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

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Contents:

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

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 deficiency[1]						
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 haematopoetic 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		
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. 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.		1.1–1.3
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. 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.		5.8, 5.21
Current practice		
Nature of the condition, including availability of other treatment options	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.	5.1, 5.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	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.	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

Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	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. 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.	5.12, 5.13
Incorporation of health-related quality-of-life benefits and utility values 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?	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.	5.14
Cost to the NHS and PSS	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.	5.10
Value for money	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.	5.18
Impact beyond direct health benefits and on the delivery of the specialised service	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.	5.20
Additional factors taken into account		
Access schemes	Not applicable	

Equalities considerations and social value judgements	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.	

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

ECD - Consultees & Commentators: (Lysosomal acid lipase deficiency - sebelipase alfa) [737]

Response by the British Inherited Metabolic Disease Group

Firstly, the BIMDG would like to record its ongoing concerns regarding the current high costs of licensed medications for rare inherited metabolic diseases. UK patients have always been at the forefront of participation in international clinical trials to determine safety and efficacy of such medications prior to licensing. The high costs associated with these medications and subsequent refusal for funding of such treatments post-licensing based on cost-benefit analyses, will deny the UK patient population the long-term benefits of such participation.

The BIMDG is agreed that sebelipase alfa is a life-saving treatment for infants with rapidly progressive LAL deficiency, and that this is sufficiently proven by the existing studies and clinical expert opinion. The evidence base for HSCT is currently weaker than that for sebelipase alfa and to insist therefore that all infants can only be treated with sebelipase alfa within the context of a clinical trial may be unethical. Parents with a very unwell child, who significantly improves with 'bridging' sebelipase alfa treatment are unlikely to then accept HSCT as an option. The BIMDG feels that HSCT for this condition has had mixed results, [Gramatges et al 2009], and that clinicians treating patients will find it very difficult to recommend this as an equally efficacious and safe option in a child who is responding well to sebelipase alfa ERT. While successful engraftment can correct the metabolic defect [Stein et al 2007, Tolar et al 2009], HSCT has also been associated with morbidity and mortality [Yanir et al 2013]. It is likely that only English patients would be obliged to participate in such a clinical trial and hence recruitment would be very low, at an estimated rate of 1 patient per year, and will therefore be unfeasible, both financially and as a tool for determining best treatment long-term.

The BIMDG therefore strongly requests that NICE reconsider its decision to only recommend sebelipase alfa in the context of a clinical trial as a bridging treatment prior to HSCT in such infants and seeks clarification on who would be expected to fund this clinical trial (the Company or the NHS?). The BIMDG believes that all infants diagnosed with rapidly progressive LAL deficiency should be considered for funded treatment with sebelipase alfa and that, while further studies on HSCT are warranted, clinical trial participation should not be compulsory.

If funding is not recommended for patients with LAL deficiency then this will be the first patient group with a lysosomal storage disorder for which the only available specific ERT has been denied. The BIMDG believes that sebelipase alfa is at least as efficacious as some other funded ERTs and therefore that a decision not to fund would discriminate against this particular patient group.

Members of the BIMDG have extensive experience with use of other ERTs longer-term (> 20 years for Gaucher disease) and think it is highly unlikely that significant adverse events (not already documented in the clinical trials) will arise in future to worsen the risk profile of treatment.

The BIMDG agrees with the Committee that it remains uncertain if sebelipase alfa will delay or stop progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events or death in patients who present after infancy as these longer-term clinical outcomes could not be assessed in the reported clinical trials. Nonetheless, in other disorders of liver fibrosis, liver biopsy with histology is a well-studied accepted marker of disease progression and the BIMDG feels that the reduction in steatosis seen in a greater number if patients on sebelipase alfa compared with placebo (whilst not statistically significant) should be acknowledged [Burton et al 2015] and that improvements in all markers studied indicates that disease progression is highly likely to be slowed by sebelipase alfa.

The BIMDG is aware that the budget for high cost drugs is limited, and that further treatments for other inherited metabolic disorders likely to impact on this budget are in development, and hopes that ultimately the Company will be able to agree a lower price for sebelipase alfa with NICE / NHS England.

The BIMDG therefore proposes that access to sebelipase alfa in children > 1 year and adults should be in the context of a managed 'patient access scheme' drawn up and agreed by clinical experts, the patient representatives (MPS society), NHS England and the Company. Such an access scheme document is already in the later stages of preparation and would define treatment start criteria, monitoring criteria, response criteria and stop criteria, in a similar manner to the patient access scheme recently agreed for elosulfase alfa for MPS IV.

MPS Society Response to the ECD – Sebalipase alfa for treating lysosomal acid lipase deficiency.

We at the MPS Society were very disappointed with the interim decision of the Evaluation Committee not to recommend Sebelipase alfa for treating lysosomal acid lipase deficiency (LAL D).

Having been a part of the process, reviewing all the clinical evidence, clinical trial outcomes, clinical data and speaking and hearing the patient experience, it appears that the Evaluation Committee although acknowledging the importance of treating patients with LAL D have disregarded the clinical evidence, heavily weighting their decision on cost. Although we acknowledge and accept that cost does have a role to play in decision making this should not be at the detriment to patients, against clinical evidence and decisions to treat and certainly not at a risk to life.

Response to the decision and points raised by the Evaluation Committee not to recommend Sebelipase alfa as a treatment for LAL D.

