

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Sebelipase alfa for treating lysosomal acid lipase deficiency

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sebelipase alfa in the context of national commissioning by NHS England. The Highly Specialised Technologies Evaluation Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this evaluation (see section 10) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Evaluation Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of sebelipase alfa in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age,

gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Evaluation Committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final evaluation determination (FED).
- Subject to any appeal by consultees, the FED may be used as the basis for NICE's guidance on using sebelipase alfa in the context of national commissioning by NHS England.

For further details, see the [Interim process and methods of the highly specialised technologies programme](#).

The key dates for this evaluation are:

Closing date for comments: 5 pm, 10th March 2016

Second Evaluation Committee meeting: 22nd March 2016

Details of membership of the Evaluation Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Evaluation Committee's preliminary recommendations

- 1.1 Sebelipase alfa is not recommended for treating lysosomal acid lipase (LAL) deficiency in people who presented with rapidly progressive LAL deficiency before they were 6 months old except as part of a clinical trial.
- 1.2 Research should be designed to generate robust evidence about the benefits of long-term treatment with sebelipase alfa compared with shorter-term treatment with sebelipase alfa ('bridging therapy') followed by haematopoietic stem cell transplant with curative intent.
- 1.3 Sebelipase alfa is not recommended for treating LAL deficiency in people who did not present with rapidly progressive LAL deficiency before they were 6 months old.
- 1.4 People currently receiving treatment initiated within the NHS with sebelipase alfa that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their clinician consider it appropriate to stop. For children with LAL deficiency, this decision should be made jointly by the clinician and the child, and the child's parents or carers.

2 The condition

- 2.1 Lysosomal acid lipase (LAL) deficiency is an inherited autosomal recessive lysosomal storage disorder. Mutations in the lysosomal acid lipase gene result in deficiency of the LAL enzyme. This causes abnormal accumulation of lipids, mainly in the gastrointestinal, hepatic and cardiovascular systems.

- 2.2 The prevalence of LAL deficiency in England is unknown. The estimated incidence of LAL deficiency is 1 in 500,000 to 1 in 1,000,000 in children presenting in infancy and 1 in 40,000 to 1 in 300,000 in those presenting in childhood or adulthood.
- 2.3 The rate of progression of LAL deficiency and its mortality differs markedly depending on when people present with symptoms. Babies under 6 months who present with LAL deficiency generally have 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 babies. Most people present with symptoms during childhood: 83% of patients present by 12 years, with a median age of onset of 5 years.

3 The technology

- 3.1 Sebelipase alfa (Kanuma, Alexion Pharma UK) is a recombinant human lysosomal acid lipase. It has a marketing authorisation in the UK for long-term enzyme replacement therapy in patients of all ages with lysosomal acid lipase (LAL) deficiency. For babies under 6 months 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 do not present with rapidly progressive LAL deficiency before they are 6 months old, 1 mg/kg sebelipase alfa is administered by intravenous infusion once every other week.
- 3.2 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 sebelipase alfa has been reported, especially in babies. If antibodies develop sebelipase alfa may not work effectively. For full details of adverse reactions and contraindications, see the summary of product characteristics.

- 3.3 Sebelipase alfa is available in vials containing 20 mg of sebelipase alfa, at a list price of £6,286 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).

4 Evidence submissions

The Evaluation Committee (section 9) considered evidence submitted by Alexion Pharma UK, a review of this submission by the Evidence Review Group (ERG; section 10) and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

- 4.1 Rapidly progressing lysosomal acid lipase (LAL) deficiency in babies 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 a baby with rapidly progressing LAL is 3.7 months.
- 4.2 Children and adults with LAL deficiency frequently have abdominal pain, fatigue, diarrhoea, nausea, loss of appetite, itchy skin and a swollen abdomen. Lipid accumulation can lead to liver cirrhosis, liver failure, other systemic complications such as an enlarged spleen, anaemia and blood platelet deficiency and probably atherosclerosis. In around 87% of patients more than 1 organ is affected by LAL deficiency. It is estimated that approximately 50% of children and adults with LAL deficiency progress to have liver complications such as fibrosis or cirrhosis, or need a liver transplant within 3 years of the start of their symptoms. The life expectancy of people with LAL deficiency that presents after infancy is not

clear because of the variability of symptom severity and rate of progression.

- 4.3 Because the condition is rare, delays in diagnosis are common. Parents of babies who have symptoms of LAL deficiency 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 without knowing why. 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 to be with their child in hospital, which may be far from the family home. People with symptoms presenting later in life find that their wellbeing is impaired by constant pain and nausea. Symptoms affect their ability to carry out everyday tasks, and can stop them working and taking part in sport. They may be anxious about being in crowded places because of the chance of being accidentally knocked, which increases their pain.
- 4.4 Approximately half of people diagnosed with LAL deficiency will need a liver transplant. A patient organisation explained the experiences of patients and their families facing the possibility of a liver transplant in the future. For parents, there is the constant anxiety of knowing their child will need a liver transplant one day but not knowing when that is likely to be. The uncertainty about when a suitable liver will be available is stressful because the child may die before a liver donor is found. Patients (and their families) need to be immediately available when a suitable liver is found, which affects daily activities and travel. People who have had a transplant need 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.

Clinical evidence

- 4.5 The company submission described 6 clinical trials (LAL-CL01, LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08) and 2 retrospective cohort studies (LAL-1-NH01 and LAL-2-NH01). 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.
- 4.6 LAL-1-NH01 was a natural history study that retrospectively evaluated data from 35 children with confirmed LAL deficiency presenting before age 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 children in this study who had growth failure within the first 6 months of life, but who did not have a haematopoietic stem cell transplant or liver transplant as a historical control for LAL-CL03.
- 4.7 LAL-CL03 is a single-arm, open-label multicentre study in 9 children aged 2 years or under with rapidly progressive LAL deficiency (defined primarily on growth failure within the first 6 months of life). Median age was less than 1 month at onset of symptoms and 3 months at the start of the study. Children receive sebelipase alfa 1 mg/kg every other week and dose escalation is permitted. Follow-up of children in this study is ongoing.
- 4.8 The primary outcome in LAL-CL03 was the proportion of babies 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 babies survived beyond 12 months (67% survival, 95% confidence interval [CI] 30% to 93%). The median age at death for the 3 babies who died before they were 12 months was 2.92 months (range 2.80 to 4.30 months). None of the historical control group from LAL-1

NH01 survived past 12 months (the median age at death was 3.00 months).

- 4.9 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 for 20 weeks. An open-label follow-up period of up to 130 weeks is ongoing. The duration of each patient's treatment is expected to be at least 78 weeks. The primary outcome in the 'full analysis set' was defined as randomised patients who received any amount of sebelipase alfa or placebo.
- 4.10 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 because of lipid accumulation resulting from LAL deficiency. At 20 weeks, 31% of patients 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).
- 4.11 Secondary outcomes in LAL-CL02 included relative reduction in low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol, normalisation of aspartate aminotransferase (AST), relative reduction in triglyceride, relative increase in HDL cholesterol, 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 outcomes apart from improvement in liver histopathology and reduction in liver volume. There were no data available on longer-term complications such as liver disease.

