo) did not negatively impact the HRQoL of patients in the LAL-CL02 study and therefore the company did not include them in the cost-consequence analysis.

The ERG team understands the challenges of incorporating adverse events into the model with limited evidence. However, not incorporating adverse events into the model adds an additional level of uncertainty and results in QALY outcomes and costs that may be too optimistic. Hence the ERG requested to perform scenario analyses incorporating utility decrements and costs for these allergic reactions. Assuming that 3% of sebelipase alfa patients get an anaphylaxis reaction, the company performed a sensitivity analysis including event costs for anaphylaxis, but no health utility decrement. Further details and results of this analysis are reported in Section 5.4.2.

1.2 Effect on other organ systems not modelled

LAL Deficiency affects multiple organ systems and its manifestations can extend to for instance cardiovascular effects and gastrointestinal problems. While it is estimated that 87% of patients with LAL Deficiency experience manifestations in more than one organ,[14] these are excluded from the model owing to lack of data. In the CS it is stated that this is a serious shortcoming of the model and that "by excluding these other severe disease manifestations associated with LAL Deficiency, it is likely that this model underestimates the value of sebelipase alfa in the treatment of LAL Deficiency. This statement is however regarded as speculative and should be supported with data. The exclusion of other organ systems might potentially also overestimate the value of sebelipase alfa. For instance, not including cardiovascular effects may underestimate health state costs and overestimate utilities of health states.

1.3 Post-liver transplant state excluded

Instead of including a post-liver transplant state the CS model assumes that following a successful liver transplant, patients return to the "LALD without CC, DCC or HCC" state. Hence it was assumed that a previous liver transplant would not affect HRQoL or costs as the CS model assumed no utility decrement nor cost increase after liver transplant. The ERG considered this a conservative assumption as only BSC patients will receive a liver transplant in the model.

1.4 Exclusion of treatment options for HCC

In the CS it is stated that "the model is based on the structure in Mahady et al (2012) with a few exceptions".[2] One of these exception is the exclusion of the treatment options for HCC (Resection, Locoregional Therapy, Sorafenib & Palliation) as these "are a function of treatment decisions and patient access that may not apply to LAL deficiency patients" (stated in Section 12.1.4 of the CS). The ERG requested to justify why this does not apply to LAL Deficiency and hence why these treatment options have been omitted. The company has responded that "There are no data on the efficacy or effectiveness, or any other outcome measure, on using resection, locoregional therapy, or sorafenib in a LAL deficiency patient population" and "exclusion of these states is consistent with other liver disease models including the HCV models that were published and sponsored by NICE, for example Hartwell et al. (2011)." However, it was already concluded that the Mahady model had to be used as a proxy model, because of the limited available data, and that NASH/NAFLD was most similar to LAL Deficiency. It is unclear why, concerning these treatment options, the disease is then more similar to other liver diseases for which these states were also not modelled as well as how these adjustments of the model structure affect the outcomes.

2. Appropriateness of discount factor

The NICE Technology Appraisal Methods Guide specifies that a rate of 1.5% may be considered by the Appraisal Committee if it is highly likely that the long-term benefits will be achieved.[58] The ERG agrees that as the company states in the response letter 'For LAL deficiency, the cost-consequences model estimates incremental QALYs = 20.48 using a 1.5% discount rate. When discounted at 3.5%, these gains fall by more than half to 9.99, representing the situation described above in the NICE Methods Guide where "cost-effectiveness analyses are very sensitive to the discount rate used".[11] However, it is not specified that this rate should be applied in the base case analysis. Therefore, the ERG will additionally present the ERG base case with a discount rate of 3.5%.

5.3.3 Evidence used to inform the company's model parameters

The main evidence the company used to inform transition probabilities in the model was retrieved from the economic model by Mahady et al[2] considering NASH, the LAL-CL02 trial[4] and a paper by Hartwell et al.[5] In addition, for the infants scenario analysis the LAL-1-NH01 study[6] and LAL-CL03 study[7] were used to inform the transition probabilities for the first year. Health state utilities were retrieved from the economic model by Mahady[2] and based on assumptions for the infant scenario analysis. Costs were based on published papers[3] and for the infant scenario analysis NHS reference costs.

5.3.3.1 Relative treatment effects of sebelipase alfa versus best supportive care

No relative treatment effects were calculated nor explicitly used in the cost-consequences analysis.

5.3.3.2 Transition probabilities for best supportive care

The transition probabilities for BSC were mainly retrieved from the economic model by Mahady et al.[2] Only the transition from the "LALD without CC, DCC or HCC" health state to the "CC" health state was based on the LAL-CL02 trial.[4] Survival analysis was conducted to estimate this transition probability using the time to "CC". Specifically, the subset of

patients with a known baseline Ishak score (N=32) was analysed. For this purpose, the data collected prior to the treatment period in the LAL-CL02 trial were used (presumably retrospectively collected data). The event was defined as the earliest mention of a confirmed case of "CC" (N=12). Date of LAL Deficiency symptom onset was defined based on the earliest medical history of a LAL Deficiency symptom. If the month or day of symptom onset is missing, it was assumed to be January and the first of the month respectively. The resulting probability was 3.2% (standard error: 3.1%). Although this is not explicitly stated by the company, giving that the estimated probably is constant over time, the ERG suspects that an exponential parametric survival model is fitted by the company.

It was assumed based on Mahady et al[2] that it was not possible to transit back to the "LALD without CC, DCC or HCC" health state from the "CC" health state. The transition probability from the "HCC" health state to the "Death" health state was retrieved from a paper by Hartwell et al[5] as this probability could not be retrieved from Mahady et al.[2] An overview of transition probabilities is provided in Table 5.3.

5.3.3.3 Transition probabilities for sebelipase alfa

There were multiple differences in sources and assumptions for the transition probabilities used for sebelipase alfa (compared with those for BSC):

- The probability to transit from the "LALD without CC, DCC or HCC" health state to the "CC" health state was calculated differently (using the FIB-4 score; see below).
- It was assumed that patients could transit back from the "CC" health state to the "LALD without CC, DCC or HCC" health state (probability calculated using the FIB-4 score; see below).
- It was assumed that it was not possible to transit to the "DCC", "HCC" and "Liver transplant" health states (hence transition probabilities from these health states were not applicable for sebelipase alfa).
- No additional mortality (in addition to the background mortality from the general population of England[56]) was assumed for patients in the "CC" health state.

The transition probabilities between the "LALD without CC, DCC or HCC" and "CC" health states for sebelipase alfa were calculated by comparing the baseline and 20-week FIB-4 score using a threshold of 1.45. The FIB-4 score is developed as a non-invasive scoring system to predict liver fibrosis in patients with HIV/hepatitis C virus co-infection and is particularly used in Hepatitis C and NASH. The FIB-4 score can be calculated by using age, aspartate aminotransferase (AST), platelet count and alanine transaminase (ALT).[59] Depending on whether patients had a baseline FIB-4 score (calculated based on the LAL-CL02 trial[4]) above or below the threshold of 1.45 it is assumed whether they had "CC" (n=4) or not (n=25) at baseline. Similarly, if patients had a 20-week FIB-4 score above or below the threshold of 1.45 it is assumed whether they had "CC" (n=3) or not (n=26) at 20-weeks. Based on this a transition probability of 0% (=0/25) was calculated for transiting from the "LALD without CC, DCC or HCC" health state to the "CC" health state. Additionally, a transition probability of 25% was calculated (=1/4) is calculated for transiting from the "CC" health state to the "LALD without CC, DCC or HCC" health state. This is illustrated in Table 5.2.

Table 5.2: Transition probabilities between the "LALD without CC, DCC or HCC" and "CC" health states for sebelipase alfa (based on Table D12.6 from the CS)

		Week 20	
		No CC; FIB-4 ≤ 1.45 (n=26)	CC; FIB-4 > 1.45 (n=3)
Baseline	No CC; FIB-4 ≤ 1.45 (n=25)	100%	0%
	CC; FIB-4 > 1.45 (n=4)	25%	75%

An overview of transition probabilities is provided in Table 5.3.

5.3.3.4 Additional transition probabilities for the infant scenario analysis

In addition to the transition probabilities described above, alternative transition probabilities were used for the first year in the infant scenario (afterwards the abovementioned probabilities were used). During the first year in the infant scenario, only two health states were used "Alive" and "Death". During this first year, survival for BSC was 0% (based on the LAL-1-NH01 study,[6] considering the subpopulation of 21 infants with growth failure within the first six months of life) while this was 67% for sebelipase alfa (based on the LAL-CL03 study[7]). Afterwards, equal transition probabilities were used as in the base case.

5.3.3.5 Overview of transition probabilities

An overview of transition probabilities is provided in Table 5.3.

Table 5.3: Overview of annual transition probabilities (retrieved from the submitted model)[a]

Transition		BSC			Sebelipase alfa			Distribution[c]
From	To	Estimate	Standard error	Source	Estimate	Standard error	Source	
LALD without CC, DCC or HCC	CC	0.032	0.022	LAL-CL02[4]	0.000	Not applicable	LAL-CL02[4]; based on FIB-4	Beta
LALD without CC, DCC or HCC	DCC	0.010	0.020	Mahady[2]	0.000	Not applicable	Assumption	Beta
LALD without CC, DCC or HCC	HCC	0.003	0.003	Mahady[2]	0.000	Not applicable	Assumption	Beta
CC	LALD without CC, DCC or HCC	0.000	Not applicable	Assumption / Mahady[2]	0.250	0.125	LAL-CL02[4]; based on FIB-4	Beta
CC	DCC	0.063	0.032	Mahady[2]	0.000	Not applicable	Assumption	Beta
CC	HCC	0.032	0.012	Mahady[2]	0.000	Not applicable	Assumption	Beta
CC	Death[b]	0.042	0.005	Mahady[2]	0.000	Not applicable	Assumption	Beta
DCC	HCC	0.030	0.011	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
DCC	Liver transplant	0.050	0.050	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
DCC	Death[b]	0.160	0.058	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
HCC	Liver transplant	0.200	0.050	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
HCC	Death[b]	0.430	0.030	Hartwell[5]	Not applicable	Not applicable	Assumption	Beta
Liver transplant	Death[b]	0.120	0.053	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
Infant scenario								
Alive	Death[b]	1.000	Not applicable	LAL-1-NH01[6]	0.330	0.156	LAL-CL03[7]	Beta

[a]The transition probability of staying in the "LALD without CC, DCC or HCC", "CC", "DCC" and "HCC" health states is calculated by 1 minus the sum of the probabilities to transit to another health state. Moreover, the transition from "Liver transplant" to "LALD without CC, DCC or HCC" was calculated by 1 minus the probability of dying.
[b]This is excess mortality (in addition to the background mortality from the general population of England[56]).
[c]The distribution only applies if a standard error is provided (otherwise this parameter is fixed in the probabilistic sensitivity analysis or not applicable)

In addition to the probabilities reported in Table 5.3, age-dependent background mortality from the general population of England is incorporated for both BSC and sebelipase alfa.[56]

ERG comment:
The main critiques on the transition probabilities used in the economic are described in Box 5.2:

Box 5.2: Main critiques on transition probabilities

1. Lack of transparent reporting of input parameters
2. Unclear whether the transition probabilities used are the most appropriate transition probabilities
3. Uncertainty due to using FIB-4 scores
4. Inconsistency in assumptions regarding input parameters
5. Incorrect usage of 20-week data
6. Survival for infant scenario

1. Lack of transparent reporting of input parameters

Despite requested (clarification question B3[11]), the company did not provide details on the primary sources for the transition probabilities retrieved from Mahady et al.[2] The requested information included details how the transition probabilities (and its confidence intervals) are calculated and a description of the accompanying assumptions. Therefore, the ERG did check a random sample of the transition probabilities reported by Mahady et al[2] and the primary source reported by Mahady et al.[2] Based on this assessment, it was unclear how multiple transition probabilities reported by Mahady et al[2] and hence also the company[1] were calculated from their primary sources (e.g. probability of developing hepatoma from Bhala et al[60]). Additionally, it was unclear how transition probabilities were calculated if multiple sources are reported by Mahady et al[2], as was the case for most transition probabilities. Moreover, the company applied an artificial correction as not all transition probabilities by Mahady et al[2] summed up to 100% (see CS[1] and clarification question B3[11]) instead of determining the correct transition probabilities from the original sources (this might well be induced by a typographical or rounding error in Mahady et al[2]). It was also unclear how the survival analyses, to estimate the time to "CC", were exactly applied by the company (e.g. which parametric distribution is exactly used, which covariates were used and what the coefficients were). This extremely hampers the ERG´s assessment of the validity of the economic model and hence the outcomes of the cost-consequence analysis reported in the CS[1] should be interpreted with extreme caution.

2. Unclear whether the transition probabilities used are the most appropriate transition probabilities

The transition probabilities were mainly retrieved from the economic model by Mahady et al.[2] The company identified this economic model from a systematic review focusing on the use of the non-invasive liver tests (NILT) in a NAFLD population. Given the restriction to NILT, it is unclear whether there are more appropriate economic models available that were not identified in this systematic search (e.g. the economic model by Zhang et al[51, 52] identified in the additional searches performed by the ERG). Moreover, it might have been more

appropriate if the company would have aimed to identify clinical studies considering NAFLD to inform transition probabilities instead of limiting itself to cost-effectiveness studies identified in a systematic review which is not entirely suitable for this assessment (see Section 5.2). Also, the observation that a certain transition probability is used by Mahady et al,[2] does not justify the usage for the present model neither does it indicate that it is the most appropriate transition probability even if it would be the only NAFLD economic model available. Therefore, even when NAFLD would be considered the most appropriate analogue for LAL deficiency, it is unclear whether the transition probabilities used are the most appropriate transition probabilities. The impact of this potential selection bias is however unclear.

3. Uncertainty due to using FIB-4 scores

Despite the fact that the FIB-4 score was not developed using data from NAFLD patients, it is considered better than other non-invasive tests in diagnosing advanced fibrosis in NAFLD.[61] The sensitivity and specificity of the FIB-4 score for assessing liver fibrosis are 66.7% and 71.2% when applying the commonly used threshold of 1.45 (using liver histology as reference standard).[59] Although the 1.45 threshold is commonly used, it can only reliably be used to determine the absence of cirrhosis. FIB-4 scores between 1.45 and 3.25 are considered inconclusive.[62] However, in the current assessment the patients with a FIB-4 score above 1.45 are assumed to have cirrhosis while for the majority of these patients this should be considered inconclusive (see Table 5.4). To illustrate this: a recent UK study showed that only five out of 40 NAFLD patients (12.5%) with a FIB-4 score between 1.30 and 3.25 had a confirmed cirrhosis on biopsy.[63] Therefore, the usage of the FIB-4 score, although considered reasonable, induces uncertainty which is neglected by the company, nor is it completely explored in the sensitivity analyses (e.g. the 3.25 threshold is not used for BSC in any of the analyses). The ERG is unable to explore the impact of this uncertainty given the low number of patients with a FIB-4 score larger of equal than 3.25.

Table 5.4: Compensated cirrhosis based on the FIB-4 scores (based on Table D12.6 of the CS and the response to clarification question B5

	Sebelipase alfa		**BSC**	
	Baseline N (%)	**20 week** N (%)	**Baseline** N (%)	**20 week** N (%)
Absence of CC (FIB-4 ≤ 1.45)	25 (86%)	26 (90%)	25 (86%)	26 (90%)
Inconclusive (FIB-4 > 1.45 and < 3.25)	3 (10%)	3 (10%)	4 (14%)	3 (10%)
Presence of CC (FIB-4 ≥ 3.25)	1 (3%)	0 (0%)	0 (0%)	0 (0%)

4. Inconsistency in assumptions regarding input parameters

As illustrated in Table 5.3, for sebelipase alfa the LAL-CL02[4] data are exclusively used to inform the transition probabilities whereas for BSC also transition probabilities retrieved from Mahady et al[2] and Hartwell et al[5] were used. Moreover, to estimate transition probabilities for sebelipase alfa, the FIB-4 score is used while this is not used for BSC. No appropriate justification was found for these inconsistencies. Based on the comparable FIB-4 categorisations (Table 5.4), the ERG does not see any reason to use different sources or

assumptions for both comparators. This also holds true for the probabilities to transit to "DCC" and "HCC". These were assumed to be 0% for sebelipase alfa whereas these were assumed >0% for BSC. No plausible justification was found for this inconsistency. The 0% "DCC" probability is justified by the company by stating that this was not observed in the LAL-CL02[4] trial. This is however equally true for BSC (clarification question A8[11]). Moreover, it can be questioned whether it is plausible to assume 0% probabilities of "CC", "DCC" and "HCC" for sebelipase alfa based on a follow-up period of 20 weeks. Therefore, the ERG would prefer to assume:

1. Equal probability of transiting from "LALD without CC, DCC or HCC" to "CC" for both comparators, using the annual probability of 3.2% obtained through the survival analysis.
2. Probability of transiting from "CC" to "LALD without CC, DCC or HCC" based on FIB-4 scores for both comparators.
3. All other transition probabilities based on Mahady et al[2] (equal for both comparators).

5. Incorrect usage of 20-week data

The transition probabilities derived from the LAL-CL02[4] trial using the FIB-4 scores reflect a 20-week period, these 20-week probabilities were included in the model as annual probabilities without adjustment. These probabilities were adjusted to reflect an annual period in the ERG preferred base case.

6. Survival for infant scenario

For the infant scenario analysis, the company did use data from the LAL-CL03 study[7] for the first year only. Despite requested (clarification question B2[11]), the company did not provide a scenario analysis using data from the LAL-CL03 study[7] to inform (mortality) transition probabilities after the first year. According to Table A4.1 of the CS,[1] follow-up from the LAL-CL03 study is substantially longer than 1 year, i.e. up to 260 weeks (five year). In the infant scenario analysis provided by the company (in their initial submission), there is a substantial decrease in the annual probability of excess mortality for sebelipase alfa from 33% (first year) based on the LAL-CL03 study[7] to 0.0%-2.5% thereafter based on Mahady et al[2] (Table 5.3). It is unclear whether this steep decrease is plausible and hence adds to the uncertainty considering the interpretation of the outcomes for the infant scenario.

In addition to the estimation of long-term survival in the infant scenario, it is unclear to what extent patients included in the in LAL-1-NH01 study[6] and the LAL-CL03 study[7] are comparable. Hence, it is unclear to what extend the survival gain presented in the infant scenario is due to sebelipase alfa or due to differences between patients.

Conclusion

The results of the cost-consequences analysis presented by the company should be interpreted with extreme caution given the abovementioned issues. To salvage these issues the ERG proposed several adjustments for the ERG preferred base case (see Table 5.5). In particular, the ERG did not find any plausible justifications to use different sources and assumptions for the probabilities to develop "CC", "DCC" and "HCC" nor for the probability to transit back "LALD without CC, DCC or HCC" (from "CC"). Hence, this was adjusted in the ERG base case.

Table 5.5: Overview of annual transition probabilities (ERG base case)[a]

Transition		BSC			Sebelipase alfa			Distribution[c]
From	To	Estimate	Standard error	Source	Estimate	Standard error	Source	
LALD without CC, DCC or HCC	CC	0.032	0.031	LAL-CL02[4]	0.032	0.031	LAL-CL02[4]	Beta
LALD without CC, DCC or HCC	DCC	0.010	0.020	Mahady[2]	0.010	0.020	Mahady[2]	Beta
LALD without CC, DCC or HCC	HCC	0.003	0.003	Mahady[2]	0.003	0.003	Mahady[2]	Beta
CC	LALD without CC, DCC or HCC	0.528	0.282	LAL-CL02[4]; based on FIB-4	0.528	0.282	LAL-CL02[4]; based on FIB-4	Beta
CC	DCC	0.063	0.032	Mahady[2]	0.063	0.032	Mahady[2]	Beta
CC	HCC	0.032	0.012	Mahady[2]	0.032	0.012	Mahady[2]	Beta
CC	Death[b]	0.042	0.005	Mahady[2]	0.042	0.005	Mahady[2]	Beta
DCC	HCC	0.030	0.011	Mahady[2]	0.030	0.011	Mahady[2]	Beta
DCC	Liver transplant	0.050	0.050	Mahady[2]	0.050	0.050	Mahady[2]	Beta
DCC	Death[b]	0.160	0.058	Mahady[2]	0.160	0.058	Mahady[2]	Beta
HCC	Liver transplant	0.200	0.050	Mahady[2]	0.200	0.050	Mahady[2]	Beta
HCC	Death[b]	0.430	0.030	Hartwell[5]	0.430	0.030	Hartwell[5]	Beta
Liver transplant	Death[b]	0.120	0.053	Mahady[2]	0.120	0.053	Mahady[2]	Beta
Infant scenario								
Alive	Death[b]	1.000	Not applicable	LAL-1-NH01[6]	0.330	0.156	LAL-CL03[7]	Beta

[a]The transition probability of staying in the "LALD without CC, DCC or HCC", "CC", "DCC" and "HCC" health states is calculated by 1 minus the sum of the probabilities to transit to another health state. Moreover, the transition from "Liver transplant" to "LALD without CC, DCC or HCC" was calculated by 1 minus the probability of dying.
[b]This is excess mortality (in addition to the background mortality from the general population of England[56]).
[c]The distribution only applies if a standard error is provided (otherwise this parameter is fixed in the probabilistic sensitivity analysis or not applicable)

5.3.3.6 Health-related quality of life

The company did not identify health state utilities in their systematic literature review (see Section 5.2). Instead the company referred to a recent systematic review by Crossan et al.[64] In this systematic review, three studies that contained information on HRQoL for NAFLD/NASH patients were identified,[65] two of which had estimated HRQoL values for these patients.[65] For the economic model, the health state utilities were retrieved from Mahady et al[2] and not from David et al (2009)[66] and Donnan et al (2009).[65] The company argued that: "In light of the methods used and data reported by David et al. (2009) and Donnan et al. (2009), utilities reported by Mahady et al (2012) were deemed the most appropriate to use in the cost-consequence analysis." However, no specific methods used to calculate the health state utility scores retrieved from Mahady et al[2] were provided by the company. The utility scores retrieved from Mahady et al[2] ranged between 0.60 and 0.92 (Table 5.6).

No health state utility data were found for infants. Hence for the infants scenario analysis, utilities of 0.25 and 0.50 were assumed for infants that die within the first year of life and infants that survive beyond the first year respectively. No further justification for these utility scores was provided. For infants dying during the first year it is assumed based on LAL-1-NH01[6] that infants die after 3.45 months.

Table 5.6: Overview of health state utilities

Health state	Estimate	Standard error	Source	Distribution[c]
LALD without CC, DCC or HCC	0.92	0.08	Mahady[2]	Beta
CC	0.82[a]	0.06	Mahady[2]	Beta
DCC	0.60[b]	0.09	Mahady[2]	Beta
HCC	0.73[c]	0.08	Mahady[2]	Beta
Liver transplant	0.69	0.06	Mahady[2]	Beta
Infant scenario				
Alive	0.50	0.19	Assumption	Beta
Dying	0.07[d]	0.04	Assumption	Beta

[a]The utility for the "CC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "LALD without CC, DCC or HCC" health state in all simulations.
[b]The utility for the "DCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[c]The utility for the "HCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[d]The utility for the "dying" infants is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility for the infants "alive" in all simulations. For this health state a QALY of 0.07 is calculated ((3.45 / 12) × 0.25) which is subsequently incorporated as utility in the model for infants dying during the first year.

ERG comment:

The company mentioned that the systematic literature review by Crossan et al[64] considered HRQoL in NAFLD. This is incorrect as this review by Crossan et al[64] considered treatment effectiveness and also identified three studies that contained information on HRQoL in

patients with NAFLD. Given this systematic review did not focus on identifying HRQoL studies, potentially relevant HRQoL studies might have been missed by the company.

Based on the review by Crossan et al[64] the company selected Mahady et al[2] as source for health state utilities. Similarly as for the transition probabilities, there was a lack of transparent reporting (despite the requested clarifications[11]). It was unclear why the utilities from Mahady et al[2] were considered most appropriate. Additionally, it was unclear how the health state utilities were calculated if multiple sources are reported by Mahady et al,[2] as was the case for all but one health state utility. To salvage this issue, the ERG used the health state utilities as reported by Crossan et al.[64] These health state utilities were measured using the EQ-5D for hepatitis C patients and in part measured in the UK.[54, 67] Here it is assumed that the utilities for the different health states would be similar for different liver diseases irrespective of the initial cause. Please note that this latter assumption is also applicable to the health state utilities reported by Mahady et al[2] as these were primarily retrieved from hepatitis C populations.

The health state utility used in the economic model by the company did exceed the UK general population utility scores,[8] e.g. in the economic model approximately 90% of the patients are still expected to be alive at age 65 with a utility of 0.92 whereas the UK general population utility for persons aged 65 is expected to be 0.784. Despite requested (clarification question B6[11]), the company did not provide a plausible justification for the seemingly implausible high health state utility nor any scenario analyses using alternative health state utilities (e.g. age dependent utilities). Therefore, the ERG implemented a minimum function in the model to ensure the health state utilities in the model would not exceed those of the general population with the same age.[8]

The health state utilities used for infants in the infant scenario were assumed by the company without any evidence neither were these infant utilities specifically considered by clinical experts (as mentioned by the company in response to clarification question B7[11]). Given the lack of evidence to sustain the infant utilities and particularly the difference between the utilities, the ERG adopted a more conservative approach using a utility of 0.5 for all health states during the first year for the infant scenario. This would result into a QALY of 0.144 for infants dying during the first year (= (3.45 / 12) × 0.50) instead of 0.072. In addition, given that the QALY is calculated for infants dying in the first year and subsequently incorporated as a utility, the half-cycle correction should not be applied. The half-cycle correction applied by the company for the first year leads to an underestimation of the total QALYs. This is corrected by the ERG.

Table 5.7 provides an overview of the health state utilities used in the ERG base case.

Table 5.7: Overview of health state utilities used in the ERG base case

Health state	Estimate	Standard error	Source	Distribution[c]
LALD without CC, DCC or HCC	0.66	0.02	Crossan[64]	Beta
CC	0.55[a]	0.03	Crossan[64]	Beta
DCC	0.49[b]	0.06	Crossan[64]	Beta
HCC	0.49[c]	0.06	Crossan[64]	Beta
Liver transplant	0.51	0.05	Crossan[64]	Beta
Infant scenario				
Alive	0.50	0.19	Assumption	Beta
Dying	0.14[d]	0.07	Assumption	Beta

[a]The utility for the "CC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "LALD without CC, DCC or HCC" health state in all simulations.
[b]The utility for the "DCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[c]The utility for the "HCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[d]The utility for the "dying" infants is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility for the infants "Alive" in all simulations. For this health state a QALY of 0.14 is calculated ((3.45 / 12) × 0.50) which is subsequently incorporated as utility in the model for infants dying during the first year.

5.3.3.7 Resources use and costs included in the model

Resources use and costs included in the cost-consequences analysis include technology costs and non-drug direct medical costs. The former consists of drug and administration costs while the latter entails health state costs.

Technology costs

The annual costs of the technology consist of drug costs and administration costs. Drug costs are determined by two dosing schemes and by patients' weight. The first dosing scheme concerns infant patients, who are diagnosed within their first year of life and the second concerns children/adult patients, who are diagnosed after their first year of life. The infant patients dosing scheme consists of a weekly 3 mg/kg dose of sebelipase alfa. As there was no evidence of dose reduction after one year of treatment in the infant patient population,[7] the company assumes that infant patients receive a weekly 3 mg/kg dose of sebelipase alfa for the remainder of their life. Children/adult patients are administrated a 1 mg/kg dose of sebelipase alfa every other week.