1.1 Sebelipase alfa is not recommended for treating lysosomal acid lipase deficiency (LAL D) in people who present with rapidly progressive LAL D 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 ('bridging therapy') followed by Haematopoietic stem cell transplant with curative intent.

1.3 Sebelipase alfa is not recommended for treating LAL D in people who did not present with rapidly progressive LAL D before they were 6 months old.

Response to 1.1 – 1.2

The Society feels that the recommendation of the evaluation committee to suggest that infants diagnosed before the age of 6 months are only treated as part of a clinical trial to be wholly unethical and an infringement to their basic human rights. Sebelipase alfa has been through a robust appraisal process to receive marketing approval by the European Medicines Agency. The clinical data and outcomes submitted have allowed for this therapy to be recognised and licensed as a treatment for LAL D and therefore it should be reviewed as a drug that based on clinical evidence and review should be available to infants diagnosed with LAL D. Sebelipase alfa is an innovative treatment and clinical opinion as stated; is that this is the first therapy that specifically targets the underlying cause of LAL D and this is considered to be a step change in managing the condition (5.4). However; although acknowledging this breakthrough in treating not just the infants but those with the late onset form of the disease and giving patients the potential of extended life and improved quality of life the evaluation committee have decided not to approve the treatment for this condition. Surely the purpose of clinical trials is to try and breakthrough treatment barriers and to improve, sustain and reverse effects of disease burden on a person's life. What is this for if a person is not able to access a licensed treatment? What is the cost of a life?

Your reference to only recommend treatment within a clinical trial for infant patients was on one hand acknowledging that this patient group should be treated but renouncing any responsibility over the decision of the evaluation committee to approve treatment. This recommendation in our

opinion was unethical, especially given that there was no forethought or suggestion as to how such a clinical trial might be implemented or funded.

The Society is also concerned that the treatment cut off for infants with LAL D has been set at 6 months. Due to the rarity of the condition and the lack of expertise in diagnosing and referring outside of the specialist centres we are concerned that this will exclude any infants who may present with symptoms before 6 months but are not formally diagnosed until after this time. We would request that all infants under 12 months of age be assessed for immediate access to treatment.

The Evaluation Committees comment regarding the lack of long term data in our opinion is biased against Sebalipase alfa. It is our experience that most clinical trial data spans the same time frame (approx. five years) and therefore if this was the view for this technology why has it not be the case for other ERT's approved? Furthermore given that the average life expectancy of infants with LAL D prior to Sebalipase alfa is approximately 4 months of age, five years of clinical data from surviving patients in our opinion constitutes considerable long term data.

The Society was alarmed that the evaluation committee was suggesting that research should be designed to generate robust evidence about the benefits of long term treatment with Sebelipase alfa compared with shorter-term treatment ('bridging therapy') followed by Haematopoietic stem cell transplant (HSCT)with curative intent. This is especially concerning given the evidence on HSCT that has been made available to us and also clinical opinion on this course of treatment. Nowhere that we have read, has indicated that HSCT is curative and in fact has a high morbidity and mortality for this group of patients. Findings from ten patients who underwent HSCT (Described by Jones et al 2015). Confirmed that out of 10 patients who underwent HSCT at a mean age of 5.4 months only two of the ten patients survived post-transplant. Survival age for these patients were 3yrs 10 months and 2yrs 2 months. D Bernstein MS, CGC; Director of the Lysosomal Storage Diseases Program at North Shore Hospital in Manhasset, New York, shared with me her experience of HSCT. At their hospital they have diagnosed seven patients with LAL D. Five of these patients underwent a HSCT. Three died in infancy during the transplant process and one died as a teenager soon after HSCT. Only one patient has survived transplant (she is one of only two LAL D patients in the world who did not die secondary to HSCT). The child under [redacted] care is spending much of her life in the hospital for uncontrolled seizures, severe abdominal pain and recurrent infections.(This is patient 4 as described in Toler et al 2009) The other patient is under the care of [redacted] at the Children's Hospital, Chicago. [redacted] confirmed to me that this patient was transplanted at 2 months old. She has short stature, restricted growth, is cognitively impaired and has recurrent liver disease.

The high morbidity and mortality of patients who have undergone HSCT and the fact that only two patients in the world have survived a HSCT and continue to present with significant disease related deterioration does not indicate that this procedure is ethical or curative. It is our opinion that Sebalipase alfa has already shown significant improvement in patient's clinical outcomes without the risk to life. It would be unfair and unjust to suggest at this present time that Sebalipase alfa only be given in the short term with HSCT being the longer term treatment for LAL D. We acknowledge and appreciate that this is an area that should in due course be explored further but this has to be done on a medical evidence basis with the full understanding by clinicians and the family of the risks involved. Current survival rate is less than 20% with poor cognitive and physical outcome.

How could any clinician justify an unsafe procedure as a first course of treatment when there is an alternative that has minimal risk and is already proving to have good clinical outcomes, surpassing that of HSCT for patients?

Response to 1.3

We believe that the evaluation committee have failed to understand the prevalence and epidemiology of LAL D. This is a multi-system disease that can cause multi organ damage and premature death. Although there is a wide spectrum of disease severity and symptoms for LAL D, literature suggests that for those not diagnosed with the aggressive infant form of LAL D this is in fact a paediatric disease with a high population of patients being diagnosed in childhood with a high proportion between the age of 2-5 years. I was fortunate to attend the WORLD symposium on Lysosomal Storage Disorders (Feb 29 – March 3 2016) and attended a presentation by [redacted] She spoke about the key findings of their research which I have highlighted below.