Economic evidence

4.12 No published economic studies of LAL deficiency were found. The company adapted a cost–utility Markov model of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NAFLD and 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 in patients with LAL deficiency the condition affects the cardiovascular, gastrointestinal and other systems, it considered it appropriate to focus on modelling liver disease progression because this is often the most prominent effect of the condition. The model had a cycle length of 1 year with a half-cycle correction, a lifetime time horizon and 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.

4.13 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 remaining 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 move 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.

4.14 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 historical control cohort for LAL-CL03. The modelled age when starting treatment was 11 years and the mean starting weight was 42.2 kg. In a scenario analysis the company modelled babies (reflecting the combined populations of LAL-CL03 and the natural history comparator cohort) and children and adults (reflecting the population in LAL-CL02) separately. All were modelled to have lifelong treatment with sebelipase alfa without any stopping rules or adjustment for treatment adherence.

4.15 People started treatment either in the 'LAL deficiency without CC, DCC or HCC' health state or the 'compensated cirrhosis' health state. Because liver biopsies were not routinely done in the clinical trials, the company estimated the proportion of people with cirrhosis when starting treatment using a published method that mapped AST and ALT levels and platelet count to a fibrosis or cirrhosis score called FIB-4 (Sterling, 2006). In its base case, the company assumed a FIB-4 score of over 1.45, which meant that people had compensated cirrhosis. A score lower than this meant that people did not have cirrhosis. In the base case, based on the AST or ALT scores in the combined population from the clinical trials (LAL-CL02, 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 that no one with

more advanced liver disease would start treatment because these people had been excluded from its clinical trials.

- 4.16 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 moving 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 one without cirrhosis at baseline in the sebelipase arm developed cirrhosis by week 20; however, 1 of 4 people (25%) who had cirrhosis at baseline had an improved FIB-4 score (consistent 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 did 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 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.
- 4.17 The company assumed that no one 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 moving between liver disease health states with best supportive care were from Mahady et al. (2012).

4.18 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 childhood by allowing extra transitions. It assumed that patients aged under 1 year could die while in the 'LAL deficiency without CC, DCC or HCC' state. All patients aged under 1 year 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).

4.19 The company used utility values from Mahady et al. (2012) for liver outcomes. These were:

- LAL deficiency without cirrhosis or liver cancer: 0.92
- compensated cirrhosis: 0.82
- decompensated cirrhosis: 0.60
- hepatocellular carcinoma: 0.73
- liver transplant 0.69.

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 babies. It therefore assumed that quality of life was 0.25 for babies who die in the first year of life (averaged to a value of 0.07 for a full year taking into account that patients will not live the full year) and 0.50 for babies 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.

4.20 The list price for sebelipase alfa is £314.30 per mg or £6,286 per 20 mg vial. The company noted that it will be making sebelipase alfa available in

5 mg vials, at an equivalent price per mg to the 20 mg vials currently available. It said that these 5 mg vials will likely be available from January 2017 but this could not be confirmed. The company used the costs for 20 mg vials in the first year of its model and the costs for 5 mg vials thereafter. The company also presumed a reduced price of sebelipase alfa by 30% after 10 years to account for the potential price reduction 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 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.

- 4.21 The company did not identify published resource costs for LAL deficiency. It used cost data from a UK cost study and economic evaluation for patients with hepatitis C (Backx 2014; Shepherd 2007) which were inflated to 2014 values using the Office for National Statistics Consumer Price Indices for Health. 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 babies who had treatment with sebelipase alfa and survived would have a 3-month hospital stay; babies 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).
- 4.22 The company presented the modelled survival curves for sebelipase alfa compared with best supportive care for the whole population (the whole modelled cohort) and for babies presenting with LAL deficiency (the infant-only cohort). In the whole 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's base case, it stated that the total costs associated with sebelipase alfa were commercial in confidence and as such cannot be reported here; the total costs with best supportive care were £46,748. In sensitivity analyses factors that had a larger impact on the costs and QALYs were the discount rate used (1.5% or 3.5%) and the methods for estimating the number of people whose liver disease progressed in the sebelipase alfa or best supportive care arm. For the cohort of patients presenting with LAL deficiency in infancy, 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 babies) based on the LAL-CL02 population, incremental (undiscounted) life years gained were 38.2 and the incremental QALYs were 20.4. The company has stated that the costs of sebelipase alfa and the incremental costs for these subgroup analyses are confidential and cannot be reported here.

4.23 The company estimated that the prevalence of LAL deficiency (number of people with the condition at any one time) 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 under 1 year, the company estimated the incidence (number of new cases of LAL deficiency per year) 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 life expectancy is less than 1 year in this group. The company assumed that there would be 237 patients with LAL deficiency in the 1 year and over age group in 2016, and between 5 and 8 newly diagnosed patients, and 1 newly diagnosed patient in the 0–1 year age group.

4.24 The budget impact model had the following assumptions:

- **Weight by age or sex (for sebelipase alfa treatment cost).** The company estimated weight by age and sex as in its cost–consequence model based on the expected weight for age percentile. The age distribution was based on Bernstein et al. (2013).
- **Death rates in the model.** Mortality in babies was based on LAL-CL03 and LAL-1-NH01(33% in the first 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.
- **Diagnosis rate.** This was based on the company’s experience with other ultra-rare conditions (including eculizumab for treating paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome). The diagnosis rate was assumed to increase when sebelipase alfa had market access but to remain less than 100%. The company stated that its estimates of diagnosis rates are confidential and cannot be reported here.
- **Treatment rate with sebelipase alfa.** The company assumed that not all people diagnosed as having LAL deficiency would receive sebelipase alfa in clinical practice. The company has stated that its estimates of treatment rates are confidential and cannot be reported here.
- **Treatment continuation.** The company noted that dose modifications because of 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. The company has stated that its estimates of treatment continuation rates are confidential and cannot be reported here.
- **Compliance rates.** The company assumed that all babies with LAL deficiency presenting in infancy and 85% of people with LAL deficiency presenting at 1 year or over would comply with treatment.
- **Drug dose.** The average weekly 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 used in the cost consequence model.

4.25 The company estimated the total 5-year net budget impact to be £53,548,573. This estimate increased to £63,866,314 if the company assumed only the 20 mg vial was available rather than a 5 mg vial. The estimate increased to £82,194,168 by assuming the age distribution of people presenting with LAL deficiency at 1 year or older was the same as in LAL-CL02 rather than as in Bernstein et al. (2013), in which people were younger on average.