Patients' weight is estimated based on their age. The UK growth charts from the Royal College for Paediatrics and Child Health[68] and a 50/50 ratio of male and female patients[4] is used to determine the mean weight for each age. After their 18th birthday, patients are not assumed to gain weight anymore; consequently, the average patient weight remains 68.25 kg until the maximum age of the model (101 years).

The list price that is used for sebelipase alfa is £6,286 for 20 mg vials. After a period of 10 years in the model, the price of sebelipase alfa is reduced by 30%. The company assumes this discount because of patent expiration and hence the introduction of biosimilar competition.[69] The company includes wastage by taking into account entire vial prices whether or not it was

fully emptied during administration. It is assumed that 5 mg vials at a list price of £1,572 are available from the second year of the model onwards. This reduces waste and therefore the net drug costs of sebelipase alfa treatment. The list price of a single infusion in an outpatient setting is £68.66.[70] The number of administrations is dependent on the patients' dosing scheme.

ERG comment:

In the company's cost-consequences analysis, infant patients receive a weekly 3 mg/kg dose of sebelipase alfa during their entire life. This results in markedly higher drug costs in later life for infants patients than for patients with a later start of treatment. Furthermore, patients are assumed to stop to gain weight after their 18th birthday. The ERG questions the validity of this assumption. If patients would still gain weight after their 18th birthday, sebelipase alfa costs are underestimated in the company's base case cost-consequences analysis. After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market. Therefore, the ERG asked the company to perform all analyses without 30% discount on sebelipase alfa after a period of 10 years. The ERG did not incorporate this 30% discount in its base case cost-consequences analysis. Furthermore, drug costs is influenced by the introduction of 5 mg vials of sebelipase alfa after the first cycle. This reduces waste and costs associated with sebelipase alfa. The ERG did not incorporate the 5 mg vials of sebelipase alfa in its base case cost-consequences analysis because these are not yet available.

Non-drug direct medical costs

Health state costs are retrieved from the literature on hepatitis C patients because LAL deficiency-specific costs were not available in the literature.[1] The two main sources are Backx et al[71] and Shepherd et al.[3] Backx et al is a retrospective chart review of 193 HCV patients who had received at least two months of pegylated interferon and ribavirin therapy. The aim of that study was to quantify resource use and costs depending on whether patients had achieved a sustained virological response (SVR) to therapy or not. The mean age of patients was 40.5 years in the SVR group and 48.0 years in the non-SVR group.[71] Shepherd et al is an economic evaluation which assesses the cost-effectiveness of interferon alfa and ribavirin for the treatment of mild chronic HCV.[3] In this economic evaluation, health state costs are retrieved from an observational study conducted by Wright et al[54] which is a retrospective database review of 358 UK patients with HCV. Wright et al[54] identify resources use and costs for different liver disease stages: "moderate disease", "CC", "DCC" and "HCC". Resources use and costs for each of these health state are based on 183, 115, 40 and 20 observations respectively. The mean age of the population was 42.1 years.[54]

Both Backx et al[71] and Shepherd et al[3] contain health state costs for the "LALD without CC, DCC or HCC", "CC" and "DCC" health states. However, Backx et al[71] was used for the "LALD without CC, DCC or HCC" and "CC" health state costs and Shepherd et al [3] for the "DCC" health state costs in the cost-consequences analysis.[1] Shepherd et al[3] further provided health state costs for the "HCC" and "Liver Transplant" health states. Costs of these studies

are inflated to 2014 values based on the Office for National Statistics Consumer Price Indices for Health.[72]

In the infant scenario of the cost-consequences analysis, infants incur specific costs in their first year of life because of long-term hospitalisation. The costs associated with resource use of infant patients in their first year of life is based on NHS reference costs[70] and assumptions. The company assumes that the annual costs of infant patients who die in their first year of life is equal to 3.45 months of hospitalisation because the mean survival of this group is 3.45 months.[6] Infant patients treated with sebelipase alfa are assumed to stay three months at the hospital in their first year of life. The cost of a hospitalisation day is £1,001.[70] An overview of health state costs is given in Table 5.8 (CS, Table D12.13 [1]).

No adverse events and miscellaneous costs are included in the cost-consequences analysis. A half-cycle correction is applied to all health care costs in the first and last cycles of the base case and sensitivity analyses performed by the company.

Table 5.8: Health state costs, variation in health state costs, population used to obtain health state costs and source of these costs, as used in the cost-consequence analysis (based on CS, table D12.13)

Health state	Mean cost (£)	Variation*	Population characteristics from which the estimate is retrieved*	Source
Base case scenario				
LALD without CC, DCC or HCC	620	439 - 877	54 HCV patients, mean age = 48.0 years	[71]
CC	962	590 – 1,570	27 HCV patients, mean age = 48.0 years	[71]
DCC	12,523	10,018 - 15,028	40 observations of HCV patients, mean age = 51.6 years	[3] from [73]
HCC	11,159	8,927 - 13,391	20 observations of HCV patients, mean each not specified for this subgroup, general mean age of sample = 42.1 years	[3] from [73]
Liver Transplant	50,515	40,412 - 60,618	Not able to retrieve, no access to original article67 HCV patients eligible for liver transplant	[3] from [74]
Infant scenario				
1st year cost for dying infants	103,604	82,883- 124,324	-	
1st year cost for surviving infants	90,090	As mentioned in cost-consequences model attached to the CS[1]: "varies proportionally vs. base cost for infants dying"	-	

* Added by the ERG

ERG comment:
Health state costs used in the cost-consequences analysis are predominantly based on two studies in adult hepatitis C patients (Backx et al[71]; Shepherd et al[3]). It is unclear to the ERG how these studies were identified, and hence whether these sources of evidence are the most appropriate ones. The ERG asked the company to justify why cost estimates from these studies were considered most applicable to the LAL Deficiency patient population because these studies included older patients (affected by HCV) than modelled in the cost-consequences analysis. The company replied as follows: "We included costs for an HCV patient population because they are available in a UK setting; costs for LAL deficiency or NAFLD patients in the UK are not available".[11] No details were provided on why Backx et al[71] and Shepherd et al[3] were appropriate sources for the cost-consequences analysis.

Furthermore, the ERG asked why Backx et al[71] was used for the "LALD without CC, DCC or HCC" and "CC" health states and Shepherd et al[3] for the "DCC" health state since both studies provide health state costs for these three health states. The company considers the cost estimate of Back et al[71] for "DCC" unreliable because it is based on 12 patients only. Therefore, Shepherd et al[3]'s cost estimate was used for the "DCC" health state. However, the "DCC" cost estimate of Shepherd et al[3] is based on Wright et al[54] who used the data of 40 patient observations to determine "DCC" costs.

The ERG is aware that LAL Deficiency-specific costs might not be available in the literature. However, the company was not transparent in the methodology used to retrieve studies providing health state costs and why these studies might be the most appropriate sources for the current economic evaluation. The ERG would also like to note that the recent review and economic evaluation from Crossan et al[64] used health state costs provided by Longworth et al[67] for the following health states: "DCC", "HCC" and "Liver Transplant" (for a hepatitis C population). It is uncertain which health state costs are the most appropriate for the current cost-consequences analysis. Therefore, the ERG performed a sensitivity analysis using the health state costs retrieved from Crossan et al.[64]

Furthermore, the company was not transparent about the variation in costs used in the cost-consequences analysis (CS, table D12.13[1]). After clarification, it was clear that these costs were varied by +/-20% around the mean. However, the company did not provide the rationale behind these +/-20% variations.

The ERG noted an inconsistency between health state costs provided in table D12.11 and table D12.13 of the CS which both summarise health state costs used in the cost-consequences model.[1] The ERG asked the company to clarify why the tables did not provide the same health state costs. The company noticed that costs of Table D12.13 of the CS,[1] Table 5.8 of the current report, were correct. The company also sent an updated version of the CS on 14 November 2015, however, this inconsistency was not corrected. Table 5.8 provides an overview of health state costs, with variation and the population from which they were retrieved.

A scenario analysis includes infant patients only. In this sensitivity analysis, a half-cycle correction is applied to drug costs and non-drug medical costs (hospitalisation costs only). However, drug use and the duration of hospitalisation were already based on actual survival.

Applying a half-cycle correction in this situation leads to an underestimation of the costs incurred by infants in this scenario analysis. Therefore, the ERG deleted the half-cycle correction from analyses for the infant population in the ERG base case.

There are no treatment adverse event costs included in the cost-consequences analysis. This might underestimate resource use and costs associated with sebelipase alfa treatment. For completeness of the model, the ERG asked the company to perform an analysis containing utility decrements and health care costs for anaphylaxis reactions, the major adverse events caused by sebelipase alfa administration. In its response to the clarification letter,[11] the company included health care costs associated with the HRG codes WA16W (Shock and Anaphylaxis with CC) and WA16Y (Shock and Anaphylaxis without CC), both of which cost £207, to model treatment adverse event costs. Results of this analysis are shown in Section 5.4.2.

The cost-consequences analysis does not include any concomitant medication costs. This makes the costs of BSC lower than can be expected. This assumption is conservative.

5.3.4 Model evaluation

The results of the health economic analysis are presented in terms of the (incremental) QALYs and costs for sebelipase alfa versus BSC. The model included a probabilistic sensitivity analysis (500 probabilistic samples), which incorporated both sampling uncertainty (i.e. second order uncertainty) and variability (i.e. first order uncertainty) simultaneously. In addition to the probabilistic sensitivity analysis, a number of simple one-way and multi-way sensitivity/scenario analyses were also performed by the company. The following parameters were varied using the 95% confidence intervals in the one-way sensitivity analyses (see Table D12.4 of the CS[1] for more details):

Transition probabilities BSC

- "LALD without CC, DCC, or HCC" to "CC"
- "LALD without CC, DCC, or HCC" to "DCC"
- "LALD without CC, DCC, or HCC" to "HCC"
- "CC" to "LALD without CC, DCC, or HCC"
- "CC" to "DCC"
- "CC" to "HCC"
- "CC" to "death"
- "DCC" to "HCC"
- "DCC" to "Liver transplant"
- "DCC" to "death"
- "HCC" to "Liver transplant"
- "HCC" to "death"
- "Liver transplant" to "death"

Transition probabilities sebelipase alfa

- "LALD without CC, DCC, or HCC" to "CC"
- "CC" to "LALD without CC, DCC, or HCC"

Utilities

- "LALD without CC, DCC or HCC" utility
- "CC" utility

- "DCC" utility
- "HCC" utility
- "Liver transplant" (first year) utility
- First year utility for surviving infants
- First year utility for dying patients

Costs

- "LALD without CC, DCC or HCC"
- "CC"
- "DCC"
- "HCC"
- "Liver Transplant"
- First year cost for dying infants

Other parameters

- Discount rate

Multi-way sensitivity analyses (Table D12.16 of the CS[1]) were performed wherein the method of calculating the transition probabilities between the "LAL Deficiency without CC, DCC or HCC" and "CC" health states (described above) was adjusted by using different thresholds for the FIB-4 score and using other liver scoring algorithms (i.e. the Forns Index and the Aspartate aminotransferase to Platelet Ratio Index (APRI)). In addition, scenario analyses (Table D12.15 of the CS[1]) were performed by the company for the infant population (modelled age: 0 year; based on the LAL-L03[7] and LAL-1-NH01[6] studies) and the children/adult population (modelled age: 17 year; based on the LAL-CL02 trial[4]). For the infant population, also different transition probabilities, health state utilities and costs were used for the first year (see Table 5.3 and Table 5.6).

ERG comment:

The standard errors of the input parameters were used in the sensitivity analyses. The ERG noted that multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges (e.g. the transition from "CC" to "LALD without CC, DCC, or HCC" for sebelipase alfa, health state utility for infants and health state costs for the "DCC", "HCC" and "Liver transplant" states). Moreover, the standard errors for the transition probabilities were underestimated by 2% as these were calculated by dividing the 95% confidence interval by four (instead of 3.92). Also, some standard errors are (re)calculated incorrectly based on the range. For instance, the annual transition probability of 0.032 to transit to the "CC" health state for BSC is calculated based on a survival analysis. This survival analysis also provided a standard error of 0.031, however based on the range the standard error was incorrectly recalculated (a standard error of 0.022 is used in the probabilistic sensitivity analysis). Hence, this was adjusted in the ERG base case (Table 5.5). Finally, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect[75] and therefore variability was not incorporated in the probabilistic sensitivity analysis performed by the ERG (i.e. age and hence also weight were assumed to be fixed). Moreover, the number of simulations was relatively low and hence increased to 1,000 in the ERG base case.

5.4 Headline results reported within the company's submission

This section summarises the results of the cost consequence analysis as presented in the CS. Figure 5.2 presents the base case Markov traces for sebelipase alfa while Figure 5.3 presents the base case Markov traces for BSC. Patients treated with sebelipase alfa are expected to spend the majority of their time alive in the "LALD without CC, DCC, or HCC state", whereas the BSC patients spend the majority of their time in the death state.

Figure 5.4: Base case: sebelipase alfa Markov trace

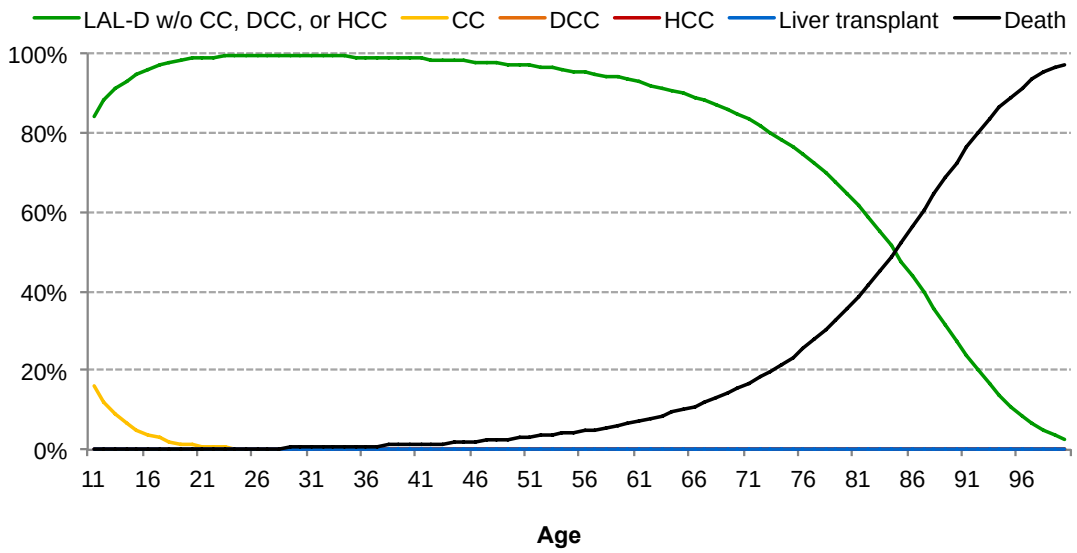
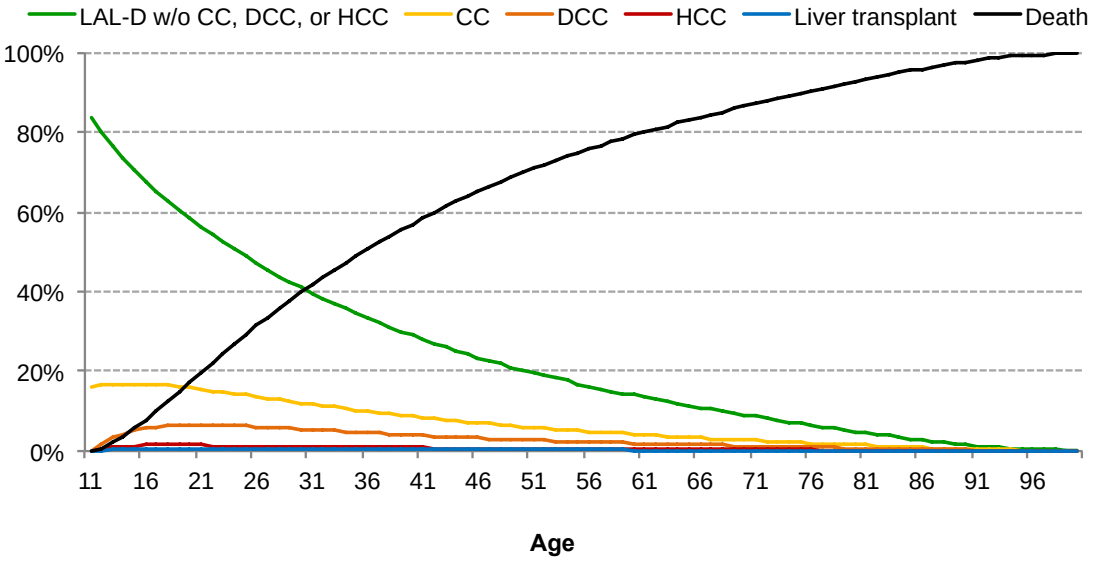


Figure 5.5: Base case: BSC Markov trace



5.4.1 Headline total QALYs and total costs for sebelipase alfa versus standard care

The estimates of incremental QALYs and costs for sebelipase alfa versus BSC are presented in Table 5.9. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient

compared to BSC and the incremental costs would be [redacted] per patient compared the BSC.

Table 5.9: Summary results of the company's model

	Costs (Disc.)	Mean (PSA)	95% CI (PSA)	QALYs (Disc.)	Mean (PSA)	95% CI (PSA)
BSC	£46,748	£45,093	(£29,721; £75,624)	19.24	20.6	(10.9; 31.8)
sebelipase alfa	£[redacted]	[redacted]	[redacted]	39.73	39.8	(31.5; 44.6)
Incremental	£[redacted]			20.48		

Table 5.10 and Table 5.11 below present a breakdown of discounted QALYs and costs for sebelipase alfa and BSC. The company's model suggests that under the sebelipase alfa treatment patients survive longer; they stay longer in the "LALD without CC, DCC, or HCC" state, stay shorter in the "CC" state and spend no time in the "DCC", "HCC", or "Liver transplant" state. Although much shorter, because of shorter survival, patients receiving BSC also spend most of their time in the "CC" state, and much shorter in the "CC", "DCC", "HCC", and "Liver transplant" state. This difference between the distributions of years spent in each disease state with and without sebelipase alfa treatment results in more than 20 incremental discounted QALYs.

On the other hand, health state costs (in terms of background resource use) barely make a difference between sebelipase alfa and BSC. The difference between sebelipase alfa and BSC is almost fully associated with sebelipase alfa drug costs, summing up to approximately [redacted]

Table 5.10: QALY gain by health state for the base case analysis

Health state	QALY BSC	QALY sebelipase alfa	Increment	% Increment
LALD without CC, DCC, or HCC	14.37	39.29	24.92	173%
CC	3.49	0.44	-3.05	-87%
DCC	1.01	0.00	-1.01	-100%
HCC	0.27	0.00	-0.27	-100%
Liver transplant	0.11	0.00	-0.11	-100%
Death	0.00	0.00	0.00	
Total	**19.24**	**39.73**	**20.48**	106%

Table 5.11: Costs associated with sebelipase alfa and BSC per health state for the base case analysis

Health state	Costs BSC	Costs sebelipase alfa	Increment	% Increment
LALD without CC, DCC, or HCC	£9,685	£26,480	£16,796	[redacted]
CC	£4,095	£512	-£3,582	[redacted]
DCC	£21,066	£0	-£21,066	[redacted]
HCC	£4,090	£0	-£4,090	[redacted]
Liver transplant	£7,813	£0	-£7,813	[redacted]
Drug Costs	£0	£[redacted]	£[redacted]	
Total	**£46,748**	**£[redacted]**	**£[redacted]**	[redacted]

5.4.2 Sensitivity analyses presented within the company's submission

Five sensitivity analyses were conducted to test structural assumptions, specifically with regard to the transition probabilities between the "LALD without CC, DCC or HCC" and "CC" states, the effect of sebelipase alfa on a cohort of only patients with infant-onset LAL Deficiency, and the effect of sebelipase alfa on a cohort of only patients with infant- or adult-onset LAL deficiency.

Furthermore, deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were undertaken. PSA was conducted using 500 model runs. For details on the distributions and parameters used for the PSA we refer to Table D12.11 of the CS. Results of the PSA are given in Table 5.9. Mean results of PSA are comparable to the deterministic point estimates of the base case analysis.

5.4.2.1 One-way sensitivity analyses presented within the company's submission

For DSA, the following variables were varied using the 95% confidence intervals: health state utilities (including first year utilities for surviving infants and dying patients), health states costs (first year cost for dying infants), BSC transition probabilities, natural history transition probabilities for BSC and sebelipase alfa, sebelipase alfa transition probabilities, and discount rates. The results of the DSA are presented in Figures 5.6 – 5.8.

Figure 5.6: Tornado diagram of incremental QALYs

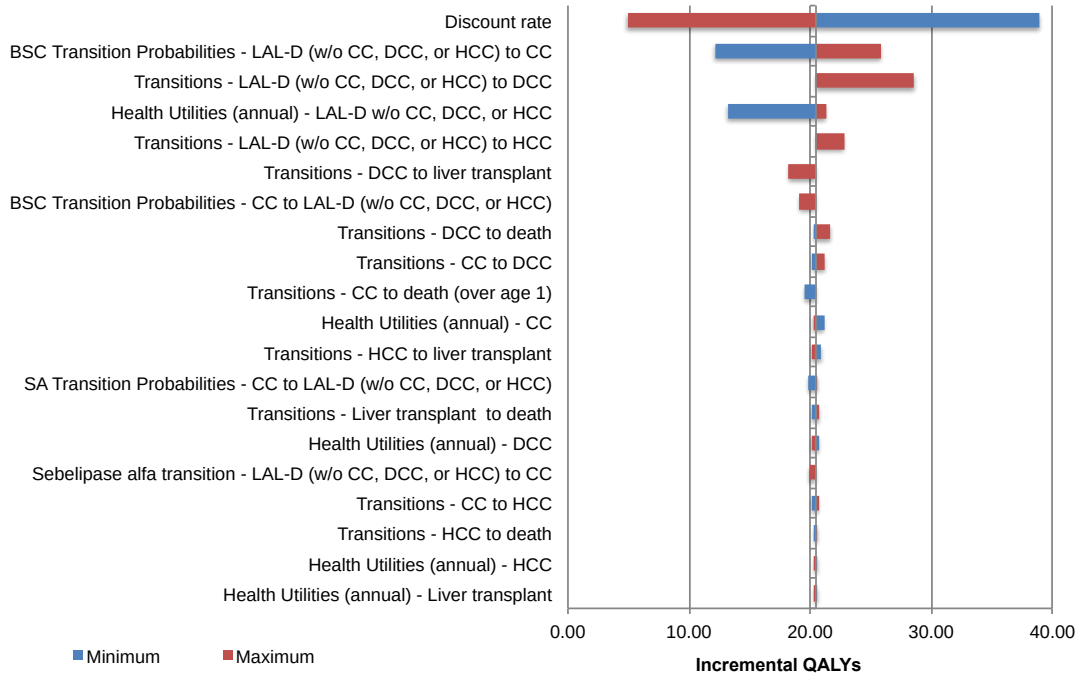


Figure 5.7: Tornado diagram of incremental life years (undiscounted)

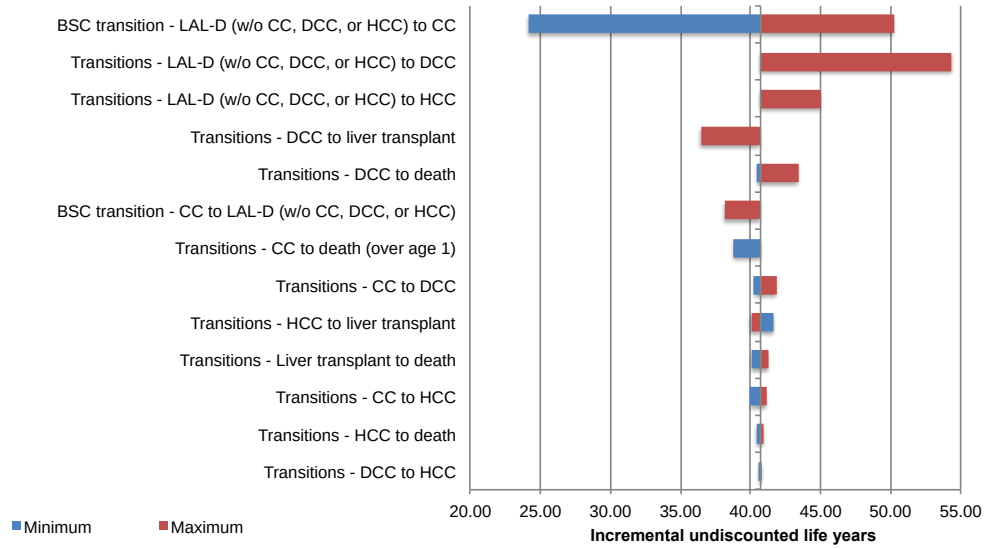


Figure 5.8: [redacted]

[redacted]

Among these one-way DSA results, it seems that the discount rate has the biggest impact on total incremental costs (apart from the cost of sebelipase alfa) as well as on the incremental QALYs. Besides the discount rate, transition probabilities to and from the LAL Deficiency without CC, DCC and HCC state has the highest impact on incremental life years (undiscounted) and incremental QALYs.

5.4.2.1 Multi-way sensitivity analyses presented within the company's submission

On top of the one-way DSAs, additional scenario analyses were performed. The population was varied by changing the baseline age, corresponding health state distribution, and transition probabilities. In Table 5.12 the incremental QALYs and costs of sebelipase alfa compared to BSC for the base case (age 11), the infant population (age 0; LAL-L03 and LAL-1-NH01) and the LAL-CL02 cohort (age 17) are presented.

Table 5.12: Multi-way scenario-based sensitivity analysis of patient scenarios

Scenario	N	Average Age	Modelled Age	Percentage at Baseline					
				LALD without CC, DCC or HCC	CC	DCC	HCC	Incr. Costs	Incr. QALYs
Base case	96	11.46	11	84%	16%	0%	0%	[redacted]	20.5
Infants (LAL-L03 and LAL-1-NH01)	30	0.08	0	100%	0%	0%	0%	[redacted]	28.6
LAL-CL02 cohort	66	16.63	17	69%	31%	0%	0%	[redacted]	20.4

In the multi-way scenario-based sensitivity analyses of the transition probabilities, several scenarios are compared for the transition probability between the "LALD without CC, DCC or HCC" and CC states for the BSC and sebelipase alfa group:

BSC:

Base case: Based on Mahady et al, adjusted

1. FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4>1.45)
2. FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)
3. Potentially Significant Fibrosis (Forns>4.2)
4. Potentially Significant Fibrosis (APRI>1.5)

SA:

Base case: FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4>1.45)

1. FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)
2. FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)
3. Potentially Significant Fibrosis (Forns>4.2)
4. Potentially Significant Fibrosis (APRI>1.5)

The results of these scenario analyses are given in Table 5.13 below. Among all the scenario analyses the costs remain comparable. The incremental QALYs however, largely differ in the BSC scenarios. In BSC scenario 1, where FIB-4 cut-offs of 1.45 are used for both BSC and sebelipase alfa, incremental QALYs are approximately half of that in the base case. In BSC scenario 2, using the FIB-4>0.6 cut-off for BSC and the FIB-4>1.45 cut-off for sebelipase alfa, incremental QALYs are slightly higher, whereas in BSC scenario 4, using the APRI for the BSC group (and FIB-4>1.45 for sebelipase alfa), the incremental QALYs are much lower. Among the different scenarios for the sebelipase alfa group, incremental QALYs remain similar.