The key outcomes and findings from this study concluded the following:

- High population of patients were diagnosed between the ages of 2-5 years with the mean age of diagnosis being 5 years.
- LAL D storage was found in one or more organs in 87% of patients reviewed
- 86% of patient's livers were affected
- 87% had cardio vascular involvement
- 21% of patients had Gastrointestinal involvement
- Children were at high risk of growth failure and short stature
- 50% of deaths occurring in patients under 21 years was due to liver disease.
- No patients reviewed lived over the age of 58 years.

In a separate study presented on LAL D 32 paediatric patients had liver biopsies. 50% of these progressed to fibrosis / cirrhosis and required a liver transplant.

The general view in respect of liver transplantation is:

a) Although it may help dyslipidaemia it will not prevent arthrosclerosis in the arteries, or correct the gastrointestinal system, spleen and kidneys.

b) Liver transplant is associated with morbidity and mortality and although it may provide a temporary prolongation of life by delaying immediate liver failure associated death, in the long term it does not prevent systemic accumulation of cholesteryl esters (view given by [redacted] also made reference to Kale at al *(Kale et al 1995)* who described a patient who succumbed to renal failure, post liver transplantation. On autopsy the patient's kidneys were found to be sclerotic with massive lipid and cholesteryl ester accumulation.

Given the evidence presented above and our understanding of this multi systemic disease the prevalence and severity of disease can be rapid and life threatening. Excluding any patient described as having the late onset form of LAL D who presents with any of the clinical symptoms indicative of treatment would be condemning a person to die without any reasonable interventions or regard to their right to life. It is our opinion that treatment should be available to patients who have been clinically assessed as meeting the start criteria and who are managed and monitored by one of the specialist centres in England.

The Society was concerned that the numbers represented in the ERG's submission was not a true representation of known numbers in the UK. After consulting with all specialist centres the following summary of known numbers under a specialist centre have been confirmed as;

Known numbers under a specialist centre in England

Paediatric patients

- 7 infants born in last five years with infant form of LAL D. All 7 infants commenced treatment as part of clinical trial.
- 3 infants died in last five years (1 while on trial / 1 line complication / 1 HLH)
- 2 paediatric patients diagnosed with late onset LAL D – 1 treated / 1 diagnosed after the clinical trial; likely to request treatment if available.

Adult patients

16 adult patients are known to the specialist centres. (10 out of the 16 patients were diagnosed as children)

- 5 enrolled on the clinical trial treated
- 6 declined treatment (1 has since indicated that they may wish to receive treatment if available)
- 3 were not eligible (2 received liver transplant) / 1 not eligible)
- 2 diagnosed after the trial (1 patient is receiving compassionate treatment while waiting a transplant, the other patient was diagnosed after the clinical trial but is likely to want treatment.

In conclusion, the NHS prides itself on having a fair and just system but how can this be when clinical evidence and views are disregarded in favour of cheaper alternatives with little clinical evidence and efficacy? An individual's right to life should be protected and no one should be deprived of life, no matter what the cost, especially when there is a treatment which is showing efficacy and improved clinical outcomes in patients currently receiving this treatment.

Report written by Sophie Thomas on behalf of The MPS Society
March 2016

References

Jones S, et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. Genet Medicine 2015; advance online publication; doi: 10.1038/gim.2015.108.

Kale S,et al. End Stage renal disease in a patient with Chloesteryl Ester Storage Disease following successful liver transplantation and cyclosporine immunosuppression. Journal of gastroenterology and nutrition. 1995

Tolar J, et al. Long term metabolic, endocrine and neuropsychological outcome of hematopoietic cell transplantation for Wolman disease. Bone Marrow Transplantation 2009; Macmillan Publishers Limited.

NHS England response to:

Evaluation consultation document - Sebelipase alfa ID 737

1. NHS England believes that the relevant information has been taken into account.

2. NHS England believes that the summaries of the criteria considered by the Committee, and the clinical and economic considerations are reasonable interpretations of the evidence.

3. NHS England believes that the provisional recommendations are sound and a suitable basis for guidance on the use of sebelipase alfa in the context of national commissioning by NHS England.

It is my view that in relation to non-infantile CESD, the committee weighed up the evidence fairly and made a decision, as it is appointed to do, based on the health economic cost and budget implications. Further negotiations may take place, focused on cost, and this may lead to a different outcome in time.

NICE also took the decision not to recommend Sebelipase Alfa for the infantile-onset form of the disease. This is despite acknowledging the life-saving impact of the treatment in the short- to medium-term. Instead, the recommendation was to treat infants as part of a clinical trial, especially as a bridge to stem-cell transplantation, which to date has been unsuccessful. NICE commends such a trial as value for money for the NHS however it remains to be determined whether this recommendation will translate into an NHS-funded clinical trial. NICE appears to recommend treatment within a clinical trial, without providing a mechanism for such a trial to take place and should facilitate the development of such a trial.