Evidence Review Group review

4.26 The ERG made the following comments on the clinical evidence submitted by the company. 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 control cohort from LAL-1-NH01 was uncertain because of differences in eligibility criteria and the natural history study recruited people earlier (1985 compared with 2010). It stated that most people in LAL-1-NH01 (21 out of 36) were diagnosed before 1995 and it was likely that best supportive care options have since improved. The ERG noted that the average monthly weight gain for 4 patients in LAL-1-NH01 who were diagnosed after 2010 was 0.49 kg, whereas in LAL-CL03 this was 0.34 kg. 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.

4.27 The ERG noted that there were several outcomes listed in the final scope issued by NICE that were not assessed in the clinical trials (liver synthetic function, liver disease progression, liver transplant and cardiovascular events). The ERG agreed that sebelipase alfa 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 babies had treatment for up to 208 weeks and 8 older patients had 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 highly uncertain.

4.28 The ERG tested the impact of some of the company's assumptions in the cost–consequence model by doing sensitivity analyses; its main criticisms included:

- Different sources of data were used to determine transition probabilities for people receiving best supportive care or sebelipase alfa. The ERG stated that the company had used pre-trial data from LAL-CL02 to support its modelling assumption that liver disease progressed with best supportive care and data from the randomised phase of LAL-CL02 to support its modelling assumption that liver disease did not progress with sebelipase alfa. The ERG suggested that data from the 20-week randomised phase of LAL-CL02 were not long enough to determine whether liver disease had not progressed and it was inappropriate to use separate sources of data for sebelipase alfa and best supportive care. It further stated that the company's modelled treatment effect on liver disease progression, for sebelipase alfa compared with best supportive care, was not supported by the trial data.
- The ERG considered that the way the company had identified utility values used in its model had not been transparently described. The ERG presented utility data from Crossan et al. 2015. This 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 preferred these utility values:

- LAL deficiency without cirrhosis or liver cancer: 0.66
 - compensated cirrhosis: 0.55
 - decompensated cirrhosis: 0.49
 - hepatocellular carcinoma: 0.49
 - liver transplant 0.51.
- The ERG also commented that the utility values used in the company's model were higher than those estimated in the general UK population. For example, in the company's model 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 0.78. In its exploratory analyses, the ERG capped the utility values in the model so that they would not exceed those of the general population. Given there were no data for quality of life in babies, 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.
 - The ERG considered that it was appropriate for the company to present costs and benefits when using a 1.5% discount because the [NICE technology appraisal methods guide](#) specifies that this rate may be used when cost-effectiveness results are very sensitive to the discount rate used, as was the case for costs and benefits here. However, the ERG considered it appropriate to also present results using the standard 3.5% discount rate.
 - 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 costs for sebelipase alfa should not be based on using 5 mg vials because they are not yet available.

4.29 The ERG's preferred base case:

- adjusted health-related quality of life to UK population norms
- used the utility values from Crossan et al. (2015)
- used the same approach as the company had used for best supportive care to model probability of liver disease progression in both the best supportive care and sebelipase alfa arms
- did not include a price reduction of sebelipase alfa after 10 years and
- assumed continued use of a 20 mg vial.

The ERG presented results with both 1.5% and 3.5% discount rates. Sebelipase alfa was associated with no additional QALYs compared with best supportive care. The incremental costs cannot be reported here because the company stated that these are commercial in confidence. The ERG carried out an additional scenario analysis which used its preferred assumptions, but also decreased the probability of developing cirrhosis with sebelipase alfa by 50% and increased the probability of cirrhosis improving with sebelipase alfa by 50%. This resulted in incremental QALYs of 1.53 for sebelipase alfa compared with best supportive care.

4.30 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 mutations in the lysosomal acid lipase gene were not transparent and because of this it could not validate them.
- An annual mortality rate of 100% for babies receiving best supportive care did not appear to have been included in the model.
- It considered that without data, basing diagnosis, uptake, adherence 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 alfa in the fifth year was

half the proportion of people on eculizumab with haemolytic uraemic syndrome.

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

4.31 The ERG applied a 100% mortality rate for babies and recalculated non-drug 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 aged over 1 year presenting with LAL deficiency. In these analyses it varied these estimates by 50%. The ERG considered that it was highly probable that all diagnosed babies would receive sebelipase alfa, but diagnosis and treatment rates in adults 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 aged over 1 year presenting with LAL deficiency. The results of these analyses ranged between £23,439,245 and £126,845,895. The ERG also carried out sensitivity analyses around treatment adherence and continuation, in which both were set to 100%. It combined this with its sensitivity analyses around diagnosis and treatment rates. The 5-year net budget impact varied between £36,137,359 and £206,367,686. 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.

4.32 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the **Evaluation report**.

5 Consideration of the evidence

The Evaluation Committee reviewed the data available on the benefits and costs of sebelipase alfa, having considered evidence on the nature of lysosomal acid lipase (LAL) deficiency and the value placed on the benefits of sebelipase alfa by people with the condition, those who represent them, and clinical experts. It also took into account the value for money that sebelipase alfa represents and the effective use of resources for specialised commissioning.

Nature of the condition

- 5.1 The Committee discussed the natural history of LAL deficiency. It noted that LAL deficiency with symptoms presenting in babies aged under 6 months was typically rapidly progressive. It heard that symptoms included pain, poor feeding, growth failure and severe hepatic disease, and were associated with a very short life expectancy of less than a year. Conversely, the Committee heard that the natural history, and particularly the rate of symptom progression, was highly variable in people presenting with symptoms of LAL deficiency later in childhood or adulthood. The Committee heard that the possible long-term effects of LAL deficiency included liver cirrhosis and liver failure (clinical features that are shared with non-alcoholic steatohepatitis [NASH]). The clinical experts explained that the type of lipid dysregulation seen in people with LAL deficiency would be expected to be a risk factor for cardiovascular disease, but the long-term cardiovascular effects of LAL deficiency have not been established. The clinical experts stated that a person's genotype or presenting symptoms did not predict the rate of disease progression. The Committee concluded that the severity of symptoms varied widely in people with LAL deficiency. It further concluded that although the rate of disease progression was rapid when symptoms started in babies aged under 6 months, in people presenting with symptoms later in life the rate of progression was more variable.

5.2 The Committee heard from patients and carers about their experiences of living with LAL deficiency. It heard about the extreme distress to parents of having a child with the symptoms of LAL deficiency without an effective treatment option and of losing a child to LAL deficiency. The Committee heard about the impact of the symptoms on older patients and how the pain and nausea affected their ability to take part in everyday activities including work and the impact on their quality of life. The Committee discussed whether patient experience would vary because it heard that the course of the disease in people who did not present with rapidly progressive LAL deficiency before 6 months varied widely. The Committee noted that the patient experts had taken part in, or had a child who had taken part in, the sebelipase alfa trials. As such, the Committee considered that their perspectives may represent those of a population with more severe LAL deficiency because not all people need treatment (see section 5.3). The Committee concluded that LAL deficiency had a very large impact on some patients with the condition, but that it was unclear about the quality-of-life impact of symptoms of less severe forms of LAL deficiency.