Table 5.13: Multi-way scenario-based sensitivity analysis of transition probabilities

	Transition probabilities					
	Remaining in LALD without CC, DCC, or HCC	**LALD without CC, DCC, or HCC to CC**	**CC to LALD without CC, DCC, or HCC**	**Remaining in CC**	**Incr. costs**	**Incr. QALYs**
BSC						
Base case	97%	3.2%	0%	100%	[redacted]	20.5
1	100%	0%	25%	75%	[redacted]	10.2
2	92%	8%	0%	100%	[redacted]	24.9
3	96%	4%	0%	100%	[redacted]	20.6
4	96%	4%	33%	67%	[redacted]	15.2
sebelipase alfa						
Base case	100%	0%	25%	75%	[redacted]	20.5
1	94%	6%	33%	67%	[redacted]	19.9
2	100%	0%	100%	0%	[redacted]	20.5
3	100%	0%	0%	100%	[redacted]	19.8
4	100%	0%	86%	14%	[redacted]	20.5

After a request from the ERG, an additional sensitivity analysis was performed assuming that 3% of sebelipase alfa patients get an anaphylaxis reaction. This analysis assumed that the cost per event is equal to HRG codes WA16W (Shock and Anaphylaxis with CC) and WA16Y (Shock and Anaphylaxis without CC), both of which cost £207. Despite the ERG request, no health utility decrement for anaphylaxis, with the company explaining that this was "owing to the brief, episodic nature of the events, which is consistent with the literature".[76] According to these assumptions, the change in the base case output would be an additional £6.27 in incremental costs per sebelipase alfa treated patient."

ERG comment:
The sensitivity analyses for the transition probabilities between the "LALD without CC, DCC or HCC" and "CC" states contain unsystematic comparisons. Only BSC scenario 1, comparing the use of FIB-4 with equal cut-offs in the BSC and sebelipase alfa group, contains a fair and useful comparison. This scenario results in only half the incremental QALYs of the base case scenario.

5.4.3 Validation

Face validity

The company reported that "an advisory board was conducted in October 2014 with four clinical experts in hepatology or rare disease and two health economists to review sebelipase alfa clinical data and discuss the health economic analysis. Four European markets were represented: UK, Spain, Germany and Italy" (CS Section 12.2.5). The health economic model framework and assumptions with emphasis on identifying the correct disease states, transition probabilities, health utilities and medical resource utilisation parameters were discussed. The

approach taken to modelling the clinical progression of LAL Deficiency patients was deemed appropriate by hepatologists.

Internal validity

The internal validity of the model was checked by the ERG through reproducing the Markov traces.

External validity

In their clarification letter the company explained that the model predicts that in 10 years, 15.6% of BSC-treated patients will have had a successful liver transplant in the base case, which is a slight overestimation when compared with the 6/48 (12.5%) subjects from the LAL-2-NH01 natural history study who required a transplant.[11]

Cross validity

No cross validity check was performed, presumably as no other relevant cost-effectiveness models were identified by the company.

5.5 Discussion of available evidence relating to value for money for the NHS and PSS

This chapter focused on the economic evidence for sebelipase alfa submitted to NICE by the company. The analysis from the company is a QALY-based cost-consequence model comparing sebelipase alfa against BSC. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient compared to BSC and the incremental costs would be [redacted] per patient compared with BSC. In the company's sensitivity analyses this result was most sensitive to discount rate and the transition probabilities to and from the "LAL deficiency without CC, DCC" and "HCC" health state. The infants' scenario analysis resulted in 28.6 QALYs gained and incremental costs of [redacted].

The ERG's critique of the cost-consequence model entails the following main points: the health economic search, model structure and estimates for transition probabilities, costs of sebelipase alfa, health state utility estimates, and the handling of uncertainty. In order to address some of the problems identified within the critical appraisal of the economic analysis, the next chapter outlines the additional analyses conducted by the ERG.

Health economic literature search

The ERG notes that one limitation of the health economic literature search is that all Ovid databases were searched in one single strategy. Moreover, the company focused the search strategy on LAL Deficiency only, while it aimed to identify all health economic studies that could be used to inform the design of the cost-consequence model or provide utilities, resource use or cost data for the model. For this purpose the ERG feels a broader definition of the population as the basis for the literature review would have been useful, in particular including non-alcoholic steatohepatitis (NASH), which was appointed by the company as the disease analogue for modelling LAL Deficiency.

Model structure and estimates for transition probabilities

The model structure used in the cost-consequence analysis differs between the comparators as a result of using different sources for transition probabilities (LAL-CL02[4] data for sebelipase alfa and Mahady et al[2] and Hartwell et al[5] for BSC). For sebelipase alfa it is assumed that,

based on surrogate endpoints in LAL-CL02, patients cannot progress to the "CC", "DCC", "HCC" health states, and, as a result, cannot receive a liver transplant. In absence of comparative evidence on the clinical endpoints underlying these health states, the ERG questions this model structure.

The transition probabilities (for BSC) were mainly retrieved from the economic model by Mahady et al.[2] The company identified this economic model from a systematic review focusing on the use of the non-invasive liver tests (NILT) in a non-acid fatty liver disease (NAFLD) population. Given the restriction to NILT, it is unclear whether there are more appropriate economic models available that were not identified in this systematic search. Specifically the economic model by Zhang et al[51] could have been used as an alternative starting point to develop a model by the company. Moreover, it might have been more appropriate if the company would have aimed to identify clinical studies considering NAFLD to inform transition probabilities instead of limiting itself to cost-effectiveness studies identified in a systematic review.

Costs of sebelipase alfa

After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price, a generic version of the drug would enter the market. Furthermore, drug costs were influenced by the foreseen introduction of 5 mg vials of sebelipase alfa one year after market access. This reduces waste and costs associated with sebelipase alfa. The ERG thinks the 5 mg vials of sebelipase alfa should not be incorporated in the cost-consequences analysis because these are not yet available.

Health state utility estimates

The health state utility used in the cost-consequence analysis exceeded the UK general population utility scores.[8] For instance, approximately 90% of the patients are still expected to be alive at age 65 with a utility of 0.92 in the "LAL Deficiency without CC, DCC, or HCC" health state, whereas the UK general population utility for persons aged 65 is expected to be 0.784. Despite requested, the company did not provide a plausible justification for the seemingly implausible high health state utility nor any scenario analysis using alternative health state utilities (e.g. age dependent utilities). Moreover, it was unclear whether the health state utility scores selected by the company were the most appropriate ones for the UK context.

Handling of uncertainty

In the probabilistic sensitivity analysis, multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges. In addition, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect.

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Introduction

In this chapter the additional analyses performed by the ERG are presented. As described in Chapter 5, the following five issues were adjusted in the ERG base case (all probabilistic analyses):

1. A minimum function was implemented in the economic model to ensure the health state utilities would not exceed those of the general population (with the same age); see Section 5.3.3.6.
2. The utilities reported by Crossan et al[64] were incorporated in the economic model; see Section 5.3.3.6.
3. The transition probabilities were adjusted according to the ERG preferred assumptions; see Section 5.3.3.5.
4. The price reduction of sebelipase alfa by 30% after 10 years is removed; see Section 5.3.3.7.
5. The use of 5 mg vials for sebelipase alfa was excluded (these are currently not available); see Section 5.3.3.7.

The ERG base case will also be presented using an alternative discount rate of 3.5%.

In addition to the adjustments above, the following adjustments were made to the infant scenario (both probabilistic analyses):

6. The application of the half-cycle correction was corrected; see Sections 5.3.3.6 and 5.3.3.7.
7. Alternative utilities were assumed; see Section 5.3.3.6.

These adjusted infant scenarios were also presented using an alternative discount rate of 3.5%.

Finally, the following explorative analyses were performed (all deterministic; conditional on the adjustments made in the ERG base case):

Base case

8. Exploring the benefit of sebelipase alfa if for sebelipase alfa 1) the transition probability from "LALD without CC, DCC, or HCC" to "CC" would be reduced by 50% and; 2) the transition probability from "CC" to "LALD without CC, DCC, or HCC" would be increased by 50%
9. Using the health state costs reported by Crossan et al[64]; see Section 5.3.3.7.

Infant scenario

10. Assuming a four year time horizon (consistent with follow-up in LAL-CL03) and assuming for sebelipase alfa that after the first year one out of six surviving patients dies at 15 months and the remaining patients survive for the remainder of the time horizon; see Section 4.3.1.1. Survival during the first year is consistent with survival in the company's analysis. Moreover, after the first year, the health state costs and utility for the "LALD without CC, DCC, or HCC" health state was applied.

11. Assuming a four year time horizon (consistent with follow-up in LAL-CL03) and assuming for sebelipase alfa equal survival as in the previous scenario analysis. For BSC it is assumed that 21 out of 25 would survive on average 3.45 months, of the remaining patients three would survive one year and the remaining patient would survive for the remainder of the time horizon; see Section 4.3.1.1. After the first year, the health state costs and utility for the "LALD without CC, DCC, or HCC" health state was applied.

6.2 Re-analysis of the company's economic analysis following the correction of technical programming errors

No technical programming errors were identified in the company's base case after reproducing the Markov trace and examining the visual basic code.

6.3 Development of the exploratory ERG model

The ERG analyses as numbered in Section 6.1 will be discussed below.

Analysis 1

The cells CP22:CU123 (worksheets "BSC calcs" and "SA calcs") were adjusted to incorporate a minimum function in the economic model. This minimum function ensured that the health state utility would not exceed the age-dependent utility of the general population. The age-dependent utility of the general population was calculated using the linear function from Ward et al[8] consisting of an intercept of 1.060 (SE: 0.029) and a coefficient for age of 0.004 (SE: 0.001). These parameters were incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 2

The cells CR7:CR11 (worksheets "BSC calcs" and "SA calcs") were adjusted to incorporate the health state utilities reported in Table 5.7. These parameters were incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 3

The cells K23:P28 and K63:P68 (worksheets "Transition probabilities") were adjusted to incorporate the transition probabilities reported in Table 5.5. These parameters were incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 4

Cell CH7 of the "SA calcs" worksheet was set to '200' to remove the price reduction of sebelipase alfa by 30% after 10 years.

Analysis 5

Cell BY7 of the "SA calcs" worksheet was set to '20' to exclude the use of 5 mg vials for sebelipase alfa.

Analysis 6

For infants dying during the first year, the half cycle-correction was removed in cells BK22:BO22 and CV22 (worksheets "BSC calcs" and "SA calcs").

Analysis 7

The cell CR14 (worksheets "BSC calcs" and "SA calcs") was adjusted to incorporate the health state utility of 0.144 (SE: 0.073) reported in Table 5.7. This parameter was incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 8

Cells L63 and K64 (worksheet "Transition probabilities"), which were already adjusted in the ERG base, are now multiplied by 0.5 and 1.5 respectively to explore an alternative for the benefit of sebelipase alfa.

Analysis 9

In this analyses, the health sate costs for "LALD without CC, DCC or HCC", "CC", "DCC", "HCC" and "Liver transplant" were assumed to be £959, £1,521, £38,871, £38,871 and £69,174 respectively.[64] These values were incorporated in cells BL11:BL15 (worksheets "BSC calcs" and "SA calcs").

Analysis 10 and 11

These analyses were performed using a simple survival model to explore the impact of the adjustments described above. Hence, no adjustments were made to the economic model of the company to perform these analyses.

6.4 Cost-consequence results produced using the ERG model

The following sections provide the scenarios analyses (Section 6.4.1) and explorative analyses (Section 6.4.2) performed by the ERG.

6.4.1 Headline cost-consequence results produced using the ERG model

Table 6.1 provides an overview of the scenario analyses described in Section 6.1 (development of these explorative analyses is described in Section 6.3). Moreover, the infant scenario analyses are conditional on the adjustments made for the ERG base case. The company base case showed incremental QALYs and costs of 19.2 and [redacted] respectively. For the infant scenario these estimates were 28.6 QALYs and [redacted].

Table 6.1: Scenario analyses performed by the ERG

Scenario 1: minimum function for health state utility (see description of scenario 1; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£45,118 (£29,930 - £73,645)	20.24 (11.28 - 29.64)
SA	[redacted]	37.15 (30.44 - 41.76)
Increment	[redacted]	16.91 (8.00 - 26.56)
Scenario 2: alternative health state utilities incorporated (see description of scenario 2; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£44,666 (£29,744 - £75,279)	15.1 (8.49 - 22.35)
SA	[redacted]	28.49 (25.23 - 30.89)
Increment	[redacted]	13.39 (5.89 - 20.62)
Scenario 3: alternative transition probabilities incorporated (see description of scenario 3; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£42,116 (£25,659 - £74,778)	27.52 (13.68 - 38.12)

SA	[redacted]	27.52 (13.68 - 38.12)
Increment	[redacted]	0.00 (0.00 – 0.00)
Scenario 4: price reduction of sebelipase alfa by 30% is removed (see description of scenario 4; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£44,875 (£29,437 - £74,198)	20.87 (11.23 - 31.47)
SA	[redacted]	39.75 (30.89 - 44.77)
Increment	[redacted]	18.87 (8.73 - 29.74)
Scenario 5: 5 mg vials for sebelipase alfa were excluded (see description of scenario 5; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£44,925 (£29,996 - £73,343)	20.88 (11.52 - 31.44)
SA	[redacted]	39.72 (30.71 - 44.64)
Increment	[redacted]	18.84 (8.33 - 29.44)
ERG base case (combination of scenario 1-5)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£41,685 (£25,857 - £76,648)	19.79 (10.19 - 26.92)
SA	[redacted]	19.79 (10.19 - 26.92)
Increment	[redacted]	0.00 (0.00 - 0.00)
ERG base case (combination of scenario 1-5) using a 3.5% discount rate		
	Costs (95%CI)	QALYs (95%CI)
BSC	£27,629 (£16,166 - £52,297)	12.92 (7.80 - 16.23)
SA	[redacted]	12.92 (7.80 - 16.23)
Increment	[redacted]	0.00 (0.00 - 0.00)
Scenario 6 (infants): half-cycle correction removed for infants dying during the first year (see description of scenario 6; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£52,212 (£43,111 - £62,193)	0.07 (0.02 - 0.15)
SA	[redacted]	14.36 (5.6 - 23.42)
Increment	[redacted]	14.29 (5.5 - 23.34)
Scenario 6 (infants): half-cycle correction removed for infants dying during the first year using a 3.5% discount rate (see description of scenario 6; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£52,595 (£42,711 - £64,149)	0.07 (0.02 – 0.15)
SA	[redacted]	9.17 (4.17 – 14.14)
Increment	[redacted]	9.1 (4.09 – 14.07)
Scenario 7 (infants): alternative utilities were assumed for infants (see description of scenario 7; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£52,466 (£42,391 - £62,459)	0.07 (0.02 - 0.16)
SA	[redacted]	14.34 (5.29 - 24.14)
Increment	[redacted]	14.27 (5.22 - 24.03)
Scenario 7 (infants): alternative utilities were assumed for infants using a 3.5% discount rate (see description of scenario 7; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£51,876 (£42,390 - £63,478)	0.07 (0.02 – 0.16)
SA	[redacted]	9.13 (4.14 – 14.14)
Increment	[redacted]	9.06 (4.11 – 14.07)

6.4.2 Exploratory analyses produced by the ERG model

Table 6.2 provides an overview of the explorative analyses described in Section 6.1 (development of these explorative analyses is described in Section 6.3). Please note that these explorative analyses are deterministic and performed conditional on the adjustments made in the ERG base case.

Table 6.2: Results of explorative analyses (conditional on ERG base case)

Explorative scenario 1: Adjustment of transition probabilities for sebelipase alfa (see description of scenario 8; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£44,744	[redacted]	[redacted]
QALYs	19.38	20.91	1.53
Explorative scenario 2: using health state costs from Crossan et al (see description of scenario 9; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£101,399	[redacted]	[redacted]
QALYs	19.38	19.38	0.00
Explorative scenario 3 (infants): using different survival assumptions for sebelipase alfa (see description of scenario 10; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£103,604	[redacted]	[redacted]
QALYs	0.14	1.59	1.44
Explorative scenario 4 (infants): using different survival assumptions for sebelipase alfa and BSC (see description of scenario 10; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£103,135	[redacted]	[redacted]
QALYs	0.28	1.59	1.31

6.5 Discussion

In this chapter the additional analyses performed by the ERG have been presented. The ERG preferred base case resulted in a substantial decrease of the incremental QALYs; from 19.2 QALYs in the company base case to 0.0 QALYs in the ERG base case, indicating no additional health benefit for sebelipase alfa. This decrease was mainly due to the use of alternative transition probabilities removing inconsistent assumptions that were incorporated by the company. In addition, the use of alternative utilities had a substantial impact on the incremental QALYs. The incremental costs estimated by the company ([redacted]) were substantially lower than the incremental costs estimated in the ERG base case ([redacted]). This could mainly be explained by removing the 30% cost reduction after 10 years. Moreover, there was also a substantial uncertainty regarding the incremental costs (95% confidence interval showed a range of approximately [redacted]; Table 6.1). The incremental costs and the uncertainty surrounding this estimate were smaller when applying a discount rate of 3.5%.

The infant scenario presented by the company showed incremental costs and QALYs of [redacted] and 28.6, respectively. In the infant scenarios performed by the ERG using the 1.5% discount rate, the incremental costs were relatively similar while the incremental QALYs were approximately halved (Table 6.1). The incremental costs and QALYs were smaller when applying a discount rate of 3.5%. Moreover, similar to the base case, the

uncertainty surrounding the incremental costs was considerable (95% confidence interval showed a range of approximately [redacted]; Table 6.1).

7. COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

The same search as used for the review of existing economic analyses section of the submission was used for costs to the NHS and PSS, therefore any limitations discussed in Section 5.2 also apply here.

7.1.1 Model approach

In the CS, a budget impact model estimates the total costs to the NHS of adopting sebelipase alfa in the UK for a period of five years. The budget impact model starts in 2016 and is related to the cost-consequences model since the latter provides inputs for the budget impact model. Two hypothetical scenarios are presented: one where a proportion of patients would receive sebelipase alfa with the remainder receiving BSC, and a second scenario in which all patients would receive BSC. The net budget impact is the difference in total costs to the NHS between these two hypothetical scenarios over the period of five years. The budget impact model includes two groups of patients. The first group contains patients diagnosed with LAL Deficiency in their first year of life (Age 0-1 presentation group) and the second group includes patients with presentation of symptoms after one year of age (Age 1+ presentation group).

ERG comment:

The ERG agrees with the model approach chosen by the company.

7.1.2 Prevalence and incidence

For both presentation groups, population size data were retrieved from the latest estimates of the Office of National Statistics.[77] Population size estimates for 2016 were obtained by increasing population size data according to a yearly average population growth of 0.63% for both groups.[78] This resulted in baseline population sizes of 689,454 and 54,200,854 for the Age 0-1 presentation and Age 1+ presentation group respectively. To determine the number of LAL Deficiency patients in the UK, the company applies prevalence and incidence rates on these population size estimates. Prevalence and incidence rates are defined for each presentation group and are based on calculations and assumptions described in the following paragraphs.

The company assumes that all patients in the Age 0-1 presentation group die within a year[6] before the start of the budget impact model because sebelipase alfa is unavailable for treatment. Therefore, no prevalent patients belong to this presentation group in the company's budget impact model. The incidence rate for the Age 0-1 presentation group is 1.52 per million which resulted in approximately one incident patient per year. This incidence rate was determined as follows (CS, Section 13.1[1]):

"[…]this (incidence) estimate is based on the frequency analysis from Scott et al. (2013) combined with null-allele assessment from Reiner et al. (2014), which enable an assessment of incidence of presentation of symptoms at birth."

The presented prevalence rate of 4.38 per million LAL Deficiency patients for the Age 1+ presentation group (corresponding with 237 prevalent patients in the first year of the budget

impact model) is the result of an adjustment of the prevalence rate estimate reported by Scott et al.[9] The steps taken in the adjustment are described in the CS as follows (CS, Section 13.1[1]):

"Starting with a prevalence-rate estimate from Scott et al. (2013), adjusted for the ethnicity mix of England, one would estimate 10.1 cases per million. However, this approach analyses a subset of LALD causal mutations (those related only to the exon 8 splice junction mutation E8SJM) and has a broad estimate range given the small number of E8SJM carriers found in the study. We take three steps to refine and improve this estimate further:

- **Step 1: Strengthen E8SJM Data**: Include a larger number of E8SJM carriers in the analysis from Stitziel et al. (2013) and the Exome Aggregation Consortium (ExAC) Broad database (ExAC, 2015) which tightens the range and reduces the estimate to 2.8-4.9 cases per million.
- **Step 2: Add Causal Mutations**: Consider all causal mutation combinations with or without E8SJM, which contribute to LAL Deficiency. Combining mutations from Reiner et al. (2014), Alexion's clinical studies, and analysis of the ExAC database, this increases the estimate to 6.7-12.5 cases per million.
- **Step 3: Incorporate Mortality**: Scott et al.'s original analysis did not consider the reduced life-span of patients with LAL Deficiency. Incorporating mortality as it is reported in Burton et al. (2015c), and also observed in Alexion's clinical studies, leads to an estimate of 1.5-7.3 cases per million."

Furthermore, the company assumes between five and eight incident patients each year in the Age 1+ presentation group. This number of incident patient is based on above-described prevalence rate and the age distribution at symptom presentation from Bernstein et al.[14]

Beside incidence and prevalence rates, mortality rates are applied in the Age 0-1 presentation group. These mortality rates are treatment-dependent and apply only to the first year of the budget impact model. Patients receiving sebelipase alfa have an annual mortality rate of 33%[7] while patients treated with BSC have a 100% annual mortality rate[6] in the first year of the model. After the first year of the budget impact model, patients in the Age 0-1 presentation group have the same mortality rate as patients in the Age 1+ presentation group.

In the absence of evidence to support a difference in mortality between patients receiving BSC or sebelipase alfa in the Age 1+ presentation group, the company assumes a mortality rate of 0% for all patients in the Age 1+ presentation group, regardless of their treatment. This assumption is considered conservative by the company (CS, Section 13.1[1]).

ERG comment:
The calculations performed to determine the incidence rates of both presentation groups and to determine the prevalence rate of the Age 1+ presentation group were unclear to the ERG since no description of the calculations was provided in the CS.[1] The ERG therefore asked the company to clarify the methodology used to adjust the prevalence rate of Scott et al.[9] The answer was the following:

"These adjustments were made by Alexion's bioinformatics department using a model, which incorporates allelic frequencies from the EXAC database and accounts for novel mutations through in-silico and statistical methods. The 4.38 per million estimate represents Alexion's most accurate estimation of the prevalence of LAL Deficiency in the Age 1+ presentation group".[11]

Because of this lack of transparency, the ERG was not able to assess the quality and the validity of the adjustments made by the company on Scott et al's prevalence rate.[9] The ERG performed sensitivity analyses in order to explore how prevalence and incidence rates influence the results of the budget impact analysis. Results of these analyses are provided in Table 7.9 in Section 7.1.6 of the current report.

The company assumes an annual mortality rate of 100% for patients in the Age 0-1 presentation group treated with BSC. However, this assumption was not respected in the budget impact model in both scenarios. The ERG corrected this and the results are provided in Table 7.8, Section 7.1.5 of the current report. This corrected model is used in further sensitivity analyses performed by the ERG.

7.1.3 Uptake of sebelipase alfa

In the company's budget impact model, the uptake of sebelipase alfa is determined by diagnosis and treatment rates. Furthermore, the model assumes that several patients will not continue sebelipase alfa treatment or will not comply with prescribed dosing. Diagnosis, treatment, treatment continuation and compliance rates are based on the company's experience in ultra-rare disease and discussions with clinical experts.[1] These rates are provided in Tables 7.1 to Table 7.4 (CS, table D13.10, D13.11, D13.13 and D13.14[1]).

Table 7.1: Diagnosis rate of LAL Deficiency (CS, table D13.10)

	Year 1	Year 2	Year 3	Year 4	Year 5
	Scenario: **sebelipase alfa with market access in England**				
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario: **sebelipase alfa without market access in England**				
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7.2: Treatment rate of LAL Deficiency (CS, table D13.11)

	Year 1	Year 2	Year 3	Year 4	Year 5
	Scenario: **sebelipase alfa with market access in England**				
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario: **sebelipase alfa without market access in England**				
Age 0-1 presentation	0%	0%	0%	0%	0%
Age 1+ presentation	0%	0%	0%	0%	0%

Table 7.3: Treatment continuation rate amongst treated patients, by years from start of treatment (CS, table D13.13)

	Years from patient's start of treatment				
	1st	2nd	3rd	4th	5th
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7.4: Compliance rate of LAL Deficiency (CS, table D13.14)

	Year 1	Year 2	Year 3	Year 4	Year 5
Age 0-1 presentation	100%	100%	100%	100%	100%
Age 1+ presentation	85%	85%	85%	85%	85%

Applying diagnosis, treatment and treatment continuation rates results in [redacted] of the total group of LAL Deficiency patients ([redacted]) treated with sebelipase alfa in the first year of the budget impact model. The proportion of treated patients increases to a maximum of [redacted] in the fifth year of the model. An overview of the number and proportion of sebelipase alfa treated patients is provided in Table 7.5 for each presentation group separately and in total.

Table 7.5: Comparison of the number of sebelipase alfa treated patients versus total number of patients after applying diagnosis, treatment and treatment continuation rates to the LAL Deficiency patient population (CS, budget impact model)

	Year 1	Year 2	Year 3	Year 4	Year 5
Children and adult patients					
Total UK LAL D patient in the Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of treated patients (%) after applying diagnosis, treatment and treatment continuation rates on the Age 1+ presentation group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infant patients					
Total UK LAL D patient in the Age 0-1 presentation group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of treated patients (%) after applying diagnosis, treatment and treatment continuation rates on the Age 0-1 presentation group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All patients					
Total number of UK LAL D patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of treated patients (%) after applying diagnosis, treatment and treat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG comment:

The diagnosis, treatment, treatment continuation and compliance rates applied to the LAL Deficiency patient population to determine the amount of patients treated with sebelipase alfa. These rates are based on the company's experience with ultra-rare disease (CS, Section 13.2; CS, budget impact model[1]). The ERG asked the company to clarify how this experience was used to determine these rates. The company provided several estimates concerning eculizumab treatment rates in paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), two other ultra-rare diseases. In the case of PNH, the company claims that "*around* [redacted] *of the patients are on eculizumab treatment"*; while the uptake of eculizumab in the aHUS population [redacted] than expected.[11] The ERG acknowledges that in absence of other evidence, these rates might be a suitable basis to determine the uptake for sebelipase alfa because similarities exist (eculizumab is an expensive drug which is administrated intravenously and with an adverse event profile comparable to the adverse event profile of sebelipase alfa). Uncertainty remains however, because aHUS and PNS are different diseases, and experience with eculizumab is based on small patient numbers. Furthermore, the company did not specify how exactly the eculizumab uptake-related rates were used to inform sebelipase alfa's uptake. As a result, the ERG was unable to assess the validity of the rates used by the company. The ERG notes that the estimated proportion of patients treated with sebelipase alfa in the fifth year ([redacted]) is half the proportion of patients with aHUS on eculizumab (around [redacted]). This seems inconsistent with the statement of the company that experience with eculizumab can be used to inform the uptake of sebelipase alfa. The ERG performed sensitivity analyses on diagnosis and treatment rates. Results of these sensitivity analyses are provided in Table 7.10 in Section 7.1.6 of this report.

In its base case analysis, the company assumes that patients might discontinue treatment (in both presentation groups) and might not be compliant with the prescribed dosing schemes (especially in the Age 1+ presentation group). Due to the nature of the disease and the treatment (sebelipase alfa is administrated by intravenous injection), the ERG thinks these assumptions might underestimate the number of patients continuing treatment and complying with prescribed doses. This also decreases the net costs of sebelipase alfa treatment. Furthermore, the company provided little insight in the experience it has with other ultra-rare diseases and did not explain how its experience was used to determine treatment continuation and compliance rates. The company only mentioned in its response to the clarification letter that "compliance rates for patients receiving homecare drug administration are high with [redacted] of patients having compliance rates of [redacted]".[11] The ERG performed sensitivity analyses on these rates in order to assess the impact of these rates on the net budget impact. Results are shown in Table 7.11 in Section 7.1.6 of the current report.