Comments on Lysosomal acid lipase deficiency - Sebelipase alfa [ID737] : Evaluation consultation : 1 by Dr Simon Jones on behalf of Willink unit, Manchester Centre for Genomic Medicine , Central Manchester University Hospitals NHS Foundation Trust, 9/3/16

We thank NICE for allowing us to comment further on the development of its guidance for Sebelipase alfa for the treatment of LALD. While we recognise the challenges for the NHS to provide a service to all patients within current budget constraints and the significant cost of this therapy, we believe this is a dramatically effective therapy which has been a step change in the management of this exceptionally rare life limiting disease. We will respond mostly to the infantile onset phenotype as this represents our greatest experience, and the most pressing need. We agree with the committee that many unknowns remain in the management and prognosis of this disorder, especially with the now surviving infantile group. This is now a new disease entity that must be understood and studied in the longer term. This is not however unique to LALD and has been seen in every one of the lysosomal storage disorders we have been involved in developing therapies for. This is also not an adequate argument for not funding a therapy – and is also recognised but he regulators (EMA/FDA) who require long term follow up registries for these reasons.

Historical control cohort for infants

We do not believe that the current evaluation document adequately understands the challenges of research and clinical trials in this ultra rare disease environment. With rare, very rapidly progressive diseases like infantile onset LALD, standard trial designs with prospective comparator groups are not only impossible to conduct but also unethical. There has been no evidence presented by the committee or by the ERG to suggest improvement in the life expectancy of these patients by changes in standard of care management, and yet the validity of the historical control cohort is repeatedly questioned (section 4.26, section 5.5). It is unclear what other comparator group the committee would view as robust. While we acknowledge that the very long term outcomes of this treated infants is unknown, this that will take many years to understand fully and is a consequence of both the universal fatality associated with this form of LALD and the current efficacy of therapy. It is unclear what type of evidence over what length of time would fully answer the committees concern to ensure that we 'fully restored life expectancy'.

The role of HSCT in the treatment of LALD

HSCT is commonly used for a number of lysosomal storage disorders and in theory should be effective for many more. The reason transplant is less effective for some diseases may be differential enzyme secretion by donor cells. This has not yet been studied in LALD. While LALD should be a transplantable disease there is very little experience and information on the outcomes available. There are only a very small number of reported survivors of HSCT (2 by Tolar et al 2009), with no more recent follow up published or able to be gleaned in communication with the authors. There is also some evidence that the liver is not fully corrected by HSCT (Gramatges et al 2009). There are few reports of unsuccessful HSCT in LALD yet most major transplant centres acknowledge the challenges of treating infants in this way. In the published historical cohort (Jones et al 2015) there were 10 infants who received HSCT, they had slightly longer survival than the untreated cases but all died.

This centre believes that HSCT may have a role in the management of LALD but before this could be widely recommended further work is required to understand the degree of correction obtained by transplanted patients. While it is clear that survival of LALD infants undergoing HSCT at diagnosis is very poor, this may be better after a period of ERT. Whether or not HSCT delivers more enzyme than ERT (as it does in MPSI) is without any evidence. Survival of other LSD children undergoing HSCT may be now as high as 95% (Manchester data), this may well not be the case for HSCT in LALD. In Manchester we have transplanted 1 child so far who developed a haemophagocytic syndrome after some months on treatment, this child unfortunately died following HSCT. Another child who has had 2 years of Sebelipase is about to be transplanted as she has only 1 remaining vein for central venous access, and so HSCT is unavoidable. There may be data from this case which we can use in the future to better understand the role of HSCT in LALD therapy. It was disappointing that at the last meeting there was not time to discuss this more fully, especially given the committee's eventual recommendations. So currently we can only say (based on evidence) that HSCT may have a role in the management of LALD but has been associated with very high mortality, and there exist very few data on long term effectiveness. The trial suggested by the committee in the consultation document using Sebelipase as a bridge to HSCT is inappropriate. The data on efficacy of HSCT so far available does not support this – and at present only those not doing well on ERT would be put forward (by clinicians) for HSCT. A patient doing well at 2 years on Sebelipase would not be a child we would put forward on clinical grounds for HSCT. Therefore the only reason for submitting such a child to a procedure with a significant but uncertain mortality risk would be cost of therapy. This seems unethical to me and an approach which would not be accepted either by patients, clinicians or research ethics committees. It is also unclear from the document if this trial was expected to be funded from within the NHS or Alexion. Even if this approach was adopted, the rates of diagnosis in England alone, combined with the existing survival of ERT patients and the follow up period required would mean such a study would take longer than 5 years to generate any significant data. While we understand the committee's intent in this suggestion, we would wish to reassure them that there have been substantial efforts to understand the benefits of ERT versus HSCT in other LSDs over the last few years, with much of this work emanating from the UK. The questions asked by the committee will be answered in time, however we feel this is best answered in a clinical/academic environment, after approval of therapy and with international collaboration. This has happened with other, similar disorders. Lastly we would take issue with the assumption that HSCT would offer a cure for LALD. The term 'curative' is not one that anyone in this field would use or recognise. Almost no treatments for genetic disorders offer a cure, and while HSCT is dramatically beneficial for a number of LSDs, it is not in any of these disorders a cure.

We deal with some specific points raised in the document in more detail:

2.2. The highest incidence of LALD as 1 in 40,000 is based on 1 paper and not recognised as anything like the true incidence of this disease on a clinical basis. We understand that a potentially large pool of undiagnosed patients is a concern in the cost analysis, however many efforts to improve the diagnosis of these patients over the last 4-5 years in the UK has yielded very few extra patients above what we would expect. In the North of England we have only had 1 new late onset diagnosis

in a child in the last 4 years. We feel it would be inappropriate to use the 1/40,000 figure ion any calculations around impact.