5.3 The Committee asked the clinical experts whether all people with LAL deficiency would benefit from treatment with sebelipase alfa. The clinical experts stated that all babies presenting with symptoms before 6 months needed sebelipase alfa because it is the only treatment that can prevent early death. However, the Committee heard that treatment would not routinely be offered to older patients whose symptoms are less severe and whose condition is less rapidly progressive. The clinical experts explained that the presence of fibrosis would indicate a need for treatment and that a review of published case reports of people with LAL deficiency suggested that around 80% had fibrosis. The Committee noted that such a review may be subject to bias (that is, it may overestimate the proportion of people with fibrosis at diagnosis) because case reports would be likely to report on people with more severe LAL deficiency with complications needing diagnosis and treatment. The Committee stated it

was not possible to determine the extent of the potential bias. The clinical experts stated that they would not start treatment with sebelipase alfa in people who had other explanations for liver disease, such as alcohol misuse or obesity. Furthermore the clinical experts stated that they would not offer treatment with sebelipase alfa to people who had received a liver transplant or who had cardiovascular complications without significant liver disease because there were no data on the efficacy of sebelipase alfa in these people. The Committee concluded that, in clinical practice in England, it expected all babies diagnosed with LAL deficiency to be treated with sebelipase alfa, but that treatment in older people may be started when evidence of significant liver disease is present.

Impact of the new technology

- 5.4 The Committee acknowledged the patient experts' view that sebelipase alfa offered a lifeline for babies presenting with rapidly progressive LAL deficiency. It also noted the views of patient experts with symptoms starting later in life; how sebelipase alfa had stopped their symptoms, enabled them to do day-to-day activities again and restored their quality of life. The Committee heard from the clinical experts that because sebelipase alfa was the first therapy that specifically targets the underlying cause of LAL deficiency, they considered it to be a step change in the management of the condition.
- 5.5 The Committee discussed the evidence for the efficacy of sebelipase alfa for treating babies presenting before 6 months with rapidly progressive LAL deficiency. It noted that the company had compared 12-month death rates from the single arm study LAL-CL03 with data from a historical control. It also noted that the ERG considered that people receiving best supportive care in the past potentially may have had poorer outcomes than people receiving best supportive care now because of changes in available treatments over time. The clinical experts stated that any changes in best supportive care had not improved survival in this patient population. The Committee noted that no one receiving best supportive

care in the historical cohort survived past 12 months whereas two-thirds of the babies in the sebelipase alfa trial had survived past 12 months. The Committee further considered the patient submissions which reported that, with continued use of sebelipase alfa beyond 12 months, children had shown improved feeding and growth and were meeting developmental milestones. The Committee noted that the oldest child in the LAL-CL03 trial is currently 4 years of age and is doing well. The Committee considered that the short-term clinical trial evidence suggested that sebelipase alfa was effective for treating babies presenting before 6 months with rapidly progressing disease but, because no robust comparative data were available, it was unable to determine the size of variability in response, extent of maintenance of response and whether the response was sufficient to prevent long-term complications of LAL deficiency and fully restore life expectancy.

- 5.6 The Committee discussed the evidence for the efficacy of sebelipase alfa for treating children and adults who did not present with rapidly progressive LAL deficiency before 6 months. The Committee noted that the randomised control period of LAL-CL02 was 20 weeks. In this study biochemical markers of liver function were measured (alanine aminotransferase [ALT] and aspartate transaminase [AST]) and lipid levels. The Committee agreed that patients showed a response to sebelipase alfa measured using these markers over 20 weeks. The Committee discussed the relationship between raised ALT and AST levels and liver fibrosis. It noted that liver damage was associated with raised ALT and AST in most, but not all, conditions affecting the liver. The Committee noted that direct measurement of liver damage by biopsy was more robust, but accepted that repeated biopsies were not feasible in the clinical trial and not always acceptable to patients. The Committee noted that sebelipase alfa improved patients' lipid profile, but noted it was unclear how this related to long-term clinical outcomes such as loss of liver function, the need for a liver transplant or future cardiovascular disease. The Committee concluded that the clinical trial evidence showed

that sebelipase alfa had a positive effect in the short term on biochemical markers of liver disease in children and adults who did not present with rapidly progressive LAL deficiency before 6 months, but it was uncertain whether it fully addressed LAL deficiency, whether the treatment effect would be maintained and how sebelipase alfa affected long-term clinical outcomes.

5.7 The Committee noted that the marketing authorisation for sebelipase stipulates that the dose for babies under 6 months with rapidly progressive LAL deficiency is 1 mg/kg once weekly with dose escalation up to 3 mg/kg considered based on clinical response. However, the Committee noted that in LAL-CL03 dose escalation to 5 mg/kg was permitted when there was an inadequate response and neutralising antibodies were present. The Committee heard from clinical experts in their submission that they felt strongly that the initial starting dose of sebelipase alfa should be 3 mg/kg weekly, with escalation to 5 mg/kg if there is inadequate response. The Committee further heard that the clinical experts would also consider, in some instances, dose escalations up to 3 mg/kg in younger children as well as babies whose LAL deficiency did not respond to the lower dose. The Committee stated that its recommendations could only apply to the dose covered by the marketing authorisation for sebelipase alfa.

5.8 The Committee considered the potential position of sebelipase alfa in the treatment pathway for LAL deficiency. It noted that a clinical expert's evidence submission raised the possibility of using sebelipase alfa therapy to stabilise LAL deficiency presenting in babies aged under 6 months before offering a haematopoietic stem cell transplant (HSCT). The Committee noted that HSCT is potentially curative in conditions in which people have an enzyme deficiency, such as LAL deficiency, but that the procedure is associated with morbidity and mortality. The Committee understood that before the availability of sebelipase alfa, HSCT had been tried in babies with LAL deficiency, but had limited success. This was because early death was not prevented, perhaps because the babies

were too unwell at diagnosis. The Committee asked the clinical experts if sebelipase alfa could be used as a 'bridging therapy' until patients were well enough for HSCT. The clinical experts offered their view that parents of babies responding to sebelipase alfa were unlikely to want to switch to a treatment that had not been shown to be effective for LAL deficiency and may carry a morbidity and mortality risk. A Committee member with relevant expertise commented that survival after HSCT for other conditions affecting babies has increased in recent years. However, the Committee agreed that the effectiveness of HSCT for babies with LAL deficiency that had been stabilised with sebelipase alfa was unknown. The Committee considered that bridging therapy with enzyme replacement before HSCT may offer the potential to gain benefits from enzyme replacement therapy while minimising the need for its long-term use and offering a cure for the condition. As such it concluded that research into how sebelipase alfa could be used most efficiently within the care pathway for LAL deficiency would represent good value to the NHS in the context of limited research resources.