7.1.4 Technology costs

The company uses patients' weight and two dosing schemes to determine sebelipase alfa costs in its budget impact model. Patients' weight is age-dependent. The UK growth charts from the Royal College for Paediatrics and Child Health[68] and a 50/50 ratio of male and female patients[4] is used to determine the mean weight for each age. As in the cost-consequences analysis, patients' weight does not vary after their 18th birthday. Dosing

schemes are dependent on the presentation group of the patients. Patients in the Age 0-1 presentation group receive a weekly 3 mg/kg dose of sebelipase alfa. However, assuming a weekly 3 mg/kg dose in the first year for the Age 0-1 presentation group would have overestimated sebelipase alfa costs because infants escalate sebelipase alfa dose from 1 mg/kg every week to 3 mg/kg every week in their first year of life. Therefore, the company adjusted the administrated doses in the first year of the model for patients in the Age 0-1 presentation group according to the time infant patients need to escalate to the weekly 3 mg/kg dose, based on LAL-CL03.[7] This resulted in a weekly 2.3 mg/kg dose of sebelipase alfa for infant patients in their first year of life. Patients in the Age 1+ presentation group receive 1 mg/kg of sebelipase alfa every other week and are allocated to different age based on Bernstein's et al[14] age distribution of LAL Deficiency patients.

Only 20 mg vials of sebelipase alfa are available for treatment in the first year of the model at a list price of £6,286. In the remaining years of the model, 5 mg vials are also available at a list price of £1,572. The availability of 5 mg vials reduces waste and the net drug cost of sebelipase alfa.

Non-drug direct medical costs for the Age 1+ presentation group are based on the five year average non-drug direct medical costs of a 16.6 year-old patient at baseline (baseline age of ARISE/LAL-CL02[4]) as calculated in the cost-consequences analysis. Non-drug direct medical costs for the Age 0-1 presentation group are based on daily hospital costs and survival rates of infants treated with BSC and sebelipase alfa. Infant patients receiving BSC are assumed to receive care at the hospital until they decease, which equals a period of 3.45 months of hospital care.[7] Infant patients receiving sebelipase alfa are assumed to be treated three months of their first year of life at the hospital. The cost of a hospitalisation day is £1,001.[70] Non-drug direct medical costs used in the company's budget impact model are provided in Table 7.6 (CS, table D13.16[1]).

Table 7.6: Non-drug direct medical costs, by treatment option and age of presentation group (adapted from CS, table D13.16)

	Mean cost	**Source**
Age 0-1 presentation		
BSC	£103,604	Calculation (see Section 12.3.7)
Sebelipase alfa	£94,586	Calculation (see Section 12.3.7)
Age 1+ presentation		
BSC	£1,699	Calculation (see Section 12.3.7)
Sebelipase alfa	£668	Calculation (see Section 12.3.7)

ERG comment:

Sebelipase alfa costs are dependent on patients' weight and dosing scheme. However, two assumptions decrease the net costs associated with sebelipase alfa treatment: assuming that patients' weight does not vary after their 18th birthday and the availability of 5 mg vials of sebelipase alfa. For an extensive discussion of these concerns, the ERG refers to Section 5.3.3.7 of this report. In addition to these two issues, the following points needed clarification: how non-drug medical costs are obtained from the cost-consequence model, the

choice of the age distribution to determine non-drug medical costs, and the choice of the age distribution to populate the budget impact model.

The ERG was unable to reproduce the non-drug direct medical costs and asked for clarification. After explanation, non-drug medical costs could be reproduced by the ERG. However, there was a discrepancy between the calculation performed and the description of the calculation in the CS.[1] The non-drug direct medical costs were calculated based on a 18 year-old population at baseline instead of a 16.6 year-old population, as described in the CS.[1] The ERG corrected this and used these corrected non-drug direct medical costs in its analyses. The recalculated non-drug medical costs are higher for the sebelipase alfa group (£684 instead of £668) and lower for the BSC group (£1,444 instead of £1,699). As a result, non-drug direct medical costs increase for the sebelipase alfa treated patients and decrease for the BSC treated patients. The results of the corrected budget impact model are provided in Table 7.8 of Section 7.1.5 of the current report.

For the Age 1+ presentation group, non-drug direct medical costs are calculated based on the mean age at baseline of the ARISE clinical trial[4] and then applied to the age distribution of Bernstein et al.[14] The ERG thinks this is inconsistent and asked the company to clarify why the age distribution of Bernstein et al[14] was thought to be more representative for the UK patient population and used to populate the first year of the budget impact model while the ARISE age distribution was used to calculate non-drug direct medical costs[4]. The company explained that the Bernstein et al[14] age distribution was used for the prevalence and incidence rates calculation and was therefore used to populate the base case budget impact analysis. No explanation of why Bernstein et al[71] age distribution of patients was more appropriate for the UK setting was provided. The ARISE age distribution was used to calculate non-drug direct medical costs in order to be more in line with the cost-consequences analysis.[11]

Because the ERG thought it was inconsistent to apply non-drug direct medical costs based on ARISE and apply them to the Bernstein et al[14] age distribution, the ERG asked the company to perform an additional analysis where data from Bernstein et al[14] are used to determine both non-drug direct medical costs and to populate the baseline age of the population in the budget impact model. Results are provided in Section 7.1.5 of the current report.

7.1.5 Results

The five year net budget impact of granting market access to sebelipase alfa will be £53,548,573. In the first year of the company's budget impact model, the net budget impact will be £4,292,136 and will rise to £18,515,491 in the fifth year of the model (Table 7.7; CS, table D13.19[1]).

Table 7.7: Net budget impact: company's base case scenario (CS, table D13.19)

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA without market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	**£4,292,136**	**£6,952,175**	**£10,051,079**	**£13,737,692**	**£18,515,491**	**£53,548,573**

The company provides three sensitivity analyses based on its base case analysis. In the first sensitivity analysis, the ARISE[4] baseline age distribution replaces the Bernstein et al[14] age distribution to allocate patients in the different age categories in the first year of the model. The second sensitivity analysis assumes the availability of only 20 mg vials for the five year period and the last sensitivity analysis assumes an annual per-patient cost cap of [redacted]. Results of these sensitivity analyses are provided in table D13.20 to table D13.22 of the CS.[1] These sensitivity analyses highlight the influence of the patients' age distribution on the net budget impact. Patients in ARISE[4] are older than in Bernstein et al[14] which increases the five year net budget impact from £53,548,573 to £82,194,168. Furthermore, the unavailability of 5 mg vials of sebelipase alfa would increase the five year net budget impact by £10,317,741, while the per-patient cost cap of [redacted] would decrease the five year net budget impact by [redacted].

ERG comment:

The company did not implement its budget impact model as described in the CS.[1] First, the assumption that infant patients receiving BSC die within their first year of life was not incorporated in the calculations. Second, the non-drug direct medical costs were not calculated as described in the CS.[1] The ERG has re-calculated non-drug direct medical costs and has set mortality of infant patients treated with BSC to 100%. Furthermore, the ERG did not account for the availability of 5 mg vials of sebelipase alfa after the first year of the model because these are not available yet. This led to a five year net budget impact of £63,689,818 (Table 7.8) which corresponds to approximately a 19% increase in five year net budget impact compared with the company's net budget impact analysis. This increase is caused by the unavailability of 5 mg vials in the ERG corrected model. Sensitivity analyses of the ERG are performed on this corrected budget impact model. The sensitivity analyses presented in the CS were not performed again by the ERG since the results of these analyses will not be dramatically influenced by the corrections made on the budget impact model.

Table 7.8: Net budget impact: base case analysis (ERG correction)

Total costs	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**TOTAL**
SA with market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA without market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	**£4,296,378**	**£8,423,173**	**£11,909,493**	**£16,436,536**	**£22,624,238**	**£63,689,818**

Because the ERG thinks it is inconsistent to apply non-drug medical costs based on the age distribution of one population (ARISE/LAL-CL02[4]) to another (Bernstein et al[14]), the ERG asked the company to provide an analysis where both non-drug medical costs and the age distribution of the population were based on Bernstein et al.[14] Using Bernstein et al[14] for both non-drug medical costs and age distribution led to a five year net budget impact of £ 53 million,[11] which is equal to the company's base case analysis.

7.1.6 ERG additional analyses

The ERG performed additional analyses to assess the influence of remaining uncertainties around certain model parameters. These analyses concern the prevalence and incidence rates and the uptake of sebelipase alfa over the five year period. All analyses are performed on the ERG corrected version of the budget impact model, presented in Table 7.8 of Section 7.1.5 of the current report.

The ERG performed analyses on incidence and prevalence rates in the Age 1+ presentation group as these were considered uncertain due to the lack of transparency concerning the calculations of these rates in the CS[1] and in the clarification letter.[11] The prevalence rate and incidence rates were varied +/-50%. The results show that a 50% increase of the prevalent population will increase the five year net budget impact by more than 40% (and vice versa for 50% decrease of the prevalence rate). The incidence rate does not dramatically influence the five year budget impact. The five year net budget impacts of these sensitivity analyses are displayed in Table 7.9.

Table 7.9: Five year net budget impact resulting from sensitivity analyses on prevalence and incidence rates (based on ERG corrected model)

Prevalence rate\ incidence rate	Incidence rate -50% [redacted][1]	Incidence rate as in base case [redacted][1]	Incidence rate +50% [redacted][1]
Prevalence rate -50% (119)[2]	£34,250,930	£36,837,511	£39,423,151
Prevalence rate as in base case (237)[2]	£61,102,333	£63,689,818	£66,276,670
Prevalence rate +50% (356)[2]	£87,953,498	£90,541,337	£93,128,707

[1] Number of incident patients in the age 1+ presentation group in Year 1 until Year 5 of the budget impact model.

[2] Number of prevalent patient in the age 1+ presentation group in the first year of the budget impact model.

The ERG acknowledges that it is highly probable that all diagnosed infant patients will receive sebelipase alfa treatment. However, diagnosis and treatment rates for the adult population are highly uncertain. The ERG therefore performed sensitivity analyses on diagnosis and treatment rates in the Age 1+ presentation group by increasing and decreasing these rates with 10% or 20% in the sebelipase alfa with market access scenario. The ERG only focused on the Age 1+ presentation group and did not modify diagnosis and treatment rates of the Age 0-1 presentation group for the same reasons as above-described (small number of patients and hence small influence of these patients on budget impact). When varying diagnosis and treatment rates, the five year net budget impact ranged from £23,439,245 to £126,845,898 and the number of treated patients in the fifth year of the budget impact model varied from [redacted] to [redacted]. Results of these analyses are provided in Table 7.10.

Table 7.10: Five year net budget impact resulting from sensitivity analyses on diagnosis and treatment rates of the Age 1+ presentation group (based on ERG corrected model)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates - 20% [redacted]	Treatment rates - 10% [redacted]	Treatment rates as in base case [redacted]	Treatment rates +10% [redacted]	Treatment rates +20% [redacted]
Diagnosis rates -20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£23,439,245	£28,853,852	£34,268,458	£39,683,065	£45,097,672
Diagnosis rates -10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£32,423,548	£40,701,343	£48,979,138	£57,256,933	£65,534,728
Diagnosis rates as in base case [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£41,407,851	£52,548,835	£63,689,818	£74,830,802	£85,971,785
Diagnosis rates +10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£50,392,155	£64,396,326	£78,400,498	£92,404,670	£106,408,842
Diagnosis rates +20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£59,376,458	£76,243,818	£93,111,178	£109,978,538	£126,845,898

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955); [2] Rates were varied to a minimum of 0% and a maximum of 100%; [3] Treatment rates in Year 1 until 5; [4] Diagnosis rates in Year 1 until 5.

The ERG performed sensitivity analyses on treatment continuation and compliance rates because these parameters influence drug costs, and because the ERG was not able to assess the validity of these estimates due to lack of reporting by the company. Furthermore, the ERG considers it probable that LAL Deficiency patients will continue treatment and comply with the dosing schemes due to the nature of the disease and of the treatment (sebelipase alfa is administrated through an intravenous infusion). Sensitivity analyses on treatment continuation and compliance rates were performed by setting both rates on 100% in both presentation groups. The sensitivity analyses were performed on the above described sensitivity analyses where diagnosis and treatment rates were varied by +/-10% or 20%. Results of the different sensitivity analyses where treatment continuation and compliance rates are set on 100% are provided in Table 7.11. All ERG sensitivity analyses concerning diagnosis, treatment, treatment continuation and compliance rates were also performed assuming the availability of 5mg vials of sebelipase alfa one year after its introduction. Results of these analyses are provided in Appendix 2.

Setting treatment continuation and compliance rates on 100% increases the number of treated patients and the five year net budget impact in each sensitivity analysis. The number of treated patients varies between [redacted] and [redacted] and the five year net budget impact varies between £36,137,359 and £206,367,686. The company stated that approximately [redacted] of the PNH patients are on eculizumab treatment.[11] Based on this information, the ERG thinks that the sensitivity analysis where treatment rates are increased by 10%, diagnosis rates increased by 20% and both treatment continuation and compliance rates are set on 100% may be the most plausible because it provides [redacted] of treated patients with sebelipase alfa. This scenario results in a five year net budget impact of £178,527,667 which is more than three times higher than the company's base case five year net budget impact.

Table 7.11: Five year net budget impact resulting from sensitivity analyses on treatment continuation and compliance rates of the Age 1+ presentation group (based on ERG corrected model)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates -20%	Treatment rates -10%	Treatment rates as in base case	Treatment rates +10%	Treatment rates +20%
Diagnosis rates -20% [redacted]	Number (%) of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£36,137,359	£45,211,920	£54,286,481	£63,361,042	£72,435,603
Diagnosis rates -10% [redacted]	Number (%) of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£50,854,922	£64,620,848	£78,386,773	£92,152,698	£105,918,624
Diagnosis rates as in base case [redacted]	Number (%) of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£65,572,486	£84,029,775	£102,487,065	£120,944,355	£139,401,644
Diagnosis rates +10% [redacted]	Number (%) of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£80,290,050	£103,438,703	£126,587,357	£149,736,011	£172,884,665
Diagnosis rates +20% [redacted]	Number (%) of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£95,007,613	£122,847,631	£150,687,649	£178,527,667	£206,367,686

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955); [2] Rates were varied to a minimum of 0% and a maximum of 100%; [3] Treatment rates in Year 1 until 5; [4] Diagnosis rates in Year 1 until 5.

In conclusion, the implementation of the company's budget impact model did not totally correspond to its description in the CS.[1] Furthermore, the ERG performed several sensitivity analyses which revealed that the model parameters used by the company to determine the net budget impact of granting market access to sebelipase alfa dramatically influenced the outcomes of the model. Cautions should therefore be taken when interpreting the results of the budget impact model because the validity of the parameters used by the company could not be assessed. The ERG most plausible scenario resulted in a five year net budget impact which is more than three times higher than the five year net budget impact provided by the company.

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the CS

8.1.1 Nature of estimates presented

The CS includes estimates of impacts of sebelipase alfa for LALD in (i) lost productivity in patients due to premature death and morbidity, (ii) lost productivity in carers, (iii) respite care and other welfare payments, (iv) out of pocket costs associated with transportation and dietary requirement, and (v) carer's time. The main source of information was the EU-LAL-D Survey.(Appendix 5 MS[1]) This online survey was conducted by Alexion and distributed through three patient organisations from the UK, Spain and the USA. Eleven participants participated in the survey (median age 11 years, range 3 to 49 years). Eight (73%) of participants were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa. The company states: "Due to the very low sample size of the survey and the fact that not all patients answered all questions, the results must be interpreted with caution." (Section 7.1 MS[1]).

8.1.2 Societal costs

Section 14.1 of the CS describes the impact of LALD on productivity in patients and carers. Affected infants with rapidly progressive disease die before the age of six months after and affected paediatric and adult patients are unlikely to survive beyond 40 years of age as their life is impacted by portal hypertension, chronic liver failure and premature atherosclerosis.[26, 27, 79] No studies were identified that quantify the impact of this premature death and morbidity on lost productivity. Two of the three adult participants in the EU LAL-D Survey indicated their working status and provided useful, as stated in the CS, information (CS Section 7.1):

"One patient worked full time, 37 hours per week. This patient reported missing one hour during the previous week because of problems associated with LAL Deficiency. She also indicated a moderate impact (score 4 of 10, where 0 equals "no effect" on work and 10 equals "completely prevented" work) on her ability to work. The other patient retired early due to LAL Deficiency at the age of 48 years." (CS, Section 14.1).

Seven carers of children with LAL Deficiency and one carer of an adult patient took part in the EU LAL-D Survey. All carers were parents of the LAL Deficiency patient. Their responses are summarised in Table 8.1 (Table E14.1 in the CS). Two (Spanish female) carers were unemployed. This unemployment rate (25%) is similar to the general country and gender specific unemployment rate,[80] but higher than the EU average (9.5%[81]). The proportion of carers working part-time (83%) is higher than the EU average (32.2%[81]) In addition to this quantitative information qualitative information on the experiences of carers regarding their employability is provided. Carers stated they are unable to fully fulfil their employment obligations.

Table 8.1: Changes in hours of work and professions for carers (n=8) (CS, Table E14.1)

Employment status	Hours worked in the past week	Number of hours reduced per week	Had to reduce hours of work?	Had to change work?	Hours / week spent providing care for LAL Deficiency patients
Working part-time	16	Full time to part time	Yes	Yes	70
	24	8	Yes	No	NR
	7	30	Yes	Yes	NR
	20	NR	No	No	3
	20	12	Yes	No	
Working full-time	35	3	Yes	No	24
Unemployed	N/A	N/A	N/A	Yes	5
	N/A	N/A	N/A	No	14
MEAN	**21.2**	**14.6**			**11.5**

N/A-not applicable

8.1.3 Costs borne by patients

In Section 14.3 in the CS[1] it is stated that some LALD patients are required to follow a low fat diet, that may be more costly than a regular diet. Furthermore, it is mentioned that family members who accompany patients to the hospital will have travel expenses and may be required to take time off work. Treatment with sebelipase alfa may be associated with travel expenses to receive treatment as long as administration is not transitioned to home care.

8.1.4 Other carer costs

In Section 14.4 in the CS[1] time costs parents of LALD patients are mentioned:

"Survey carers reported providing an average of 11.5 hours of care for their children with LAL Deficiency. 38% of carers took fewer holidays to support or care for someone with LAL Deficiency, and 63% reported spending less time with other children and family members."

8.1.5 ERG discussion of wider societal (non-health) benefits

A major source of information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is the EU-LAL-D Survey (Appendix 5 CS[1]). The ERG agrees with the company that due to the very low sample size and missing values, the results of this survey must be interpreted with caution. In addition, the survey was performed in various European countries, so does not only reflect the situation in the UK. Moreover, the survey did not use validated instruments to assess impact on, for instance, labour productivity and caregiving burden. This adds to the uncertainty of the information from this survey.

In addition to information from the survey, information from the literature is presented. It is unclear to the ERG how the studies mentioned in the CS have been retrieved. As a result, the ERG is unable to assess whether the information is complete, and provides an unbiased reflection of the evidence available in the literature.

The information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is descriptive in nature. No attempt has been made to value the impact in terms of costs. The ERG thinks that, using literature and assumptions, some quantification of wider societal benefits is possible. Presumably, the impact on productivity loss would be

highest in terms of costs. Therefore, the ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency. In the searches the ERG conducted to retrieve additional information for the CCA, the study by Scalone[12] was identified. This study reports on productivity loss due to chronic hepatic diseases. Productivity loss corresponded to on average 6.8 days/patient-month by patients and caregivers, and 14.4 days/patient-month for transplant patients. This was incorporated in the ERG base case model as 6.8 days/month for the "No CC, DCC, HCC", "CC", "DCC", and "HCC" health states, and 14.4 days for a patient who receives a transplant. The costs per day with lost productivity were based on the average annual gross earnings in the UK in 2015 (£27,607[82]) and 253 workdays per year. The ERG performed the productivity loss calculations in two ways: based on the human capital approach (HCA) and the friction costs method (FCM).[83] The human capital approach assumes that the relevant value of the production loss is equal to the present value of all lost future earnings of a person. That is, income acts as a proxy for the production value of the individual and all production not produced by this person is counted as production loss. An important, implicit underlying assumption of this approach is no involuntary unemployment occurs. In reality, involuntary unemployment is rather common; ill workers are often replaced. In that case, productivity losses due to long term absence would be limited to the 'friction period', or the period it takes to replace the ill worker by a formerly unemployed person and, hence, to restore production to its initial level. Production losses and transaction costs (related to advertising, hiring, training, etc.) occur during the friction period only. Moreover, since a reduction in labour time is often assumed to cause a less than proportional decrease in production, an elasticity factor is often used in empirical studies applying the friction cost approach. Productivity costs using this method are markedly lower than using the HCA, especially in the case of long term absence and premature death. The ERG used a friction period of three months, hence time horizon does not impact these calculations. The lifetime HCA calculation resulted in productivity loss of £268,856, and the FCM resulted in £2,226. The results are presented in Table 8.2.

Table 8.2: Exploratory scenario analysis of productivity loss in patients/carers (discounted at 1.5%)

Productivity approach	Time horizon 5 years	Time horizon 10 years	Time horizon lifetime
Human capital approach	£38,096	£75,366	£268,856
Friction costs method	£2,226	£2,226	£2,226

8.2 Staffing and infrastructure requirements associated with the use of the technology

Sebelipase alfa treatment should be supervised by an experienced healthcare professional experienced in the management of patients with LAL Deficiency, other metabolic disorders, or chronic liver diseases.[10] Sebelipase alfa is administered by intravenous infusion. The administration time is approximately two hours. If patient tolerability is established, a one hour infusion may be considered. On the other hand, the infusion period may be extended in the event of dose escalation or infusion related events. During administration, appropriate

medical support must be readily available. The company states that in England, it is expected that initiation of the infusions and stabilisation of the patient will occur at specialist LSD centres followed by transition to local hospital outpatient clinics or homecare arrangements, as is the case for currently available enzyme replacement therapies. It is anticipated that besides this, no additional infrastructure is necessary. The company also notes that the management of infants is more complex than in older children and adults. Managing infants may require prolonged hospital stay and multi-disciplinary treatment approaches which may impact on resource requirements for the expert centres managing these infants.

ERG comment:
The ERG thinks it is reasonable to assume that the specialist LSD centres present in the UK will provide the necessary infrastructure to use sebelipase alfa in LAL deficiency patients. The costs of administration of sebelipase alfa in both infants and children older than one year and adults are incorporated in the CCA and the budget impact model.

9. DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

The CS presents results from four intervention studies and one historical control study. One of the intervention studies was a placebo controlled randomised trial.

Paediatric (≤ 2 years) patients with LAL Deficiency:

Two studies were included for this population: study LAL-CL03 was a single arm dose escalation study of sebelipase alfa (from 0.35 to 1 mg/kg once weekly IV; up to 3 or 5 mg/kg once weekly IV) including nine patients with follow-up up to 208 weeks; and study LAL-1-NH01 was a retrospective historical control study including 35 patients diagnosed between 1985 and 2012.

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients who survived past 12 months of age in LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics. In LAL-CL03, six of nine sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, one additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival, 95% CI: 0% to 16%).

No other comparative data were presented for this population.

Paediatric/adult (≥ 4 years) patients with LAL Deficiency:

Study LAL-CL02 (ARISE) was a 20-week placebo controlled randomised trial including 36 sebelipase alfa-treated patients (1 mg/kg) and 30 placebo patients.

A statistically significant improvement in multiple lipid parameters was observed in the sebelipase alfa-treated group as compared to the placebo group at the completion of the 20-week double-blind period of the study, as shown in Table 4.6. The absolute reduction in mean ALT level was -57.9 U/l [redacted] in the sebelipase alfa-treated group and -6.7 U/l (-6%) in the placebo group.

Sixty-five of 66 patients entered the open-label period (up to 130 weeks) at a sebelipase alfa dose of 1 mg/kg once every other week. In patients who had received sebelipase alfa during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels. [redacted].

Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period. Consistent with what was observed in sebelipase alfa-treated patients during the double-blind period, initiation of treatment with sebelipase alfa during the open-label period produced rapid improvements in ALT levels and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Adults (≥ 18 years) with LAL Deficiency:

Study LAL-CL01 was a four week single arm sebelipase alfa study including nine patients divided over three cohorts: 0.35, 1, and 3 mg/kg once weekly IV. Study LAL-CL04 was a 156-week extension including 8 adult patients who had completed LAL-CL01.

Changes in serum transaminase levels observed in adults in study LAL-CL01 were consistent with those reported in study LAL-CL02 and were maintained over long-treatment during the extension study LAL-CL04. Initiation of treatment with sebelipase alfa in study LAL-CL01 produced a rapid decline in ALT and AST. When patients went off treatment at the end of study LAL-CL01 (interval between dosing of nine to 28 weeks), both ALT and AST increased. Normalisation of transaminase levels continued during long-term treatment (through Week 104) in the extension study LAL-CL04.

Safety and tolerability

According to the EMA EPAR[10] the most serious adverse reactions experienced by 3% of patients taking sebelipase alfa in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

In addition, three deaths were reported in the sebelipase alfa clinical programme as of the data cut-off across the four primary studies evaluating safety; all patients who died were enrolled in study LAL-CL03. All fatal events were assessed as unrelated to sebelipase alfa treatment by the investigators.

Serious AEs were reported in 12 (14.3%) of the 84 subjects in the pooled safety set. SAEs were more frequent among infants in study LAL-CL03 with the most rapidly progressive form of LAL Deficiency (eight of nine subjects, 89%) and were relatively infrequent among children and adults (four of 75 subjects, 5%). The most commonly reported types of SAEs were infections (five of 84 subjects, 6%). One patient in study LAL-CL02 reported a serious infection (gastroenteritis). The only other SAE reported in more than one patient in the pooled safety set was pyrexia, reported in two patients in study LAL-CL03.

9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis

9.2.1 Cost-consequence analysis

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on quality of life, cost effectiveness and resource data for patients with LAL Deficiency or provide utilities, resource use or cost data for the economic model. The company did not identify any economic studies, health state utility data, resource use data nor cost data for LAL Deficiency patients. Hence, a de novo model-based cost-consequence analysis (CCA) is presented by the company to compare the costs, life years and QALYs of sebelipase alfa and best supportive care (BSC) for the treatment of LAL Deficiency from an NHS perspective. Costs and consequences are estimated for a population of 11 years-old over a lifetime horizon. For patients with infant disease onset, a scenario analysis is presented. The Markov model is an adaptation of a model for non-alcoholic fatty liver disease (NAFLD)

published by Mahady et al.[2] The model consists of four health states representing different stages of liver disease progression; compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and "LAL deficiency without CC, DCC, or HCC". Furthermore, it includes a liver transplant tunnel state and an absorbing death state. Adverse events were not included in the cost-consequence analysis. Patients receiving sebelipase alfa will remain on treatment for their entire lives. In the BSC group, the only treatment option is a liver transplant, which is offered to patients that have progressed to HCC. Health state utilities were retrieved from the economic model by Mahady.[2] Costs were based on literature.[3] The costs of sebelipase alfa depend on dosing scheme (different for infant onset and later onset) and patient weight. The transition probabilities for sebelipase alfa are mostly based on the LAL-CL02[4] data, whereas for BSC also transition probabilities retrieved from Mahady et al[2] and Hartwell et al[5] are used. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient compared to BSC and the incremental costs would be [redacted] per patient compared the BSC. In the company's sensitivity analyses this result was most sensitive to discount rate and the transition probabilities to and from the "LAL deficiency without CC, DCC" and "HCC" health state. In the infants scenario analysis the LAL-1-NH01 study[6] and LAL-CL03 study[7] were used to inform the transition probabilities for the first year. Health state utilities and costs were mostly based on assumptions. This scenario results in 28.6 QALYs gained and incremental costs of [redacted]

The ERG's critique of the CCA entails the following main points: the health economic search, model structure and estimates for transition probabilities, costs of sebelipase alfa, health state utility estimates, and the handling of uncertainty.