3.1. (and section 5.7). We understand the reluctance of the committee to consider doses higher than the licensed dose however this means the committee's deliberations do not accurately reflect the management of these patients currently in England. 2/3 of infantile onset patients treated in England are currently on a dose of more than 3mg/kg. Not taking this into account risks the committee's recommendations not being relevant to the patient group studied, and indeed misunderstanding the cost of therapy in this difficult group. Having to work outside licensed doses is unfortunately the norm in rare disease medicine.

4.2.3. Refer to the response to section 2.2 above also. We expect there to be one new infantile onset case in England per year and 0.5 to 1 new child diagnosed with late onset disease per year. These numbers have not changed with recent increased awareness of the disease. Intensive screening of high risk groups has not yet yielded a sudden increase in diagnostic rates.

5.18. We would disagree that the level of evidence existing for Sebelipase is limited when compared with other (approved) drugs such as Elosulfase. While we agree the costs are higher we would wish it to be noted that the decisions were made on the basis of cost and not on clinical evidence, which is not appreciably different and in fact there exists a greater degree of evidence for a survival benefit in LALD than in MPSIVA, a more slowly progressive disease. If there is a cost level at which the committee feel these treatments are acceptable, then this should be published, in line with the stated aims of transparency.

Discrimination

While we do not believe this process discriminates against any particular ethnic or gender group, in general the process discriminates against those with very rare diseases. We believe this based on the committees evaluation of both Elosulfase and Sebelipase where the level of evidence that the committee expect to see far outweighs any available evidence we have for any of our therapies, even those that are very longstanding and of widely agreed benefit.

The view of our unit is that Sebelipase alfa offers a dramatically better (although uncertain) future to infants diagnosed with LALD, and is also highly likely to improve the long term outcome for those with later onset disease, although follow up in the long term via a disease registry will be the only way to understand this.

Dear Sir Madam,

Please find patient experts Mr Amjad Akhtars response to the NICE ECD.

In response to the Evaluation Committees response I feel that you have failed to look at the key facts that this medicine is helping these children lead a normal life.

They are starting to interact and be aware of their surroundings. They are developing and growing as normal children.

Without the infusion their quality of life will be very poor or non- existent, we have been through a lot and feel our children deserve a fair opportunity and that the funding should be approved. More cases are coming forward and these children need to develop and grow so the doctors can provide the long term data to learn, expand knowledge and to better support and help future cases. Without this chance, our hopes for these children will be taken away.

As parents we need the care and support and I feel NICE and the drugs company should come to a mutual agreement and work together to help enable the best care for our children.

Everybody has their own interests and thoughts but as a parent we want what is best for our children and this is the gift of life.

As stated by a great scholar “You save one life, it is like you have saved the whole of humanity”

It is ok for people to talk about numbers and I know they have to weigh up costs but as I said before, how do you put a price tag on a child’s life? Can you look into these children’s eyes and say sorry, we cannot give you a chance to fight for your survival.

Kind regards

Amjad Akhtar

I Stuart Lancaster (Patient expert) wish to respond with the following comments, thoughts & viewpoints to the Evaluation Committee's preliminary recommendations regarding Sebalipase Alpa for treating Lysosomal Acid Lipase:

I was diagnosed with Lysosomal Acid Lipase on my 43rd birthday 2009 & at this time there was no specific treatment available.

Approximately 18 months later I was offered a place on the Clinical Trial for LAL. This was a like a light at the end of the tunnel. I am now in my 4th year & having access to this treatment has made a huge impact on my quality of life both in a physical, emotional & social way making the future look bright & not to be feared. My health is stable & I cannot imagine where I would be without this treatment & dread to think. It has allowed a great amount of normality to return to my everyday life rather than the constant pain, nausea, fatigue, stress, physical inactivity & other factors that this progressive disease causes. During my diagnosis journey a Liver Biopsy was required & the Surgeon carrying out the procedure could not perform this laproscopically due to the fibrosis of my Liver & had to perform an open procedure. I have been informed that my Liver now contains less fat than prior to the start of the clinical trial.

I would be absolutely devastated if this treatment were to be no longer made available. The thought of returning to the days of pre-treatment would be dreadful & be like getting diagnosed all over again with no specific treatment & the thought of all the acute symptoms as mentioned, returning & my quality of life being how it was previously. **This treatment has given me back my quality of life.**

A lot of emphasis seemed to favour Liver Transplantation as another option but surely this a last case scenario & in the current climate of organ donation being low waiting could cost a life. Also the health of a particular individual may not allow them to undergo the procedure. Also the poor quality of life in the meantime is a concern. I myself having reaped the benefits of Sebalipase Alpa would not like to find myself in this position & if the drug was not made available would likely find myself down this path.

I appreciate in relation to Section 1, point 1.2 research regarding stem cell transplant for a curative outcome is the ultimate aim for the future but for current sufferers of this devastating disease time is precious & the bridging therapy with Sebalipase Alpa is our only lifeline to life & a better quality of life at this moment, waiting is not an option. We have to deal with the present situation that we are in.

With reference to Section 1, point 1.3 I feel that this is discriminating as every person with this disease deserves an equal chance whether diagnosed before six months old or after & also whether they have rapidly progressing LAL or late onset LAL as we were all born with this condition.

With reference to Section 1.4 & having felt the enormous benefit of receiving this drug, surely it would be totally unethical & unkind to withdraw it at any point whatsoever based on my afore mentioned personal experience. My friends and family can see the treatment has 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. Surely I & other persons that have been on the Clinical Trial of Sebalipase Alpa & benefited, should at the very least be allowed to continue treatment.