Cost to the NHS and Personal Social Services

- 5.9 The Committee discussed the results of the company's budget impact model. It was aware that several of the parameters were the same as those in the company's cost-consequence model, and therefore the same limitations applied (see 'Value for money' section). It noted that, at list price, the total cost per person per year of treatment with sebelipase alfa is £491,992. This estimate is based on the average yearly cost over 10 years for a patient starting treatment at 11 years of age. The Committee highlighted that the dosage of sebelipase alfa was based on a person's weight. Therefore, the treatment costs were significantly higher for young people and adults with LAL deficiency than for babies and children. The Committee concluded that it was uncertain if the average annual cost of treatment calculated by the company was representative of the cost for the population likely to start receiving sebelipase alfa in clinical practice.

5.10 The Committee considered the assumptions in the company's budget impact analysis. It noted the company's estimate of the incidence and prevalence of LAL deficiency presenting in children aged under and over 1 year and the company's assumption that not all of these patients would be diagnosed. This was supported by the clinical experts who stated that the number of people diagnosed with LAL deficiency in England was approximately a tenth of the potential number of people living with LAL deficiency based on gene mutation studies. The Committee noted that the company had assumed the rate of diagnosis of LAL deficiency would increase following the availability of sebelipase alfa. The clinical experts stated that each year they could see between 0 and 3 babies with rapidly progressive LAL deficiency presenting before 6 months and that sometimes these babies were diagnosed after death. For LAL deficiency with symptoms presenting later in life, the clinical experts stated that raised awareness of the condition may result in increased diagnosis, but was unlikely to reach 100%. They explained that the dry blood spot test is a good diagnostic test for LAL deficiency but it is not a routine test and may not be considered for patients referred to a hepatologist. The Committee heard from the clinical experts that all babies diagnosed with LAL deficiency before 6 months would be treated with sebelipase alfa because it is the only active treatment available. The Committee considered it was reasonable to assume that not all people with less severe symptoms of LAL deficiency would be treated with sebelipase alfa because it had heard from clinical experts that treatment was only likely to be started in clinical practice in children or adults presenting with LAL deficiency that was not rapidly progressive when there was evidence of liver fibrosis. It noted that this proportion was estimated to be around 80% and was closer to the ERG's preferred assumption of treatment rate compared with the company's. The Committee agreed with the company that all parents or carers of babies with LAL deficiency would adhere to the treatment regimen for their child. The Committee considered that the ERG's assumption that 100% of people presenting with LAL deficiency after 1 year of age would adhere to treatment would be more likely if only

the patients with more severe symptoms were to start treatment with sebelipase alfa. The Committee noted that the budget impact of sebelipase alfa was very sensitive to diagnosis, uptake and treatment continuation and there was a 3-fold difference between the company's and ERG's estimates. The Committee concluded that the 5-year budget impact was likely to fall closer to the ERG's estimate of £179 million compared with the company's estimate of £54 million because the company may have underestimated the number of people who would receive sebelipase alfa in clinical practice in England.

5.11 Despite multiple requests from NICE, the company refused to make its estimates of the number of people likely to be treated with sebelipase alfa publicly available. To allow consultees, commentators and the public to fully engage in the consultation process, prepared an illustration of the possible budget impact of sebelipase alfa for treating LAL deficiency in England, using information available in the public domain. This was based on the list price of sebelipase alfa and the company's estimate of average yearly drug cost (£491,992 per person based on the average yearly cost over 10 years for a patient starting treatment at 11 years, see section 3.3). In this illustration, NICE has assumed that the number of people treated in year 1 is approximately the number of people currently diagnosed with LAL deficiency in England, which it heard from clinical experts to be about 10% of the estimated population from gene mutation studies (section 5.10). NICE assumed that the number of people treated with sebelipase alfa would increase over time and not all people with milder symptoms would need to start treatment immediately. NICE assumed that all people whose LAL deficiency symptoms were severe enough to need treatment would continue to take sebelipase alfa (section 5.10).

Table 1 Calculation of budget impact by NICE

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (5 years)
Uptake of sebelipase alfa in people with LAL deficiency¹						
0–1 year	100%	100%	100%	100%	100%	

1+ years	10%	20%	30%	40%	50%	
Total patients treated with sebelipase alfa						
0–1 year ²	1	2	3	4	5	15
1+ years ³	24	47	71	95	119	356
Total	25	49	74	99	124	371
Budget impact (drug costs only)⁴						
Net budget impact	£12.3M	£24.1M	£36.4M	£48.7M	£61.0M	£182.5M
¹ proportion of prevalent population; ² based on prevalence estimates assuming 100% survival on sebelipase alfa; ³ calculated by multiplying company's prevalence estimate (237) by uptake (rounded); ⁴ assumed yearly cost of £491,992 per person. Abbreviations: LAL, lysosomal acid lipase; M, million.						

Value for money

5.12 The Committee discussed the structure of the cost–consequence model, noting that it was based on an economic model for non-alcoholic steatohepatitis (NASH). The Committee heard from the clinical experts that both LAL deficiency and NASH were associated with progressive liver fibrosis and cirrhosis and some patients would need a liver transplant. The Committee asked whether the rate of liver disease progression would be the same for the 2 diseases. The Committee heard from the company that it expected liver disease progression to be more rapid in LAL deficiency, but no data were available to validate this. The clinical experts stated that in LAL deficiency there is much greater variability in the rate of liver disease progression compared with NASH. The Committee noted that in the model some people could develop hepatocellular carcinoma. The clinical experts stated that they were unaware of any cases of hepatocellular carcinoma in people with LAL deficiency but this could be because the condition is rare. The Committee noted that costs after a liver transplant and the impact of a liver transplant on quality of life had not been included in the model. The Committee heard from the company that this was a conservative assumption in its modelling because the company considered that more people on best supportive care would need a liver transplant than with sebelipase alfa. The Committee concluded that the structure of the model was broadly appropriate, but it was unclear whether

the modelling captured the variability of liver disease progression in LAL deficiency.

5.13 The Committee noted that without long-term data on clinical outcomes, the company had assumed in its modelling that sebelipase alfa would prevent further liver disease progression. The Committee further noted the ERG's view that there were no data from the trials supporting a difference in liver disease progression between people treated with best supportive care or sebelipase alfa and that the transition probabilities used in the model should be the same for sebelipase alfa and best supportive care. The Committee considered the ERG scenario to be extremely conservative. The Committee considered that the evidence from the trials and from the patient experts showed that sebelipase alfa had a treatment effect, and as such the ERG scenario was not plausible. However, it equally considered there were no data to validate the company's assumption that sebelipase alfa would stop further disease progression. The Committee heard from clinical experts that if a person's disease progression was stabilised at the point they had cirrhosis but without significant loss of liver function then the person would be expected to have near-normal quality of life and a good prognosis. The Committee concluded that it was appropriate to model a long-term treatment effect for sebelipase alfa but because there were no data to support the company's assumption that the long-term consequences of LAL deficiency would be completely prevented by sebelipase alfa, the modelled survival benefit was highly uncertain.