Health economic literature search

The ERG notes that one limitation of the health economic literature search is that all Ovid databases were searched in one single strategy. Moreover, the company focused the search strategy on LAL Deficiency only, while it aimed to identify all health economic studies that could be used to inform the design of the cost-consequence model or provide utilities, resource use or cost data for the model. For this purpose the ERG feels a broader definition of the population as the basis for the literature review would have been useful, in particular including non-alcoholic steatohepatitis (NASH), which was appointed by the company as the disease analogue for modelling LAL Deficiency.

Model structure and estimates for transition probabilities

The model structure used in the cost-consequence analysis differs between the comparators as a result of using different sources for transition probabilities (LAL-CL02[4] data for sebelipase alfa and Mahady et al[2] and Hartwell et al[5] for BSC). For sebelipase alfa it is assumed that, based on surrogate endpoints in LAL-CL02, patients cannot progress to the "CC", "DCC", "HCC" health states, and, as a result, cannot receive a liver transplant. In absence of comparative evidence on the clinical endpoints underlying these health states, the ERG questions this model structure.

The transition probabilities (for BSC) were mainly retrieved from the economic model by Mahady et al.[2] The company identified this economic model from a systematic review

focusing on the use of the non-invasive liver tests (NILT) in a non-acid fatty liver disease (NAFLD) population. Given the restriction to NILT, it is unclear whether there are more appropriate economic models available that were not identified in this systematic search. Specifically the economic model by Zhang et al[51] could have been used as an alternative starting point to develop a model by the company. Moreover, it might have been more appropriate if the company would have aimed to identify clinical studies considering NAFLD to inform transition probabilities instead of limiting itself to cost-effectiveness studies identified in a systematic review.

Costs of sebelipase alfa

After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market. Furthermore, drug costs were influenced by the foreseen introduction of 5 mg vials of sebelipase alfa one year after market access. This reduces waste and costs associated with sebelipase alfa. The ERG thinks the 5 mg vials of sebelipase alfa should not be incorporated in the cost-consequences analysis because these are not yet available.

Health state utility estimates

The health state utility used in the cost-consequence analysis exceeded the UK general population utility scores,[8] For instance, approximately 90% of the patients are still expected to be alive at age 65 with a utility of 0.92 in the "LAL Deficiency without CC, DCC, or HCC" health state, whereas the UK general population utility for persons aged 65 is expected to be 0.784. Despite requested, the company did not provide a plausible justification for the seemingly implausible high health state utility nor any scenario analysis using alternative health state utilities (e.g. age dependent utilities). Moreover, it was unclear whether the health state utility scores selected by the company were the most appropriate ones for the UK context.

Handling of uncertainty

In the probabilistic sensitivity analysis, multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges. In addition, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect.

9.2.2 Cost to the NHS and PSS

The budget impact model in the company's submission estimates the total costs to the NHS of adopting sebelipase alfa in the UK for a period of five years. Two hypothetical scenarios are presented: one where a proportion of patients would receive sebelipase alfa with the remainder receiving BSC, and a second scenario in which all patients would receive BSC. The budget impact model includes two groups of patients. The first group contains patients diagnosed with LAL Deficiency in their first year of life (Age 0-1 presentation group) and the second group includes patients with presentation of symptoms after one year of age (Age 1+ presentation group). Prevalence and incidence are based on various sources of literature and internal modelling by the company. Diagnosis, treatment, treatment continuation and

compliance rates are based on the company's experiences with other treatments for rare diseases. The applied rates result in [redacted] of LAL Deficiency patients treated with sebelipase alfa in the first year, to [redacted] of patients treated in the fifth year. The net five year budget impact amounts to £53,548,573.

The ERG's critique on the budget impact model entails three main points. Firstly, the estimation of incidence and prevalence was not transparently reported. As a result, the ERG was not able to assess the quality and the validity of the adjustments made by the company on Scott et al's prevalence rate.[9] The ERG performed sensitivity analyses in order to explore how prevalence and incidence rates influence the results of the budget impact analysis. Secondly, the estimation of diagnosis, treatment, treatment continuation and compliance rates seem to result in an underestimation of patients receiving sebelipase alfa, when compared to the company's experiences with other treatments for rare diseases. Thirdly, the costs of sebelipase alfa are conditional upon the availability of a 5 mg vial one year after market access. As this vial size is not yet available, the ERG used the 20 mg vial in its calculations.

9.2.3 Non-health benefits

The CS includes estimates of impacts of sebelipase alfa for LAL Deficiency in (i) lost productivity in patients due to premature death and morbidity, (ii) lost productivity in carers, (iii) respite care and other welfare payments, (iv) out of pocket costs associated with transportation and dietary requirement, and (v) carer's time. The main source of information was the EU-LAL-D Survey (Appendix 5 CS[1]). This online survey was conducted by the company and distributed through three patient organisations from the UK, Spain and the USA. Eleven participants participated in the survey (median age 11 years, range 3 to 49 years). Eight participants (73%) were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa. The ERG agrees with the company that due to the very low sample size and missing values, the results of this survey must be interpreted with caution. In addition, the survey was performed in various European countries, so does not only reflect the situation in the UK. This adds to the uncertainty of the information from this survey.

Based on the survey, the company gives an overview of qualitative accounts of patients and carers on productivity. In addition, quantitative accounts of changes in work hours are provided. The impact of sebelipase alfa on these accounts is unclear. It is mentioned that some LAL Deficiency patients are required to follow a low fat diet, which may be more costly than a regular diet. Furthermore, it is mentioned that family members who accompany patients to the hospital will have travel expenses and may be required to take time off work. Treatment with sebelipase alfa may be also associated with travel expenses to receive treatment as long as administration is not transitioned to home care. In addition to information from the survey, information from the literature is presented. It is unclear to the ERG how the studies mentioned in the CS have been retrieved. As a result, the ERG is unable to assess whether the information is complete, and provides an unbiased reflection of the evidence available in the literature.

The information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is descriptive in nature. No attempt has been made to value the impact in

terms of costs. The ERG thinks that, using literature and assumptions, some quantification of wider societal benefits is possible. Presumably, the impact on productivity loss would be highest in terms of costs. Therefore, the ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency.

9.3 Strengths and limitations

9.3.1 Strengths of the CS

The ERG believes that the following represent strengths within the CS:

- Despite LAL Deficiency being a rare disease, the company presented an impressive series of studies in treated patients and historical controls, including a randomised placebo-controlled trial in 66 patients.
- The CS contains details of a recent on-line survey of patients and their families from the USA and Europe which provides relevant information concerning the impact of the disease on patients and their families as well as information on resource use.
- Despite the limited evidence available, particularly regarding the long-term consequences of the disease and treatments, the company presented a CCA with a lifetime time horizon along with several sensitivity and scenario analyses

9.3.2 Weaknesses of the CS

The ERG observes the following weaknesses of the CS:

- Data from treated patients and historical controls may be biased in favour of sebelipase alfa, [redacted] while all nine patients included in LAL-CL03 were diagnosed after 2010 and supportive care will most likely have improved over time.
- Results from the randomised controlled trial show effects on surrogate endpoints, but no evidence is presented to address long-term and key clinical endpoints, such as progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death.
- The CCA and the budget impact model lacked transparency, which made it difficult for the ERG to assess whether the results are complete and valid.
- In absence of comparative evidence on long-term and key clinical endpoints, the modelling of the long-term impact of the technology is extremely uncertain.
- The calculation of the incidence and prevalence of LAL deficiency in the UK for the budget impact model lacked transparency. As a result, the ERG was unable to assess the validity of these estimates.

9.4 Uncertainties

The main uncertainties regarding the effectiveness evidence are the comparability of results from treated patients and historical control patients, the use of surrogate outcomes and the lack of long-term follow-up.

[redacted], while all nine patients included in LAL-CL03 were diagnosed after 2010. Given the likely improvements in supportive care over time, results from comparisons between treated

patients (LAL-CL03) and historical control patients (LAL-1-NH01) may be biased in favour of sebelipase alfa.

Surrogate outcomes showed a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. These measures of well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition. However, there is no evidence to address long-term and key clinical endpoints (progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death). One of the most important outcomes is slowing the progression of the liver disease and hence delaying or avoiding liver transplant. The duration of trials providing data presented in the submission was not long enough to look at this outcome.

There is no mention in the CS of possible stopping rules for sebelipase alfa. In fact the company assumes treatment will be for the full lifetime of the patient (CS, Section 2.3, page 31). However, given the many differences between patients it cannot be assumed that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

Although, there is considerable follow-up in some of the sebelipase alfa studies, with nine patients having received sebelipase alfa treatment for up to 208 weeks and eight patients receiving up to 156 weeks of treatment, this is only a fraction of the expected lifetime treatment with sebelipase alfa. Therefore, the long-term safety and efficacy profile of sebelipase alfa remains uncertain.

The availability of a 5 mg vial after one year of market access is considered uncertain. Also, after 10 years of market access, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market.

10. REFERENCES

[1] Alexion Pharma UK Ltd. *Kanuma(R) (sebelipase alfa) for patients with lysosomal acid lipase deficiency: Submission to National Institute of Health and Clinical Excellence. Highly Specialised Technology (HST)*: Alexion Pharma UK Ltd, 2015. 284p.

[2] Mahady SE, Wong G, Craig JC, George J. Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis. *Hepatology* 2012;56(6):2172-9.

[3] Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2007;11(11):1-205, iii.

[4] Synageva BioPharma Corp. A Multicenter Study of SBC-102 (Sebelipase Alfa) in Patients With Lysosomal Acid Lipase Deficiency/ ARISE (Acid Lipase Replacement Investigating Safety and Efficacy). NCT01757184. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 19.10.15]. Available from: https://clinicaltrials.gov/ct2/show/NCT01757184

[5] Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(17):1-210.

[6] Synageva BioPharma Corp. A Retrospective Natural History Study of Patients With Lysosomal Acid Lipase Deficiency/Wolman Phenotype. NCT01358370. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 19.10.15]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT01358370

[7] Synageva BioPharma Corp. Trial in Children With Growth Failure Due to Early Onset Lysosomal Acid Lipase (LAL) Deficiency/Wolman Disease. NCT01371825. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 19.10.15]. Available from: https://clinicaltrials.gov/ct2/show/NCT01371825

[8] Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11(14):1-160.

[9] Scott SA, Liu B, Nazarenko I, Martis S, et al. Frequency of the cholesteryl ester storage disease common LIPA E8SJM mutation (c.894G>A) in various racial and ethnic groups. *Hepatology* 2013;58(3):958-65.

[10] European Medicines Agency. *Kanuma: Annex I - Summary of Product Characteristics [Internet]*, 2015 [accessed 9.11.15] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004004/WC500192715.pdf

[11] Alexion Pharma UK Ltd. *Sebelipase alpha for patients with lysosomal acid lipase deficiency – Response to request for clarification from the ERG*: Alexion Pharma UK Ltd, 2015. 61p.

[12] Scalone L, Ciampichini R, Fagiuoli S, Gardini I, Gaeta L, Del Prete A, et al. Treatment and productivity costs of chronic hepatic diseases. *Dig Liver Dis* 2011;43:S106.

[13] Jones S, Broomfield A, Roberts J, Ghosh A, White F, Thomas S, et al. *Standard operating procedures for the investigation and management of infantile onset lysosomal acid lipase deficiency (LALD)*, 2015. 14p.

[14] Bernstein DL, Hulkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. *J Hepatol* 2013;58(6):1230-43.

[15] Burton BK, Deegan PB, Enns GM, et al. Clinical features of lysosomal acid lipase deficiency − a longitudinal assessment of 48 children and adults. *J Pediatr Gastroenterol Nutr* 2015:[Epub ahead of print].

[16] Jones S, Valayannopoulos V, Schneider E, et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. *Genet Med* 2015:doi:10.1038/gim.2015.108.

[17] Muntoni S, Wiebusch H, Jansen-Rust M, et al. Prevalence of cholesteryl ester storage disease. *Arterioscler Thromb Vasc Biol* 2007;27(8):1866-1868.

[18] Grabowski GA. The Wolman disease/cholesteryl ester storage disease spectrum. *The Online Metabolic and Molecular Basis of Inherited Disease* 2012:142.

[19] Meikle P, Hopwood J, Clague A, Carey W. Prevalence of lysosomal storage disorders. *JAMA* 1999;281(3):249-54.

[20] Aslanidis C, Ries S, Fehringer P, Buchler C, Klima H, Schmitz G. Genetic and biochemical evidence that CESD and Wolman disease are distinguished by residual lysosomal acid lipase activity. *Genomics* 1996;33(1):85-93.

[21] Reiner Z, 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.

[22] Assmann G, Seedorf U. Acid lipase deficiency: Wolman disease and cholesteryl ester storage disease. In: Scriver CR, Beaudet AL, Valle D, Sly WS, editors. *Metabolic and molecular bases of inherited diseases*. New York: McGraw-Hill, 2001: 3551–3572.

[23] Crocker AC, Vawter GF, Neuhauser EB, et al. Wolman's disease: three new patients with a recently described lipidosis. *Pediatrics* 1965;35:627-40.

[24] Konno T, Fujii M, Watanuki T, Koizumi K. Wolmans disease: the first case in Japan. *Tohoku J Exp Med* 1966;90:375-89.

[25] Marshall WC, Ockenden BG, Fosbrooke AS, Cumings JN. Wolman's disease. A rare lipidosis with adrenal calcification. *Arch Dis Child* 1969;44:331–41.

[26] Mayatepek E, Seedorf U, Wiebusch H, et al. Fatal genetic defect causing Wolman disease. *J Inherit Metab Dis* 1999;22(1):93-4.

[27] Anderson RA, Bryson GM, Parks JS. Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. *Mol Genet Metab* 1999;68(3):333-45.

[28] *Data on File. LAL-2-NH01 Clinical Study Report*, 2014

[29] Balwani M, Quinn AG, Burton B. Phase 3 randomized controlled trial assessing efficacy and safety of sebelipase alfa in children/adults with lysosomal acid lipase deficiency. *Hepatology* 2014;60:1 Suppl.

[30] *Data on File. LAL-CL02 Clinical Study Report*, 2014

[31] Zhang B, Porto AF. Cholesteryl ester storage disease: protean presentions of lysosomal acid lipase deficiency. *J Pediatr Gastroenterol Nutr* 2013;56(6):682–5.

[32] Hamilton J, Jones I, Srivastava R, Galloway P. A new method for the measurement of lysosomal acid lipase in dried blood spots using the inhibitor Lalistat 2. *Clin Chim Acta* 2012;413(15–16):1207-1210.

[33] Guy GJ, Butterworth J. Acid esterase activity in cultured skin fibroblasts and amniotic fluid cells using 4-methylumbelliferyl palmitate. *Clin Chim Acta* 1978;84(3):361-71.

[34] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterol Clin North Am* 2012;142(7):1592-609.

[35] Vajro P, Lenta S, Socha P, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2012;54(5):700-13.

[36] Thelwall PE, Smith FE, Leavitt MC, et al. Hepatic cholesteryl ester accumulation in lysosomal acid lipase deficiency: non-invasive identification and treatment monitoring by magnetic resonance. *J Hepatol* 2013;59(3):543-9.

[37] *Data on File. LAL-CL01 Clinical Study Report*, 2014

[38] Canadian Agency for Drugs and Technologies in Health. *CADTH peer review checklist for search strategies [Internet]*. Ottawa: CADTH, 2013 [accessed 17.7.13]. 3p. Available from: http://www.cadth.ca/en/resources/finding-evidence-is

[39] National Institute for Health and Care Excellence. *Highly Specialised Technologies Evaluation Programme: specification for manufacturer/sponsor submission of evidence (Interim) [Internet]*. London: NICE, 2013 [accessed 13.11.14]. 80p. Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/hst-interim-evidence-submission-template.doc

[40] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed

23.3.11] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[41] *Data on File. LAL-CL03 Clinical Study Report*, 2014

[42] Burton B, Balwani M, Feillet F, et al. A phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency. *N Engl J Med* 2015;373:1010-20.

[43] Balwani M, Breen C, Enns G, et al. Clinical effect and safety profile of recombinant human lysosomal acid lipase in patients with cholesteryl ester storage disease. *Hepatology* 2013;58:950-7.

[44] *Data on File. LAL-CL04 Clinical Study Report*, 2014

[45] Younossi ZM, Guyatt G, Kiwi M, et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* 1999;45(2):295-300.

[46] Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002;94(2):528-38.

[47] Varni JW, Limbers C. The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. *J Health Psychol* 2009;14(4):611-22.

[48] Varni JW, Limbers C, Burwinkle TM. Literature review: Health-related quality of life measurement in pediatric oncology: hearing the voices of the children. *J Pediatr Psychol* 2007;32(9):1151-63.

[49] Mahady SE, George J, Wong G. Cost effectiveness of therapies for non-alcoholic steatohepatitis. *J Gastroenterol Hepatol* 2011;26:52.

[50] Scaglione SJ, Volk M. Liver biopsy versus no liver biopsy in patients with suspected non-alcoholic fatty liver disease (NAFLD): A decision analysis. *Hepatology* 2012;56:910A-911A.

[51] Zhang E, Wartelle-Bladou C, Lepanto L, Lachaine J, Cloutier G, Tang A. Cost-utility analysis of nonalcoholic steatohepatitis screening. *Eur Radiol* 2015;25(11):3282-3294.

[52] Zhang E, Wartelle-Bladou C, Lepanto L, Lachaine J, Cloutier G, Tang A. Cost-utility analysis of screening strategies for nonalcoholic steatohepatitis. *Value Health* 2014;17(7):A367.

[53] Tsochatzis E, Papatheodoridis GV, Manesis EK, Kafiri G, Tiniakos DG, Archimandritis AJ. Metabolic syndrome is associated with severe fibrosis in chronic viral hepatitis and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2008;27(1):80-89.

[54] Wright M, Grieve R, et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006;10(21):1-113.

[55] Saab S, Gordon SC, Park H, Sulkowski M, Ahmed A, Younossi Z. Cost-effectiveness analysis of sofosbuvir plus peginterferon/ribavirin in the treatment of chronic hepatitis C virus genotype 1. *Aliment Pharmacol Ther* 2014;40(6):657-75.

[56] Office for National Statistics. *England, National Life Tables, 1980-82 to 2012-14*, 2015 Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Life+Tables#tab-data-tables

[57] European Medicines Agency. *European public assessment report (EPAR). Kanuma: sebelipase alfa [Internet]*, 2015 [accessed 9.11.15] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004004/human_med_001896.jsp&mid=WC0b01ac058001d124

[58] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed 2.12.15]. 93p. Available from: http://publications.nice.org.uk/pmg9

[59] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43(6):1317-25.

[60] Bhala N, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology* 2011;54(4):1208-16.

[61] Dyson JK, Anstee QM, McPherson S. Non-alcoholic fatty liver disease: a practical approach to diagnosis and staging. *Frontline Gastroenterol* 2014;5(3):211-218.

[62] Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology* 2007;46(1):32-6.

[63] Srivastava A, Gailer R, Gulati S, Warner A, Morgan S, Sennett K, et al. Analysis of new patient attendances for NAFLD at three London hospitals highlights the need to develop clinical risk stratification pathways. *Gut* 2015;64:A249.

[64] Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodriguez-Peralvarez M, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. *Health Technol Assess* 2015;19(9):1-409, v-vi.

[65] Donnan PT, McLernon D, Dillon JF, et al. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). *Health Technol Assess* 2009;13(25):1-134.

[66] David K, Kowdley KV, Unalp A, Kanwal F, Brunt EM, Schwimmer JB. Quality of life in adults with nonalcoholic fatty liver disease: baseline data from the nonalcoholic steatohepatitis clinical research network. *Hepatology* 2009;49(6):1904-12.

[67] Longworth L, Young T, Buxton MJ, Ratcliffe J, Neuberger J, Burroughs A, et al. Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. *Liver Transpl* 2003;9(12):1295-307.

[68] Royal College of Paediatrics and Child Health (RCPCH). *UK-WHO growth charts, 0-18 years [Internet]*, 2015 [accessed 6.10.15] Available from: http://www.rcpch.ac.uk/improving-child-health/public-health/uk-who-growth-charts/uk-who-growth-charts-0-18-years

[69] Mulcahy AW, Predmore Z, Mattke S. *The cost savings potential of biosimilar drugs in the United States*, 2014 [accessed 18.9.15] Available from: http://www.rand.org/pubs/perspectives/PE127.html

[70] National Health Service. *NHS schedule of reference costs 2013-2014*, 2015 Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014

[71] Backx M, Lewszuk A, White JR, Cole J, Sreedharan A, van Sanden S, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *J Viral Hepat* 2014;21(3):208-15.

[72] Office for National Statistics. *Consumer price inflation*, 2015 Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-323653

[73] Jessop EG. Sebelipase alfa for treating lyosomal acid lipase deficiency [ID 737]: Submission to National Institute of Health and Clinical Excellence. Highly Specialised Technology (HST). NHS England statement. 2015: 4.

[74] Longworth L, Young T, Ratcliffe J, Bryan S, Buxton M. *Economic evaluation of the Transplantation Programme in England and Wales: an assessment of the costs of liver transplantation. Report to the Department of Health*, 2001

[75] Halpern EF, Weinstein MC, Hunink MG, Gazelle GS. Representing both first- and second-order uncertainties by Monte Carlo simulation for groups of patients. *Med Decis Making* 2000;20(3):314-22.

[76] Lange L. Quality of life in the setting of anaphylaxis and food allergy. *Allergo J Int* 2014;23(7):252-260.

[77] Office for National Statistics. Population Estimates Analysis Tool, mid-2013 [Internet]. 2013 [accessed 9.9.15]. Available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/sty-population-estimates.html

[78] Office for National Statistics. Release: Population estimates for UK, England and Wales, Scotland and Northern Ireland, mid-2013 [Internet]. 2013 [accessed 31.10.14]. Available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/index.html

[79] Elleder M, Chlumska A, Hyanek J, et al. Subclinical course of cholesteryl ester storage disease in an adult with hypercholesterolemia, accelerated atherosclerosis, and liver cancer. *J Hepatol* 2000;32:528-34.

[80] Eurostat. *Unemployment among females (age 15-64) for Spain*, 2014 Available from: http://ec.europa.eu/eurostat/statisticsexplained/index.php/File:Table_3_Unemployment_rate_by_gender_and_age,_2007-2014_(%25).png

[81] Eurostat. *Unemployment rate for EU28*, 2015 Available from: http://ec.europa.eu/eurostat/statisticsexplained/index.php/File:Unemployment_rates,_seasonally_adjusted,_July_2015.png

[82] Office for National Statistics. *Annual survey of hours and earnings, 2015 Provisional Results [Internet]*, 2015 [accessed 1.12.15] Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-400803

[83] Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995;14(2):171-89.

Appendix 1: Further Search Critique and ERG Search Strategies

Further search strategy critique

Table 17.2

The ERG notes that the structure of Table 17.2 makes it unclear which search lines were indexing terms, and which lines were free text searches of all fields (search lines #1-#4). It is assumed that this is a transcription error, however it would be clearer if indexing terms were identified in the conventional Ovid format (e.g. 'sebelipase alfa/').

Additional search terms such as 'Kanuma', or the CAS Registry number could have been added to the strategy, but the ERG believes that it is unlikely that relevant records have been missed by not including these terms.

Table 17.5

The study design filter indexing terms used in search lines #10 and #13 appear to be Embase (EMTREE) indexing terms only. This Ovid search strategy was also used to search MEDLINE, CENTRAL, DARE, NHS EED and the HTA database, all of which use MEDLINE (MeSH) indexing terms. The ERG therefore believes that MeSH terms should have been added to the strategy to increase the sensitivity of the searches. For example, the MeSH term 'exp Cost and Cost Analysis/' would have been a useful addition to the search to retrieve records on this topic from the above databases. MeSH indexing was used in the EBSCO searches (Table 17.6), so this could have also been adopted for the Ovid search. The ERG also notes that the search terms used in #11 for resource use and #14 for HRQoL are limited, and that these search lines could have been extended with additional terms and truncation to improve the sensitivity of the search.

Given the above concerns about the filters used, and the low number of records retrieved by the search for LAL Deficiency before being limited using filters, the ERG believes that a search for the condition alone could have been a less restrictive approach to the search.

ERG Search Strategies

- Search strategies to identify economic studies, health state utility data, resource use data and cost data for NASH patients.

Embase (Ovid). 1974 to 2015 November 20
Date searched: 23.11.15
Records found: 321

1 (non alcoholic steatohepatitis or nonalcoholic steatohepatitis or non alcoholic steato hepatitis or nonalcoholic steato hepatitis).ti,ab,ot,hw. (7246)
2 nash.ti,ab,ot,kw. (8645)
3 1 or 2 (10788)
4 quality adjusted life year/ or quality of life index/ (16916)
5 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (17345)
6 "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (1986)

7 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (27673)
8 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1676)
9 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (5432)
10 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (899)
11 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (370)
12 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (530)
13 "health related quality of life".ti,ab,ot. (36477)
14 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (10875)
15 "assessment of quality of life".ti,ab,ot. (2008)
16 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (9384)
17 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (18958)
18 (hye or hyes).ti,ab,ot. (98)
19 health$ year$ equivalent$.ti,ab,ot. (39)
20 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2369)
21 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (870)
22 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (2642)
23 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (13896)
24 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (6590)
25 15d.ti,ab,ot. (1873)
26 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (359)
27 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (11999)
28 (utilities or disutili$).ti,ab,ot. (7488)
29 or/4-28 (114528)
30 health-economics/ (34952)
31 exp economic-evaluation/ (235383)
32 exp health-care-cost/ (226450)
33 exp pharmacoeconomics/ (177227)
34 or/30-33 (523296)
35 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (708995)
36 (expenditure$ not energy).ti,ab. (27511)
37 (value adj2 money).ti,ab. (1605)
38 budget$.ti,ab. (27508)
39 or/35-38 (735992)
40 34 or 39 (1024851)
41 (metabolic adj cost).ti,ab. (1048)
42 ((energy or oxygen) adj cost).ti,ab. (3465)

43 ((energy or oxygen) adj expenditure).ti,ab. (23184)
44 or/41-43 (26805)
45 40 not 44 (1019151)
46 29 or 45 (1102664)
47 3 and 46 (334)
48 animal/ or animal experiment/ or nonhuman/ (6688855)
49 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6090714)
50 48 or 49 (7718796)
51 exp human/ or human experiment/ (16590098)
52 50 not (50 and 51) (5902705)
53 47 not 52 (321)

MEDLINE (Ovid). (1946 to November Week 2 2015)
Date searched: 23.11.15
Records found: 128
1 (non alcoholic steatohepatitis or nonalcoholic steatohepatitis or non alcoholic steato hepatitis or nonalcoholic steato hepatitis).ti,ab,ot,hw. (4036)
2 nash.ti,ab,ot,kw. (4015)
3 1 or 2 (5494)
4 quality-adjusted life years/ or quality of life/ (140584)
5 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (16921)
6 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1079)
7 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (3049)
8 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (494)
9 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (344)
10 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (284)
11 "health related quality of life".ti,ab,ot. (23743)
12 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (6882)
13 "assessment of quality of life".ti,ab,ot. (1230)
14 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (4590)
15 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (11177)
16 (hye or hyes).ti,ab,ot. (60)
17 health$ year$ equivalent$.ti,ab,ot. (38)
18 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (950)
19 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (634)
20 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (1966)
21 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (7681)

22 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (4114)
23 15d.ti,ab,ot. (1227)
24 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (252)
25 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (7299)
26 (utilities or disutili$).ti,ab,ot. (4360)
27 or/4-26 (166604)
28 economics/ (27221)
29 exp "costs and cost analysis"/ (195680)
30 economics, dental/ (1888)
31 exp "economics, hospital"/ (20926)
32 economics, medical/ (9034)
33 economics, nursing/ (3957)
34 economics, pharmaceutical/ (2651)
35 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (469610)
36 (expenditure$ not energy).ti,ab. (19049)
37 (value adj1 money).ti,ab. (25)
38 budget$.ti,ab. (18550)
39 or/28-38 (601211)
40 ((energy or oxygen) adj cost).ti,ab. (2822)
41 (metabolic adj cost).ti,ab. (861)
42 ((energy or oxygen) adj expenditure).ti,ab. (17551)
43 or/40-42 (20482)
44 39 not 43 (596690)
45 27 or 44 (735564)
46 3 and 45 (135)
47 animals/ not (animals/ and humans/) (4055381)
48 46 not 47 (128)

Appendix 2: Sensitivity analyses on budget impact model (based on ERG corrected model; 5 mg vials available from the second year of the model onwards)

Appendix 2.1: Five year net budget impact resulting from sensitivity analyses on diagnosis and treatment rates of the Age 1+ presentation group (based on ERG corrected model; 5 mg vials available from the second year of the model onwards)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates -20% [redacted]	Treatment rates -10% [redacted]	Treatment rates as in base case [redacted]	Treatment rates +10% [redacted]	Treatment rates +20% [redacted]
Diagnosis rates -20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£19,346,891	£23,815,388	£28,283,886	£32,752,383	£37,220,881
Diagnosis rates -10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£26,978,260	£33,903,120	£40,827,981	£47,752,842	£54,677,703
Diagnosis rates as in base case [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£34,609,629	£43,990,853	£53,372,077	£62,753,301	£72,134,525
Diagnosis rates +10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£42,240,998	£54,078,585	£65,916,172	£77,753,759	£89,591,347
Diagnosis rates +20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£49,872,367	£64,166,317	£78,460,268	£92,754,218	£107,048,169

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955).