Yours Faithfully,

Stuart Lancaster (Patient Expert For Sebalipase Alpa)

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]

Name of your organisation: Birm 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?
- 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)
clinical clinicist, co-deciding on highly special + serious problems, all patient related, bearing co-responsibility

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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.

I have been invited as a lay-member-attendant. I find, when asked, that important pharmaco-kinetical information has not been provided in an appropriate manner/way by the pharmaceutical company. I got my information via private sources in Calgary! That is not what it should be.

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.

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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?

Like I tried to explain a few lines earlier: The first hearing was an evaluation of trial and practice, by consultants, with their patients. That's how I felt it was. I would have liked being informed about common findings on the safe-guarding principles of the trial; a compilation of side-effects; an honest and sustained support by the pharma-company, which I found absent, at least not enough.

Clinical-trial-pharmacy is extremely important, needs being surrounded by scientifical interest, looking at the great benefit for the patients, rather than receiving pennies for the participation in the trial.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

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

Because I was invited for the definition-cycle, around the disease, I missed out on the beginning of the trial. I got no professional information, though succeeded privately in acquiring the much needed pharma-kinetics of the drug; via Canada, from the FDA. I did not succeed here, in the UK, in my search. However, never give up, and I had all necessary information in the end.

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.

There is a danger that I seem to be negative. I certainly am not. On the contrary! If I have to attend an event like the lipase-deficiency one, I will be prepared. And I was prepared! Providing participant(s) with adequate scientific knowledge may be helpful; but one sometimes find ever more by private investigation.

Implementation issues

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

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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)?

I am hardly in any position of judgment here. My concern is the patient's safety. The dilemma will always remain to find a balance between success-of-treatment against the cost of the treatment. If demand will outgrow the possibity of the use + equipment + extra staff or staff education, then deciding on approval, or no approval, will become a financial household-affair rather than a medical decison. My ethics are: who do you think you are, when deciding!

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.

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Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

If the outcome of the trial is highly positive, if the side-effect(s) will be acceptable cq manageable, if certainty of the cost does not exacerbate the means of the general purse, if there is no other option for equal treatment, only then I would vote for a go-ahead.

[redacted]

12-10-2015

A statement from [redacted] & [redacted] [redacted] parents of Stuart Lancaster (Patient Expert) in response to the Evaluation Committee's preliminary recommendations regarding Sebelipase Alpa for treating Lysosomal Acid Lipase.

Stuart had been unwell for some time with abdominal discomfort, pain & nausea. When he was finally diagnosed with a rare genetic condition we were devastated & to make matters worse at that particular time there was no specific treatment available for this condition.
Approximately 18 months later he was offered a place on the Clinical Trial of Sebelipase Alpa which he accepted & during this time the difference that it has made to him both physically & mentally has been a miracle.
Although Stuart is an adult he is still our child (only child) & we fear for his future health. We hope this treatment can continue.

Yours Faithfully,

[redacted] & [redacted] [redacted]

Individual No.	Statement
1.	I would like to add an appeal for a colleague who has been diagnosed in the last year lysosomal acid lipase deficiency. I am devastated to hear that she cannot have treatment for this condition as it is deemed too expensive. She is a young lady with her whole future in front of her and she is a dedicated member of staff of the NHS. She works with premature and sick new-born infants and their parents on a neonatal intensive care unit and transitional care ward. She has only just started her working life and could dedicate many years to NHS service; however this could be greatly affected by her health if she does not receive this treatment. I know she might be one of many who are denied treatment due to cost and I would argue the case for all these people but [redacted] is the colleague I know with this condition. She works so hard in her role and is so passionate about it. Since diagnosis with this condition she has taken minimal time off sick which I feel really shows her dedication to her work and to the NHS. Please could you review the treatment for people with this condition, particularly for someone like [redacted]. She has her whole future in front of her and could potentially have a lifetime of working for the NHS if she has the support and treatment for her condition. [redacted] Family Support Sister, NICU, [redacted], [redacted]
2.	I think the decision to prevent this treatment should be reconsidered as ALL patients have a right to fair access to a licensed treatment, the treatment being expensive should not a be a factor as to whether it should be introduced; it will help better a patient's life and help them lead a better healthier lifestyle.
3.	[redacted] deserves to get her treatment funded by the NHS along with everyone else living with LALD.
4.	I know very little about LALD but what I do know is that everyone deserves the chance to try any treatment that may well improve their way of life. Money should not be a consideration.
5.	I believe this treatment should be accepted and this lovely young lady should get the treatment she needs to live a long healthy life. Many of us take being healthy for granted. Something like this that could possibly end her life short but can be treated should be funded. A young hard working woman that's paid her taxes deserves everything to help make her better. Please agree and make this country a better place.
6.	LALD is a debilitating and lifelong disease. A sufferer can potentially have a lifetime of problems that without treatment can be life threatening. LALD is a misunderstood disease but that does not mean that the disease should be ignored. ALL humans should have the right to treatment; it is inhumane to leave a person to suffer when treatment is available. I myself know somebody diagnosed with LALD who has worked for the NHS for several years and for her to be denied lifesaving treatment is insulting.
7.	I am writing a comment due to knowing [redacted] who has the above condition and needs the treatment. I would like to refer you to The Human Rights Act (1998) Article 2 'The Right To Life'. From what I can gather having Lysosomal acid lipase deficiency will eventually lead to death. Therefore refusing people this treatment is removing their right to life. This condition will often lead to