5.14 The Committee discussed the company's quality-adjusted life year (QALY) estimates from its cost–consequence model for sebelipase alfa and best supportive care, noting that these depended on the survival estimated by the modelling and the particular utility values chosen by the company to represent the quality of life of people with LAL deficiency. The Committee had already concluded that the extent of survival gain with sebelipase alfa was subject to considerable uncertainty (see section 5.13). The Committee noted that the utility values used by the

company for liver disease health states in the cost–consequence model were not calculated from quality-of-life data collected from people with LAL deficiency, they were those that had been used by Mahady et al. in modelling non-alcoholic steatohepatitis and were mostly based on data collected from people with hepatitis C. The Committee agreed with the ERG that some of the utility values used by the company for children and adults with LAL deficiency were higher than expected because they were higher than the age-dependent UK population norms for people without a chronic health condition and as such were implausible. The utility values also did not reflect patients' accounts of how LAL deficiency negatively affected their quality of life. The Committee noted that the ERG had suggested using utility values from Crossan et al., in which quality of life data from people with hepatitis C were collected. The Crossan et al. utility values were lower than those in the company base case. The Committee listened to the company's concerns that some of the people in the Crossan study had become infected with hepatitis C because of intravenous drug use and may have physical or psychological comorbidities which could affect their quality of life. The Committee concluded that there were issues with estimates of utility values identified by both the company and ERG because they had not been derived from people with LAL deficiency but that, on balance, it expected the true utility values were likely to be closer to the ERG's estimates because it was unlikely that people with LAL deficiency experienced a better quality of life than age-matched people without a chronic condition.

5.15 The Committee discussed 2 of the company's assumptions about the future costs of sebelipase alfa:

- The price of sebelipase alfa would drop by 30% after 10 years because of the potential availability of generic or biosimilar versions of sebelipase alfa after expiry of the sebelipase alfa patent.
- A reduction in drug wastage and associated costs after 2017 because of the availability of a 5 mg vial of sebelipase alfa.

The Committee stated that it had not considered price reductions resulting from the potential introduction of generics or biosimilars because this is speculative and the impact of their introduction is unknown. Similarly, the Committee considered that while it acknowledged a 5 mg vial was in development, it had to make its decisions based on the costs of sebelipase alfa available now. The Committee discussed the extent to which drug wastage with the currently available 20 mg vials would affect the costs to the NHS. It heard from the clinical experts that all efforts were made to minimise drug wastage by averaging the administered dose over the course of infusions by rounding up or down the dose administered at each infusion. The Committee concluded that an assumed price reduction after 10 years should not be included in the modelling. The Committee further concluded that the cost of 20 mg vials of sebelipase alfa should be used in the model, but noted that efforts by clinicians to minimise wastage were not currently accounted for in the model.

- 5.16 The Committee discussed the most appropriate discount rate used for costs and health effects. The Committee understood from the company's sensitivity analyses that the results of the company's cost-consequence analysis were sensitive to the discount rate. Although not binding on the highly specialised technologies evaluation programme, the Committee was aware from NICE's [guide to methods of technology appraisal](#) (2013) that a non-reference case 'discount rate of 1.5% for costs and benefits may be considered by the Committee if, based on the evidence presented, the long-term health benefits are very likely to be achieved. Further, the Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs'. The Committee noted the considerable uncertainty surrounding whether the treatment effect of sebelipase alfa would be maintained over the long term and whether sebelipase alfa would extend life expectancy to near normal in people presenting with symptoms in early childhood or later in life. The Committee therefore did not consider that there was a strong case for using a 1.5% discount rate over the more standard 3.5% rate.

The Committee concluded that it was more appropriate for the company to include a discount rate of 3.5% in its base case.

- 5.17 The Committee noted that its preferred modelling assumptions were:
- including the ERG's adjustment of health-related quality of life to UK population norms
 - the ERG's preferred utility values
 - The company's inclusion of a treatment effect for sebelipase alfa in its transition probabilities (noting its concerns about whether this represented the true treatment effect for sebelipase alfa)
 - removing the company's assumed price reduction of sebelipase alfa at 10 years
 - continued use of a 20 mg vial
 - a 3.5% discount rate applied to costs and health benefits.

Following the Committee meeting, the Committee asked the ERG to run the model with these assumptions applied. The Committee noted that applying these assumptions resulted in a total QALY gain of 17.15 with sebelipase alfa and 10.52 with best supportive care, (incremental QALYs of 6.64, incremental costs are commercial in confidence and cannot be reported here). It further noted that this incremental QALY gain was dependent on the assumption that sebelipase alfa completely halted disease progression, and that there was no evidence available to support this assumption. The Committee concluded that there was an incremental QALY gain of up to 6.64 associated with sebelipase alfa treatment, but that this was very uncertain.

- 5.18 The Committee considered the overall value for money provided by sebelipase alfa. It was aware that NHS England has a single budget for specialised services of £13 billion, which includes a budget of £156 million for high-cost drugs. The Committee considered the needs of people with LAL deficiency and their families compared with the needs of people with other rare diseases and conditions. It then discussed the overall value of

sebelipase alfa, taking into account both its health benefits (estimated to be between 0 and 20.5 additional QALYs) and associated costs, in the context of other highly specialised technologies:

- It recalled that NICE's highly specialised technology guidance on [eculizumab for treating atypical haemolytic uraemic syndrome](#) stated that eculizumab produced incremental QALY gains when compared with standard care (estimated to be 25.22 by the company and 10.14 by the ERG). NICE estimated an annual cost per patient for eculizumab of £211,000 to £340,000 using the list price for eculizumab.
- It recalled that NICE's highly specialised technology guidance on [elosulfase alfa for treating mucopolysaccharidosis type IVa](#) stated that elosulfase alfa produced incremental QALY gains when compared with standard care (estimated to be 18.18 by the company and 10.03 by the ERG). NICE estimated an annual cost of £394,680 per patient using the list price for elosulfase alfa (the annual cost per patient incorporating the patient access scheme, in which elosulfase alfa is provided at a discounted cost, is commercial in confidence and so cannot be reported here).

After considering the company's model, the Committee noted that the average annual cost per patient and the incremental costs for sebelipase alfa were significantly higher than those for eculizumab and elosulfase alfa. Furthermore, although the company's estimated incremental QALY gains (20.5) were higher than for the other technologies, the Committee considered that the actual incremental QALY gain would be much lower (up to 6.64 according to the Committee's preferred assumptions). In addition, there was a high degree of uncertainty surrounding the QALY estimates for sebelipase alfa depending on the extent and duration of the treatment effect and its influence on long-term clinical outcomes. The Committee noted that each highly specialised technology evaluation needs to take into account the criteria set out in the [Interim process and methods of the highly specialised technologies programme](#), as well as the uncertainties surrounding the estimated costs and benefits for each

technology. The Committee was mindful that, given the finite resources available to fund highly specialised technologies, prioritising technologies with greater benefits for lower costs would generate a greater overall health impact. It therefore considered that it was appropriate to take its deliberations in previous evaluations into account when reaching a decision for sebelipase alfa. The Committee noted that the long-term benefits of sebelipase alfa were uncertain because of the limited data available. It considered that, even based on more optimistic assumptions of long-term treatment effect, the cost of sebelipase alfa would be very high, and that it would be higher relative to treatment benefits than the Committee had previously regarded as acceptable. The Committee was unconvinced that sebelipase alfa represented overall good value for money to the NHS.