[2] Rates were varied to a minimum of 0% and a maximum of 100%.

[3] Treatment rates in Year 1 until 5.

[4] Diagnosis rates in Year 1 until 5.

Appendix 2.2: Five year net budget impact resulting from sensitivity analyses on treatment continuation and compliance rates of the Age 1+ presentation group (based on ERG corrected model; 5 mg vials available from the second year of the model onwards)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates -20% [redacted]	Treatment rates -10% [redacted]	Treatment rates as in base case [redacted]	Treatment rates +10% [redacted]	Treatment rates +20% [redacted]
Diagnosis rates -20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£29,814,890	£37,304,359	£44,793,827	£52,283,296	£59,772,764
Diagnosis rates -10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£42,265,899	£53,765,270	£65,264,640	£76,764,010	£88,263,381
Diagnosis rates as in base case [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£54,716,908	£70,226,180	£85,735,453	£101,244,725	£116,753,998
Diagnosis rates +10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£67,167,917	£86,687,091	£106,206,266	£125,725,440	£145,244,615
Diagnosis rates +20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£79,618,925	£103,148,002	£126,677,079	£150,206,155	£173,735,232

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955).

[2] Rates were varied to a minimum of 0% and a maximum of 100%.

[3] Treatment rates in Year 1 until 5.

[4] Diagnosis rates in Year 1 until 5.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID 737]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Friday 18 December 2015** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Note: Per NICE guidance, information that is academic in confidence (AIC) and should remain confidential is highlighted in [redacted] and underlined, and information that is commercial in confidence (CIC) and should remain confidential is highlighted in [redacted] and underlined.

Contents

Issue 1 The ERG incorrectly claims that “no evidence” was presented to address key or long-term clinical endpoints with sebelipase alfa treatment. 4
Issue 2 The ERG’s estimate that sebelipase alfa produces 0.0 incremental QALYs is based on three key factual inaccuracies, the first of which is the assumption that there is an “Equal probability of transitioning from 'LALD without CC, DCC or HCC' to 'CC' for both comparators". 12
Issue 3 The ERG’s estimate that sebelipase alfa produces 0.0 incremental QALYs is based on three key factual inaccuracies, the second of which is the assumption that BSC-treated patients likely regress from 'CC' to 'LALD without CC, DCC or HCC'. 17
Issue 4 The ERG’s estimate that sebelipase alfa produces 0.0 incremental QALYs is based on three key factual inaccuracies, the third of which is the assumption that the transition to advanced liver disease is equal for BSC- and sebelipase alfa-treated patients. 21
Issue 5 The ERG misuses health utilities from the Crossan et al. study. 24
Issue 6 The ERG incorrectly states that the structure of the model for the sebelipase alfa- and BSC- arms is different; however, the structure is not different, just the transitional probabilities are different. 27
Issue 7 The ERG implies that Alexion was unclear as to how it parameterized the survival model related to the analysis in Figure D12.2; however, the parameterization is clearly identified in our initial submission. 29
Issue 8 The ERG’s statement that Alexion’s model structure made it impossible for BSC-treated patients to transition from “CC” to “LALD without CC, DCC or HCC” is factually inaccurate. 30
Issue 9 The ERG inaccurately claims that the historical control arm (LAL-1-NH01) is not an appropriate comparator to the sebelipase alfa arm in the infant study (LAL-CL03). 31
Issue 10 The ERG claims that only one expert contributed to the validation of the economic model structure and approach when input was obtained from seven experts. 35
Issue 11 The ERG claims a different published model structure could have been used, but due to timelines, use of this model would not have been feasible and was not deemed as relevant as the one advocated by the experts. 37
Issue 12 The ERG incorrectly states that Alexion “neglected uncertainty” with regard to FIB-4 39
Issue 13 The ERG incorrectly states that LAL-CL02 data are exclusively used to inform the transition probabilities for sebelipase alfa in the economic model. 42
Issue 14 The ERG claims that Alexion did not provide details on the primary sources for the transition probabilities utilized in Mahady et al.; however, the primary source for the transition probabilities is Mahady et al. itself. 43

Issue 15 The ERG claims that sensitivity analyses varying the transition probabilities between the “LALD without CC, DCC or HCC” and “CC” states contain "unsystematic comparisons", and states that only BSC scenario 1 vs. SA base case contains a "fair and useful comparison", when all deterministic sensitivities reported were systematic and transparent. 44
Issue 16 The ERG incorrectly claims that there is inconsistency in input parameter selection. 48
Issue 17 The ERG incorrectly claims that the budget impact model was not implemented as described in Alexion’s initial submission when in fact the assumption that infant patients receiving BSC die within their first year of life was incorporated into the calculations, as well as the non-drug direct medical costs. 50
Issue 18 The ERG claims that there is a lack of transparency in Alexion’s calculations of epidemiological rates, when our calculations were presented in our initial submission; we provide further explanation below for clarity. 51
Issue 19 The ERG’s modifications to diagnosis, treatment, discontinuation, and compliance rates in the BIM rely on an arbitrary assumption and conflict with real-world evidence. 55
Issue 20 The ERG claims that the “most plausible” scenario in the budget impact model yields net budget impact over five years “more than three times higher than the company’s base case five year net budget impact”, when the most plausible scenario based on available evidence is 19% above the submitted base case. 57
Issue 21 The ERG incorrectly states that Alexion did not provide any subgroup analyses in the economic model. 58
Issue 22 The ERG uses both a 3.5% and 1.5% discount rate for costs and benefits; the ERG should use 1.5% per previous NICE guidance. 59
Issue 23 The ERG incorrectly states that systematic review methods were not reported in Alexion’s submission. 62
Issue 24 The ERG incorrectly describes the observational assessment. 63
Issue 25 The ERG’s statement that studies were omitted from the initial submission is incorrect. 64
Issue 26 The ERG incorrectly implies that no literature review was performed in Crossan et al. on natural history models in NAFLD. 64
Issue 27 The ERG alleges that the CCA and BIM models are “not transparent”; however, both models include all data used and explanations of the data source. 66
Issue 28 The ERG makes inaccurate assessments regarding the patient survey conducted and the societal impact of LAL Deficiency. 68

Issue 1 The ERG incorrectly claims that "no evidence" was presented to address key or long-term clinical endpoints with sebelipase alfa treatment.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 17 of the ERG's report, the ERG states: "Results from the randomised controlled trial show effects on surrogate endpoints, but no evidence is presented to address long-term and key clinical endpoints, such as progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death." On page 14, the ERG states "The duration of the trials providing data presented in the submission was not long enough to look at this outcome. In addition, the long-term safety and efficacy profile of sebelipase alfa is uncertain"	The ERG's text should be revised to the following: "Results from the randomised controlled trial show statistically significant effects on the surrogate endpoints, which reflect the fundamental deficiency seen in LAL-Deficiency. However, similar to other rare diseases and clinical trial design limitations, a design incorporating endpoints, such as progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events, and death, is not feasible in this patient population."	It is factually incorrect that "no evidence" was presented to address key or long-term clinical endpoints with sebelipase alfa treatment. 1. In Alexion's initial submission to NICE, the totality of available clinical evidence for sebelipase alfa was included to show the beneficial clinical endpoints of the drug, which are described again throughout this document. Alexion's initial submission to NICE included data submitted to the European Medicines Agency (EMA) for marketing authorization, on the basis of which EMA approved sebelipase alfa for "long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency" (Kanuma SmPC, 2015). The marketing authorisation for sebelipase alfa was reviewed and approved by clinical experts with	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Similar statements are made on pages 51 and 52 of the ERG's report.		experience with lysosomal storage disorders and liver disease, who found the clinical data to provide evidence of long-term benefit for patients with LAL Deficiency. Alexion's submission to NICE included these same data, illustrating the key clinical endpoints (ATL, LDL-C, and liver fat content reduction) that have significant clinical relevance to the impact of sebelipase alfa in the treatment of LAL Deficiency. These data were deemed appropriate for regulatory review and represent the longest term data (for both untreated and treated patients) available globally for this ultra-rare disease. 2. The complexity and rarity of a disease like LAL Deficiency precludes a traditional outcomes-based clinical trial design. The study size and duration for the sebelipase alfa clinical trials, which were discussed and agreed with EMA and the US Food and Drug Administration (FDA), align with addressing the root cause of	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		the disease, the rarity of the disease, and the rate of disease progression. The extreme rarity of LAL Deficiency precludes performing studies of the size and duration that would be required to directly assess the impact of sebelipase alfa on clinical events associated with progressive liver disease (e.g., decompensated cirrhosis or liver-related mortality) or cardiovascular disease (CVD) (e.g., cardiac-related mortality) in subjects with LAL Deficiency. These limitations also exist in more common chronic liver disease settings due to similar challenges. Because of these limitations, the primary endpoints in studies in other chronic diseases primarily affecting the liver such as NASH and hepatitis B/C, have included (alone or in combination) biochemical response associated with resolution of chronic liver injury (transaminase normalisation), and, importantly, evidence of an impact	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		on the root cause of disease (e.g., viremia in hepatitis B/C), where this is known. 3. The robustness of the clinical assessment of sebelipase alfa was enhanced with the incorporation of a placebo in the trial involving children and adults. LAL Deficiency results from an autosomal recessive inborn error of metabolism, in which a well-defined pathogenic mechanism leads to accumulation of cholesteryl esters and triglycerides in the liver that is not likely to be susceptible to dietary or lifestyle changes. No significant placebo effect would be expected; however, a placebo arm was selected to ensure a robust interpretation of safety and efficacy data in a controlled setting of LAL-CL02. Use of placebo was considered ethical in the LAL-CL02 study as the observational data (LAL-2-NH01) suggest that although LAL	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		Deficiency in children and adults is a progressive disease, significant progression to events such as cirrhosis, hepatocellular carcinoma, need for liver transplant or cardiovascular events was unlikely over the period of 20 weeks, and therefore would not put patients at undue risk during the placebo-controlled phase of the study. 4. Endpoints used in the sebelipase alfa clinical trials demonstrate evidence for addressing the root cause of LAL Deficiency, and are proven markers for liver progression and cardiovascular risk. Clinically important endpoints were evaluated in Study LAL-CL02 to provide a totality of evidence supporting clinical benefit of sebelipase alfa in this rare, multisystem disease, confirming that effective enzyme replacement is addressing the root cause of disease pathogenesis. Endpoints focused on the	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		importance of decreasing liver injury, along with restoring normal homeostasis to lipid and liver metabolism, as evidenced by the correction of dyslipidaemia, demonstrated improvements in hepatic injury and liver fat content. As noted in our initial submission to NICE, liver endpoints such as ALT are proven markers for liver progression. ALT is a well-accepted biomarker of liver injury, in particular, persistent elevation of serum transaminases is clinically significant in the context of known causes of chronic liver disease and/or drug-induced liver injury. Data from a highly relevant nonclinical model of LAL Deficiency show a strong concordance of elevated transaminases with progressive liver disease and development of fibrosis in untreated animals and, importantly, a concordance of transaminase reduction with subsequent improvement in liver	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		histology and improved survival in response to treatment with sebelipase alfa. Additionally, there are historical precedents for use of ALT normalisation as a relevant endpoint in other chronic liver disease settings (e.g., in combination with virological endpoints in viral hepatitis (Tyzeka, telbivudine in hepatitis B; and Hepsera, adefovir dipivoxil in pediatric patients with hepatitis B). ALT could be measured reliably in all subjects enrolled in the sebelipase alfa study (LAL-CL02), which is an important consideration in a disease that primarily impacts a paediatric population. As stated in our initial submission, lipid endpoints are proven markers for cardiovascular risk. Circulating LDL-c levels have a well-documented positive association with risk of CVD, and extensive data from randomized controlled clinical studies indicate that reductions in LDL-c are associated with reductions in that risk.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		Emerging data signal that reduction in triglycerides may also improve cardiovascular risk. These decreases in LDL-c and triglycerides, along with the benefit seen with rising HDL-c with sebelipase alfa, will be expected to result in CV event reduction over time. Additional exploratory endpoints show clinical benefit on lipoprotein profiles in those treated with sebelipase alfa compared to those untreated: [redacted]. Emerging clinical data has shown particle number to be strongly correlated with the risk of cardiovascular disease and functions as another endpoint indicating that long-term therapy with sebelipase alfa will reduce CV events in patients with LAL Deficiency. In summary, the ERG incorrectly ignores the benefit of long-term	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		treatment with sebelipase alfa, which addresses the root cause of LAL Deficiency, despite acknowledging that the endpoints are “well correlated” to markers of progression of liver disease. (See page 52 of the ERG report that states: “Surrogate outcomes showed a strong pharmacodynamic effect [of sebelipase alfa] on lipid levels, hepatic fat content, and liver enzymes. These outcomes, on well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition.”)	

Issue 2 The ERG’s estimate that sebelipase alfa produces 0.0 incremental QALYs is based on three key factual inaccuracies, the first of which is the assumption that there is an “Equal probability of transitioning from 'LALD without CC, DCC or HCC' to 'CC' for both comparators".

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 18, the ERG states: “The ERG preferred base case resulted in a substantial decrease of the incremental QALYs; from 19.2 QALYs in the company base case to 0.0 QALYs in the ERG base	ERG should use data from patients when on sebelipase alfa to represent the sebelipase alfa transition from 'LALD without CC, DCC or HCC' to 'CC'. The ERG should not conduct analyses with the	The ERG uses incorrect transition probabilities for the sebelipase alfa arm of the model because of the reasons described below: 1. The ERG’s assumption that there is an “Equal probability of transiting	LAL-CL02 showed an effect on surrogate outcomes, but this was not translated to clinical outcomes (e.g. to CC using the FIB-4 score). As a result, the effect of SA on disease progression is uncertain. The ERG incorporated this in its

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
case, indicating no additional benefit for sebelipase alfa. This decrease was mainly due to the use of alternative transition probabilities; removing inconsistent assumptions regarding the model structure and use of sources for model input estimation." There are three assumptions which essentially lead to ERG's conclusion, as ERG wrote on page 69: "Therefore, the ERG would prefer to assume: 1. Equal probability of transiting from 'LALD without CC, DCC or HCC' to 'CC' for both comparators, using the annual probability of 3.2% obtained through the survival analysis. 2. Probability of transiting from 'CC' to 'LALD without CC, DCC or HCC' based on FIB-4 scores for both	assumption that there is an "Equal probability of transiting from 'LALD without CC, DCC or HCC' to 'CC' for both comparators, using the annual probability of 3.2% obtained through the survival analysis." Implementing this change would increase the incremental QALYs in the ERG model from 0.0 to 2.3, which is 11% of the incremental QALYs estimated in Alexion's model.	from 'LALD without CC, DCC or HCC' to 'CC' for both comparators, using the annual probability of 3.2% obtained through the survival analysis" is a factual error. This analysis included in the ERG's model was conducted to estimate the transition probability for BSC patients and did not include any data for patients receiving sebelipase alfa. It is logical to use this analysis for BSC-treated patients, as Alexion did in its base case analysis; however, it is not logical to do this analysis for the sebelipase alfa arm, as this analysis was based on pre-trial observations (i.e., baseline patient data from LAL-CL02 of events before the trial started). Instead, it would seem logical to use the trial observations for sebelipase alfa-treated patients once they started receiving sebelipase alfa. In both our initial submission, and our response to the ERG's initial questions, Alexion has clarified this issue. As described on page 171 of our initial submission, "The failure	analyses, this is explained in section 5.3.3 of the ERG report. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
comparators. 3. All other transition probabilities based on Mahady et al (equal for both comparators).'" Each of these assumptions contains factual inaccuracies. To begin with, "Equal probability of transiting from 'LALD without CC, DCC or HCC' to 'CC' for both comparators, using the annual probability of 3.2% obtained through the survival analysis" is not based on logic. Without justification, the ERG is relying on a probability calculated with only BSC data to parameterize the sebelipase alfa arm, instead of using the available on-treatment data from the clinical trials for sebelipase alfa patients as was done in the company model.		event was defined as the earliest mention (either a pre-baseline medical record or at baseline of the LAL-CL02 trial) of a confirmed case of CC… Study time was defined to begin on the date of a patient's first record of LAL Deficiency symptom onset, and to end on the earlier of the date of the baseline biopsy or first record of cirrhosis in medical history." In other words, this is an analysis of the pre-trial period for patients in ARISE, when they were receiving BSC. 2. Pre-treatment data are a valid though conservative source for disease progression for patients receiving BSC. As stated in Alexion's response to question A8 of the NICE/ERG clarification letter data November 16th, "The survival analysis was conducted to approximate the rate of transitioning from fibrosis to compensated cirrhosis (CC) relied only on pre-treatment biopsy data…This analysis… did not include any data gathered during	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		the treatment period. The purpose of this analysis was to identify the transitional probability for BSC-treated patients to transition from 'LAL Deficiency without CC, DCC or HCC' to 'CC'." As previously noted, this is a conservative analysis, as only living patients without advanced liver disease were included in the ARISE trial. As such, there is most likely a selection bias that works against the value of sebelipase alfa, since including patients with advanced liver disease would result in a higher transition probability from 'LAL Deficiency without CC, DCC or HCC' to 'CC' for BSC-treated patients. 3. The base case transition probability of 3.2% for BSC-treated patients should not be used for the sebelipase alfa-treated patients. Rather than using the 3.2% transition probability, which is not applicable for sebelipase alfa-treated patients, we used clinical	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		trial data for the sebelipase-alfa treated arm. The ERG provides no justification for using data from BSC-treated patients to calculate a transition probability for sebelipase alfa-treated patients. Instead, the ERG presents this change as removing “inconsistency”, when in actuality, it uses factually inaccurate data to reflect the impact of sebelipase alfa.	

Issue 3 The ERG's estimate that sebelipase alfa produces 0.0 incremental QALYs is based on three key factual inaccuracies, the second of which is the assumption that BSC-treated patients likely regress from 'CC' to 'LALD without CC, DCC or HCC'.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The second of the three factually incorrect assumptions, which essentially leads to the ERG's flawed conclusion, is stated on page 69 of the ERG's report: "Probability of transiting from 'CC' to 'LALD without CC, DCC or HCC' [should be] based on FIB-4 scores for both comparators." It is a factual inaccuracy that the trials were parameterized for the analysis of the probability of transiting from 'CC' to 'LALD without CC, DCC or HCC', and it is an erroneous read of the data.	The ERG should use the rate adapted from Mahady et al. as representative of the natural history of disease, as opposed to a rate calculated based on one out of four placebo patients improving in the sebelipase alfa trial. Implementing this change would increase the incremental QALYs in the ERG model from 2.3 to 7.9, which is 39% of the incremental QALYs estimated in Alexion's model.	1. The ERG utilizes an analysis of one of four patients (an outlier given other analysis) to parameterize the transition probability from "CC to without CC, DC, or HCC" for BSC patients. The ERG writes on page 69 of its report that: "the probability of transiting from 'CC' to 'LALD without CC, DCC or HCC' [should be] based on FIB-4 scores for both comparators." It is a factual inaccuracy that the trials were parameterized for this analysis, and the ERG uses one of four patients who were potentially CC at baseline based on FIB-4 and received BSC to parameterize this transition probability. Instead of relying on the rate adapted from Mahady et al. as representative of the natural history disease progression, the ERG is suggesting it is more appropriate to calculate a probability based on four placebo patients beginning LAL-CL02 with FIB-4 scores >1.45, which is based on an extremely	This is not a factual inaccuracy. (see also our response on Issue 2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		small number of patients and incongruent with scientific understanding of liver disease. At week 20, one of these patients had a FIB-4 score below 1.45. Note that in all of the alternate sets of transition probabilities calculated using different thresholds for FIB-4 and the Forns index shown in Table D12.7 of the company submission, none of the placebo patients improved from 'CC' to 'LALD without CC, DCC or HCC', which is why this transition is likely an outlier. Conversely, sebelipase alfa-treated patients improved on all FIB-4 thresholds tested. Note that when using APRI, 1/3 placebo patients improved compared with 6/7 sebelipase alfa-treated patients. Furthermore, results of improvement based on significant change in FIB-4 score for these patients were provided in response to A10 of the NICE clarification letter data November 16th. When using cut-off values indicating likely significant clinical differences of 0.4 and 0.154 based on Tamaki et al. (2013), 0% and 3% of placebo patients showed improvement compared with	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		14% and 41% of sebelipase alfa patients, respectively. Yet, the ERG assumes that BSC and sebelipase alfa-treated patients have the same likelihood of improvement. 2. The ERG's assumption that 25% of placebo patients would demonstrate significant improvement is inconsistent with all other analyses performed and current understanding of the disease. The noted 25% based on one of four patients improving on one threshold measure is likely the result of measurement error, and not representative of the expected trajectory of BSC-treated patients as it is not in line with published clinical reports of LAL Deficiency. The ERG extrapolates from the very small sample size of just four placebo-treated patients to calculate an annual transition probability of 52.8% from 'CC' to 'LALD without CC, DCC, or HCC' for BSC-treated patients. That is, the ERG model assumes incorrectly that the majority of patients with 'CC' receiving only BSC will transition annually to 'LAL-D without CC, DCC, or HCC'. In short, the ERG's	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		model assumes that BSC will make the average patient's pathology reversible, which is not supported by the data or published literature. This is a factual inaccuracy because by adding this probability, the long-term NAFLD probabilities in Mahady et al. would become incorrect. If the ERG were correct, the results in Mahady et al. indicating that patients with NAFLD will live for another 6.3 to 11.0 discounted years depending on treatment would imply that LAL Deficiency is less severe a disease than NAFLD; however, cross functional data has a greater burden of disease. In addition to the nature of the fibrosis-inducing insult, the duration of liver injury is also likely to be important in conditions such as LAL Deficiency. It is well recognized for other chronic diseases including hepatitis B and C, NAFLD, alcoholic liver disease, and various metabolic diseases that by failing to remove the causative factor, fibrosis is associated with progression to cirrhosis. BSC does not remove the causative factor as it only attempts to address the co-morbid clinical	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		symptoms and signs and does not address the root cause of the disease. Therefore, with BSC alone, a patient with LAL Deficiency with 'CC' will not transition annually to 'LALD without CC, DCC, or HCC'.	

Issue 4 The ERG's estimate that sebelipase alfa produces 0.0 incremental QALYs is based on three key factual inaccuracies, the third of which is the assumption that the transition to advanced liver disease is equal for BSC- and sebelipase alfa-treated patients.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The third factually incorrect assumption, which essentially leads to ERG's flawed conclusion, is included on page 69 of the ERG report: "All other transition probabilities based on Mahady et al. (equal for both comparators)." In short, the ERG concludes that the natural history rate of progression to DCC, HCC and subsequent states should be used for sebelipase alfa-treated patients. The ERG supports	The ERG should retract its assumption that the transition to advanced liver disease is equal for BSC- and sebelipase alfa-treated patients. Instead, the ERG should calculate the transition from 'CC' to 'DCC' and 'HCC' from sebelipase alfa using data for sebelipase alfa-treated patients from the clinical trials. Implementing this change would increase the incremental QALYs in the	It is factually inaccurate to assume that transition probabilities to advanced liver disease are equal for both BSC- and sebelipase alfa-treated patients; evidence from Bernstein et al. and other sources shows that BSC-treated patients will progress. Conversely, evidence from the total sebelipase alfa clinical trials program including LAL-CL02, LAL-CL03, LAL-CL01/CL04, LAL-CL01 and LAL-CL04 show that sebelipase alfa-treated patients will not progress to DCC or HCC. The ERG incorrectly states that the likelihood of zero events for sebelipase alfa-treated patients is justified based only on LAL-CL02 and that "In the clinical trials for	This is not a factual inaccuracy. (see also our response on Issue 2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
this assumption with the following argument, stating on page 69 of its report that: "The 0% 'DCC' probability [representing the likelihood that sebelipase alfa patients transition from CC to DCC] is justified by the company by stating that this was not observed in the LAL-CL02 trial. This is however equally true for BSC." However, it is factually and logically inaccurate to state that this justification was based only on data from LAL-CL02 and to then state that it is equally true for BSC patients.	ERG model from 7.9 to 14.8, which is 72% of the incremental QALYs estimated in Alexion's model.	sebelipase alfa, which included 2,691 [cumulative] weeks of treatment (Table D12.8), there were no observed instances of patients on sebelipase alfa transitioning to DCC or HCC and no deaths (aside from the deaths in the LAL-CL03 infant trial which applies only to those under the age of 1). Consequently, a 0% transition probability to HCC or DCC is assumed for sebelipase alfa. Sebelipase alfa restores normal lipid metabolism, so it is expected that liver progression to these states will be suspended. This is also consistent with the liver score data that indicate that liver disease is on balance regressing and not progressing for patients on sebelipase alfa." Table D12.8 ("Observable weeks on sebelipase alfa by trial and overall") clearly presents results from LAL-CL01, LAL-CL02, LAL-CL03, and LAL-CL04. In contrast, prospectively gathered data were available for only about 667 study period weeks from the placebo arm of LAL-CL02. While no DCC or HCC cases were observed over this period, it is not factually accurate to say that the likelihood of zero events is equally true based on the imbalance in data availability. In the published literature, there are at least two cases of progression to HCC with BSC: one at 11 years of age and another at 52	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		years of age.(Elleder M, et al. Virchows Arch 2000;436:82–87; Riva S, et al. Dig Liver Dis 2008;40:784.) More importantly, according to Bernstein et al., 2013, “Death due to liver disease progression occurred [in their cohort of 135 patients] at 7 to 56 years of age, and 50% of deaths were in patients under 21 years of age.” Patients who are treated with BSC have a much greater likelihood of death from advanced liver disease than non-LAL Deficiency patients given that BSC does not remove the ensuing liver injury. Based on clinical evidence and understanding of metabolic liver disease, it is expected that sebelipase alfa-treated patients could have reduced progression relative to BSC-treated patients. It is clinically plausible that once the source of hepatocyte injury and necroinflammation is removed or treated, the risk for HCC or DCC is also removed. Hepatocytes are able to regenerate (unlike nerve or kidney cells) once the insult is removed, thus restoring normal liver functions of synthesis and metabolism of toxic byproducts. The reduction of ALT levels, as measured in the sebelipase alfa clinical trials, is a marker of reduced hepatocyte necrosis.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		Also, in other diseases that result in chronic hepatic necroinflammation, such as chronic viral hepatitis, the risk of HCC declines dramatically once the viral infection and consequent hepatocyte injury is removed with potent antiviral therapies. For example, HCV models commonly assume a 0% progression rate to DCC or HCC after a sustained viral response (Hartwell et al., 2011).	