	cirrhosis of the liver and eventually liver failure. According to www.nhs.co.uk people who have a liver transplant only have a fifty percent chance of living for five years. Many people will die waiting for a transplant. Getting to the stage of requiring a liver transplant would mean deterioration in health with time off work and requiring other interventions to treat the signs and symptoms impacting greatly on a person's quality of life. The person is also at risk of developing cardiovascular complications, again resulting in deterioration of health, impacting on quality of life and death including myocardial infarct and cerebral vascular event. There would also be many other complications to the person's physical health and no doubt on psychological health. My comment is not by any means saturated with all the facts to deliver my case of asking you to consider the impact of not allowing people this treatment. I would also like to mention [redacted], who is a very kind natured young lady, who works looking after other people. I urge you to appreciate this is people's lives in your hands not a list of statistics. Thank you for taking the time to read my comment. With kind regards [redacted] [redacted]
8.	My friend is [redacted] years old and has recently been Diagnosed with LALD, a lifelong a Disease. it makes me angry that the treatment is not NHS funded and she has recently been declined free treatment.as my friend has been working for the NHS a since she has left school, helping others with illnesses I think it should be about time to return the favour and allow this as a free treatment.
9.	Guess there's not enough kids suffering this genetic disease well I know at least one and one is too many just cos it's a so called minority disease doesn't mean it doesn't need treatment my other half suffers from Darier's disease also genetic but gets help even though no cure it genetic
10.	I am writing to appeal for a very good friend of mine, for whom the treatment for LALD is life dependant. I find it absolutely disgusting that someone whose parents have worked their entire lives paying into the NHS has been denied the treatment that she needs. Themselves and their family members have worked for the National Health Service and have done for many years, so I canâ€™t help but feel it begs the question, what for? Not receiving this treatment will inevitably lead to the serious deterioration of their health and a build-up of complications resulting in liver dysfunction and potentially stroke or CAD. To hear that as a young woman is absolutely devastating and having known this person personally for many years I know that she is suffering daily to come to terms with the diagnosis. It infuriates me to know that the NHS will more than happily fund treatments and care for people who are overweight (which 9 times out of 10 is a lifestyle choice) and for people who undergo plastic surgery because they â€˜have no confidence â€™ etc. , whereas the treatment for a serious life threatening disease is deemed too expensive and therefore inaccessible. To pretty much tell

	someone they are going to be left to suffer without any help from a service who has employed them since the age of [redacted] is absolutely appalling. It is inhumane to watch someone to deteriorate when needing this is completely necessary and beyond her control. It is without choice that people are left seriously needing this for the rest of their lives, so I plead with you to fund the treatment.
11.	I believe that in the case of medication being used to improve the life of someone is a must regardless of whether it will cure an illness or not if the outcome is a day extra in that person life without pain and suffering it should be a fundamental right of everyone to have treatment regardless of the cost .Every child born in this country should receive the best treatment that is available regardless of cost all that should be factored is does it help will it give some relief an extra day hour minuet second it does not matter treat every child as it was your own give them all a fighting chance .for the difference whether to not treat is that a child could miss out by not surviving long enough for a cure to be found as new treatment will appear but until it dose do the right thing treat with the best you have at this time .
12.	I would just like to comment on the treatment of [redacted] [redacted] a hard working young woman for the NHS that I work with has been told that she will not qualify for her treatment for this illness she has now been told she has, after all the things I have watched on TV programmes about people getting such things like breast enhancements and other things like that on the NHS which may seem important to that person but it is not life threatening I feel really sad that something like this is not suitable on the NHS for this young hard working woman and hope with her appeal that she gets the treatment that she deserves King Regards
13.	It is absolutely essential that those individuals who are debilitated with this illness receive the highest levels of treatment that can be provided to ensure their health and wellbeing is maintained, the cost should be balanced against alternative treatments and I feel strongly that the fairest way to proceed would be to fund the medication wholly for the duration of the illness .
14.	Lysosomal acid lipase deficiency - Sebelipase alfa is an illness that will shorten a person's life if not treated. How can you deny a person of a bright future due to funding? This illness has had successful outcomes for people who have been given the proper treatment and are having a better quality of life. To fund 1 person and deny another is not fair and does not promote equality. The NHS is there is help people and to give them the best possible life, to enable them to have a healthy future and in some cases grow old gracefully. Please make the NHS fair for all and provide this beautiful, bright, intelligent young woman the healthy future she deserves. Thank you for taking the time to read my comment
15.	This treatment needs to be available on the NHS to all those suffering with this condition. The NHS was set up to give everyone free access to the treatment they need. There are hardworking people suffering with this disease with no hope of ever being able to afford