- 5.19 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when evaluating sebelipase alfa. The Committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation of sebelipase alfa. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by sebelipase alfa.

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

- 5.20 The Committee considered the potential wider societal benefits of sebelipase alfa treatment proposed by the company and the patient experts. It understood from the patient experts that sebelipase alfa improves the general health and functioning of people with LAL

deficiency. Because it extends life in babies with the rapidly progressing form of the condition, it would enable children with the condition to be educated. For adults with the condition and carers of people with the condition, it would enable them to work or perhaps work for longer and take part in social activities. The Committee also appreciated that sebelipase alfa may reduce the need for parents and carers to visit their child in intensive care and, if liver transplant is avoided by using sebelipase alfa, this would remove the need to be prepared for a liver transplant at a moment's notice. The Committee recognised that patients need to travel to receive their infusions with sebelipase alfa and this has an effect on costs and time. However, these are expected to be lower if sebelipase alfa is available within a homecare arrangement. On balance, the Committee agreed that there would be cost savings and benefits with sebelipase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.

Conclusion

- 5.21 The Committee considered that sebelipase alfa had a treatment effect compared with best supportive care but there was a lack of data on whether sebelipase alfa completely reversed LAL deficiency over the long term and prevented complications of the condition. Because of this, the modelled survival estimates of sebelipase alfa were highly uncertain. The Committee considered that the annual cost of sebelipase alfa per person was higher than a value it had previously accepted as reasonable in a highly specialised technology evaluation and it did not consider that the benefits of sebelipase alfa justified the higher cost. The Committee noted that the severity of symptoms in people with LAL deficiency varies widely and that some people with LAL deficiency may not need treatment with sebelipase alfa. It considered that the company had underestimated the number who would receive sebelipase alfa in clinical practice. Taken together, the Committee considered that the costs were too high, and the long-term benefits of sebelipase alfa too uncertain for it to recommend

sebelipase alfa. The Committee further commented that the patient expert accounts of the benefits of sebelipase alfa for babies with rapidly progressive LAL deficiency were compelling and the Committee considered that continued research into the maintenance of these effects was needed. The Committee also commented that, for babies whose condition had been stabilised with sebelipase alfa, exploring the benefits of haematopoietic stem cell transplant with curative intent would be likely to represent good value to the NHS in the context of limited research resources. The Committee therefore did not recommend sebelipase alfa for treating LAL deficiency in people who presented with rapidly progressive LAL deficiency before they were 6 months old except as part of a clinical trial. The Committee did not recommend sebelipase alfa for children and adults who did not present with rapidly progressive LAL deficiency before they were 6 months old.

Summary of Evaluation Committee's key conclusions

Evaluation title: Sebelipase alfa for treating lysosomal acid lipase deficiency		Section
Key conclusion		
<p>Sebelipase alfa is not recommended for treating lysosomal acid lipase (LAL) deficiency in people who presented with rapidly progressive LAL deficiency before they were 6 months old except as part of a clinical trial. Research should be designed to generate robust evidence about the benefits of long-term treatment with sebelipase alfa compared with shorter-term treatment with sebelipase alfa ('bridging therapy') followed by haematopoietic stem cell transplant with curative intent.</p> <p>Sebelipase alfa is not recommended for treating LAL deficiency in people who did not present with rapidly progressive LAL deficiency before they were 6 months old.</p>		1.1–1.3
<p>For babies presenting with rapidly progressive LAL deficiency before they were 6 months old, the Committee considered that bridging therapy with enzyme replacement before a haematopoietic stem cell transplant has the potential to offer benefits of enzyme replacement therapy while minimising the need for its long-term use and offering a cure for the condition. The Committee concluded that this research would be likely to represent good value to the NHS in the context of limited research resources.</p> <p>For people who did not present with rapidly progressive LAL deficiency before they were 6 months old, the Committee concluded that it could not recommend sebelipase alfa because the costs were too high and the long-term benefits too uncertain.</p>		5.8, 5.21
Current practice		
<p>Nature of the condition, including availability of other treatment options</p>	<p>Babies with rapidly progressing LAL deficiency experience severe vomiting and diarrhoea, growth failure and death usually within 6 months. Best supportive care does not prevent premature death. People presenting with symptoms later in life typically have less rapidly progressive disease. The Committee heard that treatment would not routinely be offered to older patients whose symptoms are milder and whose condition is less rapidly progressive, and that the presence of fibrosis would indicate a need for treatment.</p>	5.1, 5.3
The technology		
<p>Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Sebelipase alfa is the only active treatment available for LAL deficiency and, in this regard, is innovative. The Committee heard from the clinical experts that, because sebelipase alfa was the first therapy that specifically targets the underlying cause of LAL deficiency, they considered it to be a step change in managing the condition.</p>	5.4

Adverse reactions	The summary of product characteristics lists the most serious adverse effects with sebelipase alfa (seen in around 3 in 100 patients) as being signs and symptoms of severe allergic reactions.	3.2
Clinical evidence		
Availability, nature and quality of evidence	The Committee discussed the evidence for the efficacy of sebelipase alfa for treating babies presenting before 6 months with rapidly progressive LAL deficiency, noting that the company had compared 12-month death rates in LAL-CL03, a single-arm open-label study with LAL-1-NH01, and a natural history cohort study. The Committee discussed the evidence for the efficacy of sebelipase alfa for treating children and adults who did not present with rapidly progressive LAL deficiency before 6 months, focusing on LAL-CL02, a randomised controlled trial comparing sebelipase alfa with placebo in people presenting with symptoms of LAL deficiency in childhood or adulthood.	4.5, 5.5, 5.6
Uncertainties generated by the evidence	The Committee was uncertain whether the effects seen in the clinical trials would be maintained over the long term, were sufficient to prevent long-term complications and would fully restore life expectancy to that of people without the condition.	5.5, 5.6
Impact of the technology	The Committee acknowledged the patient experts' view that sebelipase alfa offered a lifeline for babies presenting with rapidly progressive LAL deficiency. It also noted the views of patient experts with symptoms starting later in life; that is, how sebelipase alfa had stopped their symptoms, enabled them to do day-to-day activities again and restored their quality of life.	5.4
Cost evidence		
Availability and nature of evidence	The Committee discussed the structure of the company's cost-consequence model, noting that it was based on an economic model for non-alcoholic steatohepatitis (NASH). It heard that liver disease progression is similar between NASH and LAL deficiency, although the rate of liver disease progression may be quicker in LAL deficiency than NASH.	5.12