Issue 5 The ERG misuses health utilities from the Crossan et al. study.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 73, the ERG states that, "Based on the review by Crossan et al the company selected Mahady et al as source for health state utilities. Similarly as for the transition probabilities, there was a lack of transparent reporting (despite the requested clarifications). It was unclear why the utilities from Mahady et al were considered most appropriate. […] To salvage this issue,	The ERG should use the health utilities from the Mahady et al. NAFLD model. Implementing Mahady et al utilities would increase the incremental QALYs in the ERG model from 14.8 to 18.8, which is 92% of the incremental QALYs estimated in Alexion's model.	The ERG states that "there was a lack of transparent reporting (despite the requested clarifications)." However, we took our health utilities directly from Mahady et al., which was a model designed for a NAFLD patient population. There could not be a more transparent way of reporting the utilities. The ERG uses health utilities from an inappropriate HCV population (the UK Mild HCV Trial), though these patients are sicker than NAFLD patients owing to comorbidity burden. In the UK Mild HCV	Mahady et al is not the original source of the health state utilities. The ERG thinks age adjustment is appropriate. This is not a factual inaccuracy (see section 5.3.3.6 of the ERG report)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
the ERG used the health state utilities as reported by Crossan et al. These health state utilities were measured using the EQ-5D for hepatitis C patients and in part measured in the UK. Here it is assumed that the utilities for the different health states would be similar for different liver diseases irrespective of the initial cause. Please note that this latter assumption is also applicable to the health state utilities reported by Mahady et al as these were primarily retrieved from hepatitis C populations." It Is factually incorrect to assume that the ERG's proposed health-utility data are more relevant to a LAL-Deficiency patient population, as described in the accompanying justification. The ERG also "implemented a minimum function in the model to ensure the health state utilities in the model	Not using the age-adjustment on health utilities would increase the incremental QALYs in the ERG model from 18.8 to 20.5, which is 100% of the incremental QALYs estimated in Alexion's model.	Trial, which ERG advocates for, 53% (104/196) of enrolled patients were infected via intravenous drug abuse; 31% had "unknown" source of infection, per Wright et al., 2006, Table 8, page 16. Mahady et al. use some HCV health utilities in their estimates, but use those at the higher end of the health utility spectrum in HCV indicating a healthier population infected through the blood supply and not risky behavior; we presume Mahady et al. did this purposefully to avoid characterizing NAFLD quality of life with the large comorbidity burden associated with some HCV patients (e.g., HIV, HBV, psychiatric disorders, intravenous drug use); excess rates of these comorbidities are not present in the LAL-Deficiency patient population. Alexion demonstrated that the patients in the LAL-CL02 ARISE trial had quality of life that was no different than a general background patient population. The ERG makes a factual inaccuracy by assuming that the quality of life of the general background patient population is the same as those with HCV in the UK Mild HCV Trial. Specifically, the health utility of the healthiest person in their model is 0.66,	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
would not exceed those of the general population with the same age." ERG cites Ward et al., 2007 (Ward, S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11(14):1-160) when justifying this approach, which was a paper on statin use in patients age 45-85, which is inappropriate.		which is contrary to the data in the Alexion trials and those for the general UK population. The ERG states that "the ERG used the health state utilities as reported by Crossan et al.", but the ERG misquotes the HCV health utilities that they cite in Crossan et al. For example, they use 0.66 (page 73) for the "LAL-D without CC, DCC or HCC' state", when this state is a mix (at worst) of mild and moderate fibrosis. ERG misquotes the DCC and HCC health utilities from Crossan et al., using a value of 0.49 (page 73) instead of 0.57, which appears on page 66 of Crossan et al. ERG also "implemented a minimum function in the model to ensure the health state utilities in the model would not exceed those of the general population with the same age." ERG cites ard S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11(14):1-160. When justifying this approach, which was a paper on statin use in patients age 45-85 which is inappropriate. Our disease is an ultra-	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		rare liver disease where the average age is about 11. The utility function applied by the ERG is not applicable to our patient population, given that it starts at such a young age. Further, NICE did not require this health utility function to be used in the modelled base cases in their reviews of the all oral HCV regimen submissions. It would be odd to apply this non-validated approach here in an ultra-rare disease.	

Issue 6 The ERG incorrectly states that the structure of the model for the sebelipase alfa- and BSC- arms is different; however, the structure is not different, just the transitional probabilities are different.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG repeatedly claims that different model structures were used for the sebelipase alfa and BSC arms of the economic model. On pages 17 and 59, the ERG states: "the model structure differs largely between the sebelipase alfa and BSC group." Further, ERG states on page 60: "For the sebelipase alfa group it	The ERG should state that the structure for the sebelipase alfa and BSC arms is in fact the same, and clarify that what ERG disagrees with is the sources for and parameterization of the transitional probabilities for the sebelipase alfa and BSC arms. As described above in earlier comments,	The ERG's statements are factually incorrect—if they were true, there would be different transition matrices for sebelipase alfa and BSC, meaning that the x- and y-axes of their respective matrices would have different labels and/or numbers of rows and columns, indicating a different structure. The ERG implies that model structure is biased in favor of sebelipase alfa when it is not. The structure of the model is identical	The ERG has the opinion that using fixed zero transition probabilities for SA versus stochastic non-zero probabilities for BSC introduces a difference in the model structure between SA and BSC. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
was assumed that it was not possible to transit to the 'DCC', 'HCC' and 'Liver transplant' health states." Figure 5.2 ("Model structure as provided by the ERG for the base case scenario") only 2 states are shown for the sebelipase alfa arm: "LAL-D without CC, DCC, or HCC" and "Compensated cirrhosis (CC)." These and other similar statements about model structure being biased or otherwise different between the BSC and sebelipase alfa arms are factually incorrect—if they were true, there would be different transition matrices for sebelipase alfa and BSC, meaning that the x- and y-axes of their respective matrices would have different labels and/or numbers of rows and columns, indicating a different structure.	the ERG has misinterpreted the sources for these inputs.	between the sebelipase alfa and BSC arms, as shown in Figure D12.1 ("Cost-consequence model schematic") of our initial submission. As shown in Table D12.4 of our initial submission ("Transition probabilities for best supportive care LAL Deficiency patients over the age of 1") and Table D12.9 ("Base case transition probabilities for patients with LAL Deficiency treated with sebelipase alfa"), the same transition probabilities are populated for each arm. While some probabilities are 0% for sebelipase alfa based on data analysis described in the section titled "Sebelipase alfa transition probabilities" that are nonzero for BSC, this has no effect on the model structure. The exact transitions observed in the model are dependent on the transition probabilities and initial patient distribution. Modifying either of these could result in sebelipase alfa patients progressing to DCC or HCC, clearly demonstrating that the structures are identical.	

Issue 7 The ERG implies that Alexion was unclear as to how it parameterized the survival model related to the analysis in Figure D12.2; however, the parameterization is clearly identified in our initial submission.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 64 of its report, the ERG states: “Although this is not explicitly stated by the company, giving that the estimated probably is constant over time, the ERG suspects that an exponential parametric survival model is fitted by the company.” Similarly, on page 67, ERG states: “It was also unclear how the survival analyses, to estimate the time to 'CC', were exactly applied by the company (e.g. which parametric distribution is exactly used, which covariates were used and what the coefficients were). This extremely hampers the ERG´s assessment of the validity of the economic model and hence the outcomes of the cost-consequence analysis reported in the CS should be	The ERG should retract their statement that Alexion was not clear on the survival model used as it is stated explicitly in our initial submission.	Alexion stated explicitly in our initial submission on page 24: “An accelerated failure time (AFT) survival model was estimated assuming a constant hazard.” A survival model assuming a constant hazard is synonymous with an exponential parametric survival model so it is unclear why the ERG claims our survival model was not specified. Additional information on the modeling approach is provided on page 171 of the initial submission document where it states: "Survival analysis was conducted to approximate the rate of transitioning from fibrosis to CC using the LAL-CL02 trial data. Specifically, LAL-CL02 patients with a known baseline Ishak score (N=32) were analysed. An accelerated failure time (AFT) survival model was estimated assuming a constant hazard. The failure event was defined as the earliest mention (either a pre-baseline medical record or at baseline of the LAL-CL02 trial) of a confirmed case of CC (N=12). Study time was defined to begin on the date of a	It was not explicitly stated which parametric distribution was exactly used, which covariates were used and what the coefficients were, i.e results could not be replicated. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
interpreted with extreme caution."		patient's first record of LAL Deficiency symptom onset, and to end on the earlier of the date of the baseline biopsy or first record of cirrhosis in medical history." Moreover, no questions regarding the distribution or specification of this survival model were included in the ERG clarification letter dated November 16th so Alexion assumed the survival model was acceptable to the ERG.	

Issue 8 The ERG's statement that Alexion's model structure made it impossible for BSC-treated patients to transition from "CC" to "LALD without CC, DCC or HCC" is factually inaccurate.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 60 of its report, the ERG states: "The model structure for BSC was mainly based on the economic model by Mahady et al. It was assumed based on Mahady et al that for the BSC group it was not possible to transit from 'CC' to 'LALD without CC, DCC or HCC', whereas this was possible for sebelipase alfa group, based on the LAL-	The ERG should retract their statements about structural problems or bias with regards to the model structure as there are no inappropriate biases or validity concerns.	The ERG's statement is factually inaccurate given that the Markov traces have identical row and column headers. Also, Alexion provided sensitivity analysis for the transition from "CC" to "LALD without CC, DCC or HCC" for BSC patients using the randomized controlled trials data where placebo arm data were used for BSC. For example, see "Table D12.16: Variables used in multi-way scenario-based sensitivity analysis of transition probabilities" on page 195. The transition for BSC from CC to 'LAL Deficiency	This is not a factual inaccuracy. (see also our response on Issue 6)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
CL02 trial." The verbiage from the above statement: "…for the BSC group it was not possible to transit from 'CC' to 'LALD without CC, DCC or HCC'" is factually inaccurate.		without CC, DCC, or HCC' is 25% and 33% in sensitivities 1 and 4, respectively. If it were impossible for this transition to exist, these sensitivities could not have been performed. The ERG demonstrated that this was a factually inaccurate statement with their own revised model: they parameterized this transition by inputting a number into a cell (ERG input 52.8% into cell K24 on sheet 'Transition Probabilities'), and making no other revisions.	

Issue 9 The ERG inaccurately claims that the historical control arm (LAL-1-NH01) is not an appropriate comparator to the sebelipase alfa arm in the infant study (LAL-CL03).

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 35 of its report, the ERG states: the "subpopulation of 25 infants from study LAL-1-NH01 was used,…This comparison group was added because one patient in study LAL-CL03 did not fulfil the objective criteria for failure to thrive at the time of enrolment but was enrolled based on other clinical	The ERG should retract its statement that: "there is still considerable concern about the comparability of any of the patients in study LAL-1-NH01" with those patients in LAL-CL03.	It is factually inaccurate to state that the one patient who did not meet the growth failure criteria was unlike the other eight patients in the clinical trial as the underlying disease was likely masking the weight gain. 	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
evidence of rapidly progressive disease." On pages 37-38, the ERG states: "The broader historical control group from study LAL-1-NH01 that included all 25 patients who had not received HSCT or liver transplant, irrespective of whether these patients met the objective criteria for early failure to thrive, seems to be the most comparable control group for the nine patients from study LAL-CL03. However, there is still considerable concern about the comparability of any of the patients in study LAL-1-NH01. Patients in study LAL-CL03 were all born in 2010 or later, while patients enrolled in the historical control study LAL-1-NH01 received a clinical diagnosis of "Wolman disease" between 1985 and 2012." The ERG produced no		[redacted], this mixed clinical picture is not atypical of patients with LAL Deficiency. [redacted] Additionally, the ERG inaccurately assumes that "improvements in supportive care over time" would bias the results in favour of sebelipase alfa in LAL-CL03 (page 11 of the ERG report). No data for this	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
evidence for this concern and the ERG's own "Figure 4.1" does not support its assertion that the samples are not comparable. The factual inaccuracy is that ERG's comparability issue is based on date of enrollment; however, for BSC- treated patients, patient outcomes are the same if enrolled before or after 2010.		conjecture that supportive care has improved over time was provided by the ERG. In fact, the opposite has been stated by local UK experts. Specifically, in recent discussions with a local UK expert who specializes in diagnosing infants with LAL Deficiency, he reiterated that there have been no major improvements in care for these patients, and even with the best supportive, aggressive care, the outcome of an untreated infant with LAL Deficiency will be death. The ERG's own Figure 4.1 titled "Monthly weight gain by date of first chart review" does not support the above assertion and instead supports (the ERG's comment) that there "seems to be no obvious trend (in weight gain in the month of first diagnosis) over time. On page 38 of the ERG's report, the ERG concludes: "Nevertheless, on the basis of failure to thrive, the prognosis for patients in study LAL-CL03 appears similar to the prognosis for patients in study LAL-1-NH01 without sebelipase alfa." The outcomes of the comparable LAL-1-NH01 patients selected by the ERG (n=25) still result in death for all the infants and there is no evidence of improvement over time.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		The patient subpopulation (N=21 or N=25) in the historical control from study LAL-1-NH-1 includes patients who were enrolled in 2010 and 2011 – and therefore does represent current BSC that they had received. Given the rarity of LAL Deficiency, the LAL-1-NH-1 trial allowed cases to be as far back as 1985; however, when BSC is compared to the more recent cases (those after 2010 to those before 2010), there is no difference in outcomes. Therefore, it is factually accurate to use the data presented in LAL-NH01 as the historical control arm for LAL-CL03. Although not included in Alexion's initial submission, recent personal communication with an investigator in the LAL-CL03 study reveals that "the severity of patients included in the study should also be compared to analysis of siblings' survival where available." Specifically, this investigator stated "In at least two of my patients, results with the same supportive treatment have been growth failure followed by death (including one sibling treated with BMT)." This example disproves the ERG's belief in the improvement in BSC in the current clinical	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		environment. Additionally, recent communication with another lysosomal storage disease expert in the UK illustrates that the main stay of supportive care that is needed for these ill infants is primarily related to malabsorption and growth failure. This expert notes that no major improvements have occurred with feeding and formula and that it is factually inaccurate to assume a substantial improvement in supportive care in the time interval between LAL-CL03 and LAL-1-NH01 study.	

Issue 10 The ERG claims that only one expert contributed to the validation of the economic model structure and approach when input was obtained from seven experts.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 61: "As no formal expert elicitation has been performed and this was based on the opinion of only one expert, it remains unclear why NAFLD would be the best proxy disease."	The ERG should correct its statements questioning the external and expert validity of Alexion's model structure.	In its initial submission, on pages 181-184, Alexion discussed how seven experts were consulted to help inform the structure of the economic model. Below, we include the text from section 12.2.5 from our initial submission: "An advisory board was conducted in October 2014 with four clinical experts in	The contribution of only one expert was mentioned (by Dr. Tsochatzis) in section 12.2.5 of the CS. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
It is not clear why ERG claims that input from only one expert was used to help inform the economic model. Further, had only one expert been consulted, it is unclear why the ERG believes that one expert would be insufficient for an ultra-rare disease, as it has relied on the input from one expert for past highly specialised technology (HST) reviews.		hepatology or rare disease and two health economists to review sebelipase alfa clinical data and discuss the health economic analysis. Four European markets were represented: UK, Spain, Germany and Italy. Meeting participants: • **Professor Sandro Muntoni**, MD. Director, Centre for Metabolic Diseases and Atherosclerosis, University of Caligari, Italy. • **Carmen Ribes-Koninckx**, MD PhD. President of SEGHNP (Spanish Society for Paediatric Gastroenterology Hepatology and Nutrition) Head of the Paediatric Gastrohepatology Unit at LA FE Hospital, Valencia, Spain. • **Monica Lopez Rodriguez**, MD. Assistant Physician in Internal Medicine in IMSALUD, the Community of Madrid, Spain. • **Emmanuel Tsochatzis**, MD. Senior Lecturer and Honorary Consultant, UCL Institute for Liver and Digestive Health, Royal Free London NHS Foundation Trust, UK. • **Stefan Willich**, MD. Professor, Institute for Social Medicine, Epidemiology and Health Economics, Charite University Medical Center, Germany. • **Pippa Anderson**, BSc, MSc. Director,	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		Swansea Centre for Health Economics, Wales. The participants discussed the health economic model framework and assumptions with emphasis on identifying the correct disease states, transition probabilities, health utilities and medical resource utilisation parameters... In addition to the advisory board, review of the final model was also conducted with Dr **Simon Jones**, Consultant Metabolic Paediatrician at Manchester Children's Hospital." In summary, the approach taken to modelling the clinical progression of LAL Deficiency patients was deemed appropriate by hepatologists and other clinical experts. In an ultra-rare disease like LAL Deficiency, no published data are available to inform the structure of an economic model so input from clinical experts is paramount to developing such a model.	

Issue 11 The ERG claims a different published model structure could have been used, but due to timelines, use of this model would not have been feasible and was not deemed as relevant as the one advocated by the experts.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 61 of its report: "Following the additional search and screening by the ERG (see Section 5.2) the study by Zhang et al, assessing the cost-effectiveness of screening strategies for NAFLD, could have been used as an alternative starting point to develop a model by the company (removing the screening part of the model)." ERG states on page 67: "Given the restriction to NILT (non-invasive liver tests), it is unclear whether there are more appropriate economic models available that were not identified in this systematic search (e.g. the economic	The ERG should acknowledge that the Zhang et al. poster was not a basis for developing the economic model for sebelipase alfa. The Zhang et al. journal article was not fully published until November 2015; the first online version was available in May 21 2015. Both of these were too late to use in a coordinated fashion with experts in LAL Deficiency and in time for our required submission to NICE in October 2015.	The ERG is incorrect that the Zhang et al. model could have been used to inform the economic model. The ERG's citation #51 is a non-peer reviewed ISPOR poster of Zhang et al. published in November 2014, which is insufficient for model replication. In particular, more than 50 model parameters are presented in tables 1 and 2 on the poster, but not a single source is listed for any parameter. Citation #52 is a version of the Zhang et al. model that was peer-reviewed and published in November 2015; it first appeared online on May 21, 2015, which was less than two months prior to the final scoping document for this analysis. The May online publication date was also seven months after the review of the approach by the experts at which a model structure was agreed upon, as reported in Alexion's initial submission in section 12.2.5. Due to the time and resource-intensive task of developing an economic model for submission to NICE, clinical expert input must be sought well in advance of submission. Additionally, the ERG gives no reason why this model should be used over the Mahady et al. model. Mahady et al was published in Hepatology (2014 Impact factor: Impact Factor: 11.055; http://onlinelibrary.wiley.com/journal/10.1002/(ISSN) 1527-3350); Zhang et al. was published in	The study by Zhang et al was mentioned as an example. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
model by Zhang et al identified in the additional searches performed by the ERG)." In two instances, ERG only cites the non-peer reviewed ISPOR poster version of the model, which we do not believe is the best basis for a model. In particular, more than 50 model parameters are presented in tables 1 and 2 on the poster—no sources are listed for any parameter.		European Radiology (2014 Impact factor: Impact Factor: 4.014; http://link.springer.com/journal/330); Zhang et al.'s publication has a smaller readership and lower impact factor. Moreover, Mahady et al. was a treatment-focused model whereas Zhang et al. was a screening-focused model. Specifically, Mahady et al. focused on all NAFLD patients while Zhang et al. focused on diabetics and obese NASH patients, the former being more appropriate for developing a model for LAL Deficiency.	

Issue 12 The ERG incorrectly states that Alexion "neglected uncertainty" with regard to FIB-4.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 68 of its report: "Therefore, the usage of the FIB-4 score, although considered reasonable, induces	The ERG should withdraw these comments about Alexion not considering liver progression algorithms carefully.	The phrase "induces uncertainty which is neglected by the company" is factually inaccurate. Alexion provided robust discussion of FIB-4 in its initial submission on pages 173-178. Alexion noted that it is not the gold standard to gauge liver	The ERG thinks linking surrogate outcomes to key clinical outcomes is uncertain. This uncertainty was not reflected in the model results. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
uncertainty which is neglected by the company, nor is it completely explored in the sensitivity analyses (e.g. the 3.25 threshold is not used for BSC in any of the analyses)." The phrase "induces uncertainty which is neglected by the company" is factually inaccurate and the comment: "e.g. the 3.25 threshold is not used for BSC in any of the analyses" is misleading.		progression (page 174). We wrote on page 174: "Liver scoring algorithms specifically estimate risk of fibrosis progression at different thresholds and approximate CC; they are not exact measures." We provided additional analyses, in terms of multiple thresholds (including all thresholds we found cited in the clinical literature) of FIB-4, as well as results with the APRI and Forns algorithms. Note that sebelipase alfa-treated patients performed better than BSC-treated patients in all scenarios. In our initial submission on pages 203-204, in "Table D12.23: Results of deterministic multi-way scenario sensitivity analysis of transition probabilities", we provide eight different sensitivities to help illustrate this point. Additionally, in response to question A10 of the NICE clarification letter dated November 16th, we further tested the uncertainty of the FIB-4 threshold by presenting results on changes in FIB-4 scores, finding that considerably more sebelipase alfa-treated patients showed significant improvement than BSC patients. The ERG's comment: "e.g. the 3.25 threshold is not used for BSC in any of the	Indeed the sentence quoted by the Company: "a recent UK study showed that only five out of **40** NAFLD patients (**12.5**%) with a FIB-4 score between 1.30 and 3.25 had a confirmed cirrhosis on biopsy." Should be: "a recent UK study showed that only five out of **10** NAFLD patients (**50**%) with a FIB-4 score between 1.30 and 3.25 had a confirmed cirrhosis on biopsy." (differences printed in bold). This minor adjustment does not alter any results nor the conclusions presented in the ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		analyses" is misleading. There are no observations of placebo patients above that threshold at baseline. Therefore, it would be impossible to do such analysis. As noted in our initial submission, we wrote: "Potentially cirrhotic (n=0)" for placebo patients at baseline in Table D12.7 under the header "Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)" on page 177. Plus, in the November 16th response document, this was indicated clearly in our answer to question B5 on page 48. While acknowledging on page 68 that FIB-4 is "considered better than other non-invasive tests in diagnosing advanced fibrosis" and the threshold of 1.45 is "commonly used," the ERG attempts to emphasize its uncertainty by stating "a recent UK study showed that only five out of 40 NAFLD patients (12.5%) with a FIB-4 score between 1.30 and 3.25 had a confirmed cirrhosis on biopsy." However, the ERG appears to misinterpret the findings of the cited study (Srivastava et al., 2015) when it states: "Twenty (15%) had a liver biopsy. 10 (8%) had FIB4 <1.30, each of whom had a histological stage of ≤F2 fibrosis and could have avoided referral under the new pathway. Of 7 (5%)	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		with confirmed cirrhosis on biopsy, two had FIB4 >3.25 and 5 had indeterminate FIB4 scores (1.30–3.25)." Regardless, based on the above, biopsy data were available for 20 subjects – 10 with FIB-4 below 1.30 and 10 above. Among the latter group, 7 had confirmed cirrhosis, so 70% of subjects with FIB-4≥1.30 and biopsy data had confirmed cirrhosis, not 12.5% as claimed by the ERG.	

Issue 13 The ERG incorrectly states that LAL-CL02 data are exclusively used to inform the transition probabilities for sebelipase alfa in the economic model.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 68 of its report that: "As illustrated in Table 5.3, for sebelipase alfa the LAL-CL02 data are exclusively used to inform the transition probabilities whereas for BSC also transition probabilities retrieved from Mahady et al.[2] and Hartwell et al.[5] were	ERG should retract their factually inaccurate statement that LAL-CL02 data are exclusively used to inform the transition probabilities for sebelipase alfa.	It is factually inaccurate that LAL-CL02 data are exclusively used to inform the transition probabilities for sebelipase alfa. On page 179 in the submission (and in the Excel spreadsheet model submitted to NICE as Appendix 6), "Table D12.9: Base case transition probabilities for patients with LAL Deficiency treated with sebelipase alfa" shows the transition probabilities for sebelipase alfa treated patients. The last three rows of probabilities for transitions out of the DCC,	In the Company's base case, only (i.e. exclusively) LAL-CL02 data are used to inform the transition probabilities for sebelipase alfa. For BSC, transition probabilities are also based on Mahady et al.[2] and Hartwell et al.[5] (in addition to LAL-CL02). See Table 5.3 of the ERG report. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
used." It is factually inaccurate that LAL-CL02 data are exclusively used to inform the transition probabilities for sebelipase alfa.		HCC and Liver transplant states are sourced from Mahady et al. and Hartwell et al. While in the base case of Alexion's model, it is assumed that sebelipase alfa arrests disease progression so that patients beginning in CC or LALD without CC, DCC, or HCC do not reach these states, the model is set up so that changing earlier transitional probabilities results in progression to DCC, HCC, liver transplant and subsequent states, owing to the active non-trial data based transition probabilities.	

Issue 14 The ERG claims that Alexion did not provide details on the primary sources for the transition probabilities utilized in Mahady et al.; however, the primary source for the transition probabilities is Mahady et al. itself.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 67 of its report that: "Despite requested (clarification question B3), the company did not provide details on the primary sources for the transition probabilities retrieved from Mahady et al."	This comment should be deleted. Alexion has provided details on the primary sources for the transition probabilities retrieved from Mahady et al and they are explained thoroughly in our initial submission and follow-up response document	The statement by the ERG is factually inaccurate. Mahady did primary data analysis, and, as such, is the primary source. On page 2174, Mahady et al. state: "Our base case model incorporated a wide range of probability estimates, as shown in Table 1. These estimates were derived from a recently published systematic review, other published literature, and **supplemented with data from the largest international database**	As stated by the manufacturer in the justification for amendment, the probabilities in Mahady et al are partly based on literature review and other literature; hence Mahady is not the original source. Not referring to the original source hampers transparency. This is not a factual inaccuracy.

		of NAFLD patients with biopsy-proven F3 or 4 disease" (emphasis added). The bold font is added here to illustrate that Mahady et al is the primary data source in that they performed new data analysis, combined with the other sources that are indicated in the Mahady publication. Alexion took its natural history analysis straight from Mahady et al, which was the only cost-utility model available at the time this research was completed.	