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis</p>	<p>The Committee concluded that the structure of the model was broadly appropriate, but it was unclear whether the modelling captured the variability of liver disease progression in LAL deficiency.</p> <p>The Committee concluded that it was appropriate to model a long-term treatment effect for sebelipase alfa but that the modelled survival benefit was highly uncertain because there were no data to support the company's assumption that the long-term consequences of LAL deficiency would be completely prevented by sebelipase alfa.</p>	<p>5.12, 5.13</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee considered that the utility values used by the company for children and adults with LAL deficiency were not plausible because they were higher than the age-dependent UK population norms for people without a chronic health condition. It concluded that there were issues with estimates of utility values identified by both the company and ERG because they had not been derived from people with LAL deficiency. However, on balance, it expected the true utility values were likely to be closer to the ERG's because it was unlikely that people with LAL deficiency experienced a better quality of life than age-matched people without a chronic condition.</p>	<p>5.14</p>
<p>Cost to the NHS and PSS</p>	<p>The company estimated that the 5-year budget impact of sebelipase alfa was £54 million and the ERG's estimate was £179 million. The Committee considered that it was likely that the budget impact would be closer to the ERG's estimate because the company may have underestimated the number of people who would receive sebelipase alfa in clinical practice.</p>	<p>5.10</p>
<p>Value for money</p>	<p>The Committee noted that the long-term benefits of sebelipase alfa were uncertain and considered that, even based on more optimistic assumptions of long-term treatment effect, the cost of sebelipase alfa would be very high, and that it would be higher relative to treatment benefits than the Committee had previously regarded as acceptable. The Committee was unconvinced that sebelipase alfa represented overall good value for money to the NHS.</p>	<p>5.18</p>
<p>Impact beyond direct health benefits and on the delivery of the specialised service</p>	<p>The Committee agreed that there would be cost savings and benefits with sebelipase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.</p>	<p>5.20</p>
<p>Additional factors taken into account</p>		
<p>Access schemes</p>	<p>Not applicable</p>	

<p>Equalities considerations and social value judgements</p>	<p>During consultation on the draft scope, a consultee asked whether a definition of early and late onset lysosomal acid lipase (LAL) deficiency would be based on the person's age at diagnosis. The marketing authorisation for sebelipase alfa was granted after the scoping workshop. It stipulates different treatment regimens for LAL deficiency presenting in infancy (defined as before 6 months) according to the rate of disease progression. The evidence for 2 distinct populations based on the rate of progression were considered separately by the Committee because of differences in their treatment needs, and on the high mortality in the group with rapidly progressive LAL deficiency. Therefore, separate recommendations were made for each population but based on clinical criteria and not age.</p>	
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6 Proposed recommendations for further research

- 6.1 The Committee recommends that a study is done to compare long-term treatment with sebelipase alfa with short-term treatment with sebelipase alfa followed by a haematopoietic stem cell transplant.

7 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

There is no related guidance for this technology.

8 Proposed date for review of guidance

- 8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 5 years after publication of the guidance. This date has been set to allow data collection to address the research recommendation. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, Highly Specialised Technologies Evaluation Committee

February 2016

9 Evaluation Committee members and NICE project team

Evaluation Committee members

The Highly Specialised technologies Evaluation Committee is a standing advisory committees of NICE. Members are appointed for a 3-year term and a Chair and vice chair are also appointed for 3 years. A list of the Committee members who took part in the discussions for this evaluation appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each Evaluation Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Peter Jackson (Chair)

Consultant Physician and Honorary Reader in Clinical Pharmacology

Ron Akehurst

Health Service Researcher, Strategic Director

Sotiris Antoniou

Consultant Pharmacist, Cardiovascular Medicine, Barts Health NHS Trust

Steve Brennan

Chief Finance Officer, NHS North Kirklees Clinical Commissioning Group

Trevor Cole

Clinician – Geneticist/Consultant in Clinical and Cancer Genetics/Honorary Reader in Medical Genetics

Sarah Davis

Senior Lecturer in Health Economics, the University of Sheffield

Jonathan Howell

Public Health Physician – Consultant in Public Health

Jeremy Manuel

Lay Member

Francis Pang

Healthcare Industry – Vice President, Market Access

Linn Phipps

Lay Member

Mark Sheehan

Oxford BRC Ethics Fellow, The Ethox Centre, University of Oxford

Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's & St Thomas' Hospitals, London

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel, a project manager and the Associate Director for the Highly Specialised Technologies Programme.

Mary Hughes

Technical Analyst

Linda Landells

Technical Adviser

Jenna Dilkes / Leanne Wakefield

Project Manager

Sheela Upadhyaya

Associate Director

10 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this evaluation was prepared by Kleijnen Systematic Reviews:

- Riemsma R, Joore M, Ramaekers B, et al. Sebelipase alfa for treating lysosomal acid lipase deficiency. Kleijnen Systematic Reviews (in collaboration with Erasmus University Rotterdam and Maastricht University), December 2015

B. The following organisations accepted the invitation to participate in this evaluation as consultees and commentators. They were invited to comment on the draft scope and the evaluation consultation document (ECD). Organisations listed in I, II and III were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final evaluation determination.

I. Manufacturer/sponsor:

- Alexion Pharma UK

II. Professional/specialist and patient/carer groups:

- Addenbrooke's Lysosomal Disorders Unit
- Birmingham Children's Hospital NHS Foundation Trust
- British Inherited Metabolic Disease Group
- British Liver Trust
- Children's Liver Disease Foundation
- Children Living with Inherited Metabolic Diseases
- European Lysosomal Storage Disorder Nurses Group
- HEART UK
- London Guy's Hospital Genetic Centre
- Mark Holland Metabolic Unit for Adult Inherited Metabolic Disorders, SRFT
- MPS Society
- Royal College of Nursing
- Royal College of Pathologists

- Royal College of Physicians
- Willink Unit, Genetic Medicine, CMFT

III. Other consultees:

- Department of Health
- NHS England

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Cochrane Cystic Fibrosis and Genetic Disorders Group
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on sebelipase alfa for treating lysosomal acid lipase deficiency by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ECD.

- Dr Patrick Deegan, nominated by the Royal College of Pathologists and Alexion Pharma UK – clinical expert
- Dr Simon Jones, nominated by the Willink Unit CMFT – clinical expert
- Dr Elaine Murphy, nominated by the British Inherited Metabolic Diseases Group – clinical expert
- Sophie Thomas, nominated by the MPS Society – patient expert
- Amjad Akhtar, nominated by the MPS Society – patient expert
- Stuart Lancaster, nominated by the MPS Society – patient expert
- Charlotte Doyle, nominated by the Willink Unit CMFT – patient expert

D. The following individuals were nominated as NHS Commissioning experts by NHS England. They gave their expert/NHS commissioning personal view on

sebelipase alfa for treating lysosomal acid lipase deficiency by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ECD.

- Edmund Jessop, selected by NHS England – NHS Commissioning expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Alexion Pharma UK