Issue 15 The ERG claims that sensitivity analyses varying the transition probabilities between the "LALD without CC, DCC or HCC" and "CC" states contain "unsystematic comparisons", and states that only BSC scenario 1 vs. SA base case contains a "fair and useful comparison", when all deterministic sensitivities reported were systematic and transparent.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 86 of its report that, "the sensitivity analyses for the transition probabilities between the "LALD without CC, DCC or HCC" and "CC" states contain unsystematic comparisons. Only BSC scenario 1, comparing the use of FIB-4 with equal cut-offs in the BSC and sebelipase alfa	These comments should be deleted.	The statement made by the ERG on page 86 of its report is factually inaccurate, and its presentation of the deterministic sensitivities on pages 85-86 is incorrect. Alexion varied the liver-score metric used to calculate transitions from "LALD without CC, DCC or HCC" and "CC" independently for sebelipase alfa and BSC in different scenarios (e.g., "In BSC scenario 2, using the FIB-4>0.6 cut-off for BSC and the FIB-4>1.45 cut-off for sebelipase alfa, incremental QALYs are slightly higher,	The explanation provided by the Company in this issue does not correspond with the Company's submission (e.g. see Tables D12.16 and D12.23 of the CS). The ERG based its report on the information provided in the CS. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
group, contains a fair and useful comparison." The claim that the sensitivity analyses provided by Alexion are "unsystematic" is factually inaccurate and we are concerned that the ERG's presentation of these sensitivities is factually incorrect.		whereas in BSC scenario 4, using the APRI for the BSC group (and FIB-4>1.45 for sebelipase alfa), the incremental QALYs are much lower."). This is a misrepresentation of the parameters of the sensitivities, and suggests that the ERG failed to replicate their results. In actuality, Alexion performed two sets of deterministic sensitivities around the "LALD without CC, DCC or HCC" and "CC" transition probability: • A set of five comparing sebelipase-alfa transition probabilities calculated based on (1) CC defined by FIB-4 > 1.45 (2) CC defined by FIB-4 > 0.6 (3) CC defined by FIB-4 $\geq$ 3.25 (4) CC defined by Forns > 4.2 and (5) CC defined by APRI > 1.5, all versus BSC's transition probabilities based on Mahady et al. • A set of four comparing sebelipase-alfa and BSC transition probabilities calculated using the same measures based on (1) CC defined by FIB-4 > 1.45 for both (2) CC defined by FIB-4 > 0.6 for both (3) CC defined by Forns > 4.2 for both and (4) CC defined by APRI > 1.5 for both.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		In the first set of sensitivities, different methods for calculating the sebelipase-alfa transition probabilities are consistently compared to calculation of BSC transition probabilities based on Mahady et al. In the second set of sensitivities, different methods for calculating sebelipase-alfa and BSC transition probabilities are used, always with the same liver-score metric used for both treatment arms (e.g., CC defined by FIB-4 > 1.45, CC defined by APRI > 1.5). As such, the ERG's claim that these sensitivities "contain unsystematic comparisons" is incorrect. Further, the presentation of these sensitivities reflects the ERG's misinterpretation, including such statements as "In BSC scenario 2, using the FIB-4>0.6 cut-off for BSC and the FIB-4>1.45 cut-off for sebelipase alfa, incremental QALYs are slightly higher, whereas in BSC scenario 4, using the APRI for the BSC group (and FIB-4>1.45 for sebelipase alfa), the incremental QALYs are much lower." Had sensitivities parameterised as the ERG describes been run, the ERG would have observed that they do not match the results reported in Table D.12.23 of Alexion's	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		submission, which do not compare transition probabilities for sebelipase alfa and BSC calculated using different liver-score metrics. Also, to restate again, the ERG's comment: "e.g. the 3.25 threshold is not used for BSC in any of the analyses" is misleading. There are no observations of placebo patients above that threshold at baseline. Therefore, it would be impossible to do such an analysis.	

Issue 16 The ERG incorrectly claims that there is inconsistency in input parameter selection.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG inaccurately claims there is inconsistency in the selection of input parameters. For example, on page 68: "As illustrated in Table 5.3, for sebelipase alfa the LAL-CL02 data are exclusively used to inform the transition probabilities whereas for BSC also transition probabilities retrieved from Mahady et al and Hartwell et al were used… Moreover, to estimate transition probabilities for sebelipase alfa, the FIB-4 score is used while this is not used for BSC. No appropriate justification was found for these inconsistencies…. This also holds true for the probabilities to transit to 'DCC' and 'HCC'. These were assumed to be 0% for sebelipase alfa whereas these were	The ERG should retract statements that there is inconsistency in input parameter selection.	As shown in Table D12.9 of the company submission, Mahady et al. and Hartwell et al. were used to model transitions from DCC, HCC, and liver transplant for sebelipase alfa-treated patients, exactly as was done for BSC-treated patients as shown in Table D12.4. Transitions from LAL-D without CC, DCC, or HCC and from CC for sebelipase alfa patients were based on trial data for treated patients. Transitions to HCC and DCC states were based on outcomes in LAL-CL02, LAL-CL03, LAL-CL01, and LAL-CL04, not just the 20-week data as claimed. This is clearly described on p. 178 of the CS: "In the clinical trials for sebelipase alfa, which included 2,691 weeks of treatment (Table D12.8), there were no observed instances of patients on sebelipase alfa transitioning to DCC or HCC and no deaths (aside from the deaths in the LAL-CL03 infant trial which applies only to those under the age of 1). Consequently, a 0% transition probability to HCC or DCC is assumed for sebelipase alfa. Sebelipase alfa restores normal lipid metabolism, so it is expected that liver	This is not a factual inaccuracy. (see also our response on Issues 2 and 13)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
assumed >0% for BSC. No plausible justification was found for this inconsistency. The 0% 'DCC' probability is justified by the company by stating that this was not observed in the LAL-CL024 trial. This is however equally true for BSC (clarification question A8). Moreover, it can be questioned whether it is plausible to assume 0% probabilities of 'CC', 'DCC' and 'HCC' for sebelipase alfa based on a follow-up period of 20 weeks." Selection of input parameters is described in detail in section 12 of the company submission. ERG misunderstands the sources of transition probabilities and inappropriately insists there is inconsistency.		progression to these states will be suspended. This is also consistent with the liver score data that indicate that liver disease is on balance regressing and not progressing for patients on sebelipase alfa." Transitions between 'LALD without CC, DCC, and HCC' and 'CC' are based on LAL-CL02. The transition to CC for BSC patients is also based on data from LAL-CL02. The justification for using pre-trial data instead of 20-week FIB-4 results is provided on p. 176 of our submission: "Interestingly, the same pattern of transitional probabilities was observed for placebo-treated patients when using the FIB-4>1.45 threshold (Table D12.6). However, across the other FIB-4 thresholds and liver scores, placebo-treated patients tended to perform worse, as indicated by the lower values in the green cells of Table D12.7. Based on the natural history progression of LAL Deficiency patients and even NASH/NAFLD patients, it was deemed that the transition probabilities to the cirrhosis state from Mahady et al. (2012) were more representative of best supportive care over the long term than derived transitions from the 20-week placebo data."	

Issue 17 The ERG incorrectly claims that the budget impact model was not implemented as described in Alexion's initial submission when in fact the assumption that infant patients receiving BSC die within their first year of life was incorporated into the calculations, as well as the non-drug direct medical costs.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 102 of its report, the ERG states that: "The company did not implement its budget impact model as described in the CS. First, the assumption that infant patients receiving BSC die within their first year of life was not incorporated in the calculations. Second, the non-drug direct medical costs were not calculated as described in the CS. The ERG has re-calculated non-drug direct medical costs and has set mortality of infant patients treated with BSC to 100%. Furthermore, the ERG did not account for the availability of 5 mg vials of sebelipase alfa after the first year of the	The ERG should clarify its suggested changes, and the impact of these on budget impact, by (1) specifying where additional incorporation of the 100% BSC mortality rate is required beyond its incorporation in the original model and (2) that the ERG proposes non-drug direct medical costs based on a patient's first five years of life (including the half-cycle starting the CCA model) rather than a patient's first full five years of life (excluding the half-cycle starting the CCA model), and that these changes collectively yield a -0.33% change in net budget impact (£53,548,573, as reported in the CS, to £53,372,077). The ERG should also clarify	The ERG states that the 100% mortality rate for BSC-treated patients in their first year of life was not incorporated into the model, contrary to the description in our initial submission. This is factually inaccurate. As reflected in cells W10:AA31 of the "Patient Calcs" sheet in the budget impact model, the 100% mortality rate was included in the scenario where sebelipase alfa does not have market access, as described in our initial submission. Further, the ERG states that non-drug direct medical costs are not calculated as described in the CS. In fact, they were calculated based on the average of the first full five years of the CCA model, excluding the half-cycle in the first year. The ERG proposes costs consisting of the average of (1) the cost in the half cycle in the first year multiplied by 2 and (2) the costs in the subsequent four years. Both approaches have limitations, but importantly, do not materially impact net	The ERG agrees that the 100% mortality has been respected in cells W10:AA31 of the "Patient Calcs" sheet. However, the calculations of BSC costs in cells E43:H43 and N43:Q43 of the "Scenario Calcs" sheet were incorrect and did not respect this yearly 100% mortality rate in infants. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
model because these are not available yet." The ERG's description of the implementation is factually incorrect.	that the assumption of availability of a 5mg vial in the BIM is, contrary to statements on p. 102 of the ERG's report, well documented in Alexion's initial submission. However, Alexion accepts this adjustment since the 5mg vial is not commercially available. Collectively with the other two adjustments mentioned above, the revised BIM yields a 19% change in net budget impact (£53,548,573, as reported in our initial submission, to £63,689,818, as reported by the ERG on p. 102 of its report as its corrected base case).	budget impact (yielding a -0.02% difference), nor do they substantively deviate from the description provided in the CS.	

Issue 18 The ERG claims that there is a lack of transparency in Alexion's calculations of epidemiological rates, when our calculations were presented in our initial submission; we provide further explanation below for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 103 of its report, the ERG states that, "The ERG performed analyses on incidence and prevalence rates in the	In light of the additional explanation corroborating our description of the calculation of the prevalence rate in our base case analysis, the ERG should acknowledge that we	Alexion explained the rationale for using a prevalence rate in the Age 1+ presentation group of 4.38 per million population in our initial submission. This is the most appropriate estimate given available evidence. Below, further description of	The ERG judged the calculations of the epidemiological rates as not transparent because the descriptions of each step of these calculations were not provided. Hence, the ERG was unable to

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Age 1+ presentation group as these were considered uncertain due to the lack of transparency concerning the calculations of these rates in the CS and in the clarification letter." It is inaccurate that we lack in transparency with regards to the calculations yielding base case prevalence and incidence rates. The rationale for these rates, corroborated by additional evidence provided in this response, was described in our initial submission.	do not lack in transparency with regards to the rationale for calculations yielding "most plausible" prevalence and incidence rates.	Alexion's internal modelling to identify this most plausible estimate of prevalence in England is presented. As described in our initial submission, the starting point for our calculation of the prevalence rate of 4.38 per million population in England is Scott et al. (2013), from which the following relevant points are sourced. Clinical terminology of CESD is utilized in line with the historical clinical descriptions. • Lysosomal acid lipase (LAL) is encoded by the LIPA gene, and the most common mutation associated with "CESD" phenotype (Age 1+ presentation LAL Deficiency) is an exon 8 splice junction mutation (E8SJM). • Scott et al.'s analysis addresses a total of 110 LIPA mutations all related to "CESD" phenotype. ○ Of these, 65 (60%) are E8SJM, and 45 (40%) are a mix of other mutations. • LAL Deficiency is found primarily in Caucasian and Hispanic populations – no carrier frequency has been found in people of African ancestry, and very small presence in Asian populations.	assess the validity of the prevalence estimate. The ERG therefore asked for clarification of the calculations steps of the prevalence but the company did not provide information that made the calculation more clear. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		• Scott et al. assembled E8SJM screening on 4,112 Caucasians to find a 0.0021 carrier frequency. • All mutations described by Scott et al. generate "CESD" phenotype, and in their analysis, given the 0.0021 carrier frequency estimate, they calculate a (110/65) x 0.0021 = ~0.0035 prevalence for all LIPA mutations, assuming the ratio of non-E8SJM to E8SJM ratio is comparable in this sub-population. • Applying Hardy-Weinberg proportions to determine the prevalence of the LAL Deficiency phenotype: ○ q x q = 0.0035 * 0.0035 = 12.25 per million population Given there is a minimal Hispanic population in England (less than 0.2%), we focus estimates on the 86% Caucasian population. Considering that the total population of England is approximately 54 million, we have: 54 million x 86% x 12.25 per million = 569 cases in England. However, in addition to the E8SJMs included in Scott et al., we include an additional ~80,000 alleles from Stitziel et al. (2013) and another ~67K from the Broad ExAC Genomic	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		databases, refining the estimate for E8SJM incidence: • Using over 10x the data resolution for E8SJM carrier frequency as used by Scott et al., we arrive at approximately a 40% reduction in the E8SJM carrier frequency. • 60% * 0.0035 = 0.0021 per million population • Applying Hardy-Weinberg proportions to determine the prevalence of the LAL Deficiency phenotype: ○ q x q = 0.0021 * 0.0021 = 4.4 per million population As described in Section 13 of our submission, various other steps are taken to refine this estimate. However, for purposes of illustrating the magnitude of the prevalence estimate, we present this explanation of the most significant step of the calculations.	

Issue 19 The ERG's modifications to diagnosis, treatment, discontinuation, and compliance rates in the BIM rely on an arbitrary assumption and conflict with real-world evidence.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 106 of its report, the ERG states that, "The company stated that approximately [redacted] of the PNH patients are on eculizumab treatment. Based on this information, the ERG thinks that the sensitivity analysis where treatment rates are increased by 10%, diagnosis rates increased by 20% and both treatment continuation and compliance rates are set on 100% may be the most plausible because it provides [redacted] of treated patients with sebelipase alfa."	The ERG's reliance on an arbitrary assumption that the percentage of prevalent LAL Deficiency patients treated with sebelipase alfa should equal the percentage of prevalent PNH patients treated with eculizumab leads them to identify "most plausible" continuation and compliance rates directly contradicting the real-world evidence that Alexion provided in response to NICE's clarification letter (see bolded and underlined text in the justification). In determining the "most plausible" parameters underlying treatment uptake, rather than assuming a target percentage of prevalent patients treated (i.e., [redacted]) and attempting to find a combination of diagnosis, treatment, continuation, and compliance rates yielding the	The ERG's assumption that the percentage of prevalent LAL-Deficiency patients treated with sebelipase alfa is the same as the percentage of PNH prevalent patients treated with eculizumab is arbitrary and ignores available evidence supporting Alexion's estimates of uptake in England of sebelipase alfa treatment. The fact that the ERG relies upon to cite that "approximately [redacted] of the PNH patients are on eculizumab treatment" directly states that compliance and continuation rates are [redacted], and close to those in our base case analysis (for the Age 1+ presentation group, [redacted] continuation, and 85% compliance): *"Alexion has experience with two other ultra-rare diseases, PNH and aHUS. In PNH, patients are managed through a national service which logs all patients referred, providing a prevalence estimate of around 500 patients in the UK. Of these patients around [redacted] are on eculizumab treatment. All stable patients receive eculizumab through home care provision and compliance rates for patients receiving*	The ERG presents analyses with alternative inputs for uncertain parameters. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
	target, the ERG should support each component rate of treatment uptake with real-world evidence, to avoid contradictions such as those in continuation and compliance rates resulting from their approach. Unless the ERG can provide new evidence supporting changes to our base case diagnosis, treatment, continuation, and compliance rates, these should be considered the "most plausible".	*homecare drug administration are high with* ***of patients having compliance rates of*** *. For aHUS, the number of patients on eculizumab treatment today is , which is below the 170 estimated by NICE for year 1. This number is close to the total number of patients who have ever been treated with eculizumab ( ) and figures suggest that* ***around of patients who start treatment will stay on chronic treatment****. Figures suggest that the number of patients diagnosed and treated may not be totally reflective of the true prevalence in the UK as numbers are lower than in other countries with a similar population size to the UK."* The ERG therefore ignores evidence of most plausible values for compliance and continuation rates. Instead, they make an arbitrary assumption that the percentage of prevalent LAL Deficiency patients treated with sebelipase alfa should equal the percentage of prevalent PNH patients treated with eculizumab; further, its interpretation based on this arbitrary assumption leads the ERG to "most plausible" estimates of compliance and continuation rates that do not align with real-world experience.	

Issue 20 The ERG claims that the "most plausible" scenario in the budget impact model yields net budget impact over five years "more than three times higher than the company's base case five year net budget impact", when the most plausible scenario based on available evidence is 19% above the submitted base case.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 106 of its report, the ERG states that, "the ERG thinks that the sensitivity analysis where treatment rates are increased by 10%, diagnosis rates increased by 20% and both treatment continuation and compliance rates are set on 100% may be the most plausible because it provides [redacted] of treated patients with sebelipase alfa. This scenario results in a five year net budget impact of £178,527,667 which is more than three times higher than the company's base case five year net budget impact." The over three-fold	The ERG, in accordance with its amendments in response to Issue 20 above, should specify that the most plausible five-year net budget impact estimate from its analyses is 19% higher than our base case analysis (as explained in Issue 18), and significantly below the three-fold increase that is indicated on page 106 of the ERG's report.	As addressed in Issue 18, the three adjustments that the ERG proposes to our base case analysis yield an 19% increase five-year net budget impact (£53,548,573, as reported in the CS, to £63,689,818, as reported by the ERG on p. 102 as their corrected base case). As addressed in Issue 20, the ERG's additional adjustments to diagnosis, treatment, continuation, and compliance rates in order to reach around [redacted] of LAL Deficiency prevalent patients treated with sebelipase alfa are based on an arbitrary assumption and conflict with real-world evidence. These adjustments increase the ERG's "most plausible" five-year net budget impact estimate from a 19% higher than our base case analysis to over three times higher than our base case analysis. Per the reasoning in Issue 20, the most plausible five-year net budget impact estimate is therefore 19% higher than our base case analysis, driven almost	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
increase in net budget impact is factually inaccurate, as described in Issues 18 and 20.		singularly by assuming that a 5mg vial is not available in Year 2-5.	

Issue 21 The ERG incorrectly states that Alexion did not provide any subgroup analyses in the economic model.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Section 1.3 of its report, the ERG states "The company submission did not include subgroup analyses for infants with very rapidly progressing lysosomal acid lipase deficiency and for people who have had a liver transplant as requested in the scope."	The ERG should retract statements that there no subgroup analyses were performed when in fact they were.	The ERG inaccurately asserts that no sub-group analysis was performed. Subgroup analyses for infants with the rapidly progressive lysosomal acid lipase deficiency were not needed, as LAL-CL03 functions as its own subgroup of patient population. Additionally, as subgroup analyses for those with liver transplantation was not performed as patients were ineligible to participate in either LAL-CL02 or LAL-CL03 if they had undergone a liver transplant. In the scoping document, Alexion indicated that a sub-analysis with the liver transplant patients is not possible.	Not a factual error.

Issue 22 The ERG uses both a 3.5% and 1.5% discount rate for costs and benefits; the ERG should use 1.5% per previous NICE guidance.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The discount rate of 3.5% for costs and benefits used by the ERG is inappropriate according to the NICE guidelines for highly specialised technologies (HSTs). As cited in page 169 of Alexion's initial submission, the NICE guide to the methods of technology appraisal 2013 states the following: "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), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal	The ERG should update its model to prioritize results with a discount rate of 1.5% instead of 3.5%.	Based on the model the ERG submitted, the incremental QALY gains for sebelipase alfa are very large for infants and (taking into consideration Issues 1, 2, 3, and 4) non-infants. This further justifies the use of a 1.5% discount rate as outlined in the NICE guidelines where it is stated "a 1.5% discount rate should be used if "long-term health benefits are likely to be achieved".	The appropriate discount rate is for the committee to decide. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved."(Section 6.2.19 of the NICE Methods Guide to the methods of technology appraisal. NICE. April 2013. http://publications.nice.org.uk/pmg9, Last accessed September 30, 2015.) For sebelipase alfa, the ERG model assumes a discount rate of 3.5% for both costs and benefits, implying that the ERG does not accept that sebelipase alfa meets the criteria in the NICE Methods Guide. This is surprising given that the ERG's base case model for infants estimates large gains in QALYs for sebelipase alfa (i.e., the ERG model estimates incremental QALYs of 14.27 using a 1.5% discount rate; the ERG model estimates QALYs of 9.06 using a 3.5% discount rate, per scenario 7 on page 91 of the ERG report). When discounted at 3.5%, these			

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
gains fall by a third, representing the situation described above in the NICE Methods Guide where "cost-effectiveness analyses are very sensitive to the discount rate used". NICE has previously recognised that this special case should be applied in similar situations for other HST evaluations. For example, in the evaluation of eculizumab in aHUS (HST1), the ERG estimated lifetime gains of 10.14 QALYs (using a 3.5% discount rate) and on this basis NICE agreed that the special case applied so a 1.5% discount rate should be used. In the evaluation of another HST, elosulfase alfa for MPS IVa (ID744), the ERG estimated an incremental 10.03 QALYs and again NICE agreed that the special case applied and a 1.5% discount rate should be used. In the current evaluation of sebelipase alfa, the ERG has			

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
estimated that infants gain 14.27 QALYs and therefore it does not seem factually consistent to reject the special case. Of note, this issue applies to Alexion's base case, which we believe is valid given our responses to Issues 1, 2, 3 and 4 above.			

Issue 23 The ERG incorrectly states that systematic review methods were not reported in Alexion's submission.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 31, the ERG states "Methods for the systematic review process have not been reported. Therefore, there is no information regarding the number of reviewers involved in the study selection process and the data extraction process…. In this case there is no guarantee that the data extraction process was correct."	Please delete this section.	On page 74 of Alexion's initial submission, it states "Two reviewers assessed the publication title and abstracts for inclusion in the review, followed by review of the full text articles (where available). A third reviewer resolved contradictory decisions and areas of any remaining uncertainty." As such, methods for the systematic review process have in fact been reported.	Methods of the data extraction process have not been reported. Therefore, our conclusion that the methods for the systematic review process have not been reported was correct. We agree that the methods for the study selection process have been reported and were appropriate.

Issue 24 The ERG incorrectly describes the observational assessment.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 31, the ERG states "The other two intervention studies (LAL-CL03, and LAL-CL01/04) were assessed using and adapted checklist from the Critical Appraisal Skills Programme (CASP): 'Making sense of evidence, 12 questions to help you make sense of a cohort study'. No references were provided for this instrument."	The ERG's statement is factually incorrect as written. In order to be correct, the ERG should amend the statement to read as follows: "In line with NICE guidance, the other two intervention studies (LAL-CL03, and LAL-CL01/04) were assessed using and adapted checklist from the Critical Appraisal Skills Programme (CASP): 'Making sense of evidence, 12 questions to help you make sense of a cohort study'."	The adapted CASP checklist is provided in the NICE HST evidence submission template.	Not a factual error, no references were provided.

Issue 25 The ERG's statement that studies were omitted from the initial submission is incorrect.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 32 and 34 of its report, the ERG states: "However, a second historical control study (LAL-2-NH01) was performed by Alexion which is not included in the submission."	Please delete sentences that suggest Alexion did not include LAL-2-NH01 in its initial submission as this is factually incorrect.	This section of the ERG report is a critique of trials of the technology of interest. LAL-1-NH01 was included as part of the evidence for the technology because it was the historical control group for LAL-CL03. LAL-2-NH01 was not included as evidence of trials for the technology because it is an observational study that was not conducted to be a control group for a specific trial. The wording of the report suggests Alexion did not report the full clinical trial programme for sebelipase alfa. In fact, Alexion reported the results of study LAL-2-NH01 in sections 6.2, 8.2, 10.1.2 and 14.5 of its initial submission.	Not a factual error.

Issue 26 The ERG incorrectly implies that no literature review was performed in Crossan et al. on natural history models in NAFLD.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 61 of	The ERG should retract statements that	The written text provided by	This is not a factual

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
its report: “However, this literature review was not a review of NAFLD models, but aimed to identify “papers comparing the diagnostic accuracy of different non-invasive tests in the diagnosis and monitoring of liver fibrosis and cirrhosis with liver biopsy”. Hence, if NAFLD would be the best proxy for LAL deficiency then this review may not have found the best available model as this was not the intention of their search strategy.” The written text provided by ERG is misleading: Crossan et al.’s primary goal is accurately described by the ERG, but the ERG omits that systematic literature reviews were performed to identify the best natural history model in NAFLD and other liver conditions.	Mahady et al. is an inappropriate model structure, and in particular was not identified in a literature review commissioned by NICE that was published in 2015 as the most appropriate NAFLD cost-utility model describing the natural history of NAFLD.	the ERG is not factually accurate as it omitted a key element: Crossan et al.’s primary goal is accurately described by ERG, but the ERG omits that systematic literature reviews were performed to identify the best natural history model in NAFLD and other liver conditions. Crossan et al. write on page 15 in their Literature review section: “Literature searching was undertaken to populate input parameters for the models (for natural history, costs and QALY inputs). Titles and abstracts were reviewed and full papers were retrieved if deemed relevant. We started by identifying existing recent reviews. The papers identified in these were reviewed. The searches were updated, amended if needed, and rerun.” Mahady et al. was the best NAFLD model identified in	inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		Crossan et al. for NALFD, as well as by experts, for its accuracy and availability of inputs parameters.	

Issue 27 The ERG alleges that the CCA and BIM models are "not transparent"; however, both models include all data used and explanations of the data source.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 18 of the ERG report, the ERG states: "The CCA and the budget impact model lacked transparency" when the models are fully transparent and all data calculations are shown.	The ERG should retract this statement as both models are in an open Excel format, and the data inputs are transparent.	The sebelipase alfa CCA model, in particular, is in the same MS Excel format as Alexion's prior submissions (asfotase alfa for hypophosphatasia and eculizumab for atypical hemolytic uraemic syndrome), which was reviewed by the same ERG three months ago and over a year ago, respectively. Without providing additional details, it is unclear what the ERG deems as not transparent about Alexion's models, and making such sweeping statements about the models seems inappropriate.	Issues that indicate a lack of transparency include: transition matrices are provided that are not used, the Markov trace consists of overly complex formulas with many (unnecessary) references, and lack of (intuitive) naming of parameters, as well as important cells that are hidden. This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		Alexion has answered all questions as requested by NICE, and would happily make any further clarifications as requested by the ERG and/or NICE.	

Issue 28 The ERG makes inaccurate assessments regarding the patient survey conducted and the societal impact of LAL Deficiency.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 109 of its report that the information reported in the European patient survey is uncertain because the survey did not use validated instruments; however, the ERG fails to acknowledge the limited data available in the published domain on LAL Deficiency.	The ERG should revise its statements on page 109 to more accurately describe the patient survey that was conducted.	Given the paucity of information on patient and carer experience in LAL Deficiency (no data at all was identified in the literature), the survey conducted sought to obtain a broad insight into the major domains of patient and carer experience of the disease. These domains included symptom frequency, quality of life (for patient and carer), productivity loss, and other economic impacts. Given this wide focus, it was practically impossible to include validated instruments for each domain of interest in the survey; to do so would have resulted in a survey with many hundreds of items. Therefore, Alexion and the patient associations took a pragmatic approach to item selection by including only those questions deemed most relevant to the disease, based on the input and advice from clinical experts and relevant patient association. Regardless, it is not accurate for the ERG to say the survey items were not validated. Wherever possible, individual items included in the survey were selected from validated questionnaires:	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		for example, the quality of life items were from the EQ-5D and many of the patient and carer productivity questions were sourced from the Work Productivity and Activity Impairment Questionnaire. It should also be noted that there are no questionnaires that have been validated in a LAL Deficiency population, therefore, all attempts to infer patient and carer experience in this disease require pragmatism and do not make the result of the study uncertain.	