	the treatment. Not to mention the fact that without treatment, those suffering with the disease could be looking at increased hospital visits due to complications from the disease, with all the risks and costs this entails. How can it be justified that people with diseases caused by their own abuse on their bodies, i.e. alcohol, smoking, obesity, can receive treatment on the NHS and people suffering with LALD can't? Please see the light and allow the NHS to function as it should, free health care to those who deserve it.
16.	I believe all those suffering from this condition should be entitled to treatment as without having this treatment could have a very negative impact on their health and their way of living. One of these patients especially should be entitled to this treatment as she is a dedicated and committed staff member of the NHS. She works very hard to provide the best care for her patients so I feel she deserves the same care back and giving her this treatment would allow her to live a healthy life without the worries of long lasting health issues.
17.	Lysosomal Acid Lipase (LAL) deficiency is a rare disease. It only affects a few people in the UK. But, just because it is rare should not prevent those suffering from receiving treatment that could provide cure/relief. What cost to the NHS to care for these people as their condition worsens? What cost to their friends and families? What cost for liver transplant as a final resort â€“which of course may not work? LAL is a terrible, life threatening illness. But the NHS strives to deliver care for all and free at the point of delivery. This is a position that the UK should rightly be proud of and should fight to maintain. Whilst it is understood that the NHS, like all government departments, is under severe pressure to manage budgets against increasing demands, why should the burden fall to patients and their families who through no fault of their own are afflicted by LAL? This is not a disease predicated by bad life choices, this is just luck. I hope that this is not the only comment you receive on this consultation and that a review of the position leads to the NHS agreeing to fund treatment; even if only for a NHS led trial which could both offer hope to those suffering today but also to those yet to be diagnosed. I myself suffered from a rare form of cancer, Desmoplastic Small Round Cell Tumour. Diagnosed in 1997 at [redacted] I received Chemotherapy, High Dose Chemotherapy with Stem Cell Transplant and then Radiotherapy. I have the NHS, and in particular the wonderful oncology team at [redacted] led by Dr [redacted], to thank that I can provide this comment. As one of, if not the longest known survivor of this disease I have complete empathy for those with LAL and wish them all the best.
18.	I believe that the board should re consider their decision; although I understand that this treatment is expensive all patents should have fair access to a licensed treatment. The stress that is placed on these families and the individual is intolerable and I would consider in human when such a lifesaving treatment is available.

19.	Appeal on behalf of [redacted] [redacted] (and [redacted] others know to have LALD) [redacted] who was diagnosed last year with lysosomal acid lipase deficiency also known as LALD and has been awaiting to hear if she would get treatment this year ... This treatment needed for life to keep her fit and healthy... Without this treatment her health will deteriorate. Her treatment has been declined through NHS England because it is too expensive to fund through the NHS. This for her and the others diagnosed, I personally find it unacceptable and as such wish to add my concerns to that of an appeal to have this treatment available to all with this condition. I believe that it's a point of all patients to having fair access to a licensed treatment under the NHS and as a member of the tax paying public of this country wish this highlighted as an urgent case for funds to be made available.
20.	I am supporting foremost the case of [redacted] [redacted] [redacted] who has been declined by NHS England for treatment having being diagnosed with LALD last year & the other [redacted] adults who are also suffering. I understand the constraints that the NHS works under, but to refuse treatment due to the costs, compared to the quality of life these diagnosed will suffer seems very unfair& short-sighted. Surely this compared to the lottery of having transplants thus putting more people on the transplant list & affecting even more lives than is necessary.
21.	LALD patients shouldn't be denied the treatment that is needed due to cost, just to then spend more money later down the line with a costly liver transplant. Also the treatment if given now saves a lot of other liver and health problems to the patient further down the line. And how do you know if you can find a suitable donor for the patient, which then puts the patient's life in danger
22.	As one of my colleagues has been diagnosed with LALD who works within the NHS, I find it appalling that she and other sufferers of the disease have been denied treatment which could better their quality of life. I wish that you would reconsider your decision to give suffers of LALD the quality of life that they deserve.
23.	Everyone should have the right to treatment if it is available. Without this treatment she will need a liver transplant which will shorten her life through no fault of her own. People who abuse their bodies are given lifelong treatments without question.
24.	I feel that treatment that could enable someone to live a normal life should be given, no matter what the cost. This woman works for the NHS and looks after those in need, so you should look after her. Everyone should have the right to treatment if it is available, especially if the alternative is a liver transplant or a shortened life.
25.	Everyone should have the right to fair access of treatment on the NHS. Across the country, people who are suffering from Lysosomal Acid Lipase Deficiency will currently feel disappointed and unsupported as a result of being denied treatment. The treatment could transform their lives and without it their health will deteriorate. Shouldn't everyone who suffers, through no fault of their own, have fair access to treatment on the NHS?
26.	LALD is a debilitating and lifelong disease. A sufferer can potentially have a lifetime of problems that without treatment can be life threatening. LALD is a misunderstood disease but that does not mean that the disease should be ignored. ALL humans should have the right to treatment, it is inhumane to leave a person to suffer when treatment is available, many people abuse the NHS and the majority

	who has needed treatment is self-inflicted! I know somebody diagnosed with LALD who has worked for the NHS for several years and for her to be denied lifesaving treatment is insulting.
27.	My best friend's son was diagnosed with LAL D late onset. Unfortunately the trials had already finished for her son to start to trial this new treatment. Listening to the positive effects this has had on other patients I am shocked to hear that you are wanting longer term research and because of money! Should a child's life come down to money, no it shouldn't? It is heart-breaking to watch a happy family worry about their child's future, through no fault of their own. Every child should be given the opportunity to live a long and happy life and be able to look forward to growing up, one day get married and have children of their own. This treatment has already proven to reduce the effects of the disease so why not attempt to give a child a better quality of life. I will be honest and say that I have not read all the report on the website because I haven't got the time to read over 800 pages, because I work, just like my friend and her family. They all work and pay their taxes so why shouldn't society repay them by helping their helpless son. I am pleading with you to change your decision and make this treatment available to everyone who needs it. If any of you have children I hope you will think about how you would feel in this situation and have some compassion and say YES! I am more than happy to discuss anything further with you so please do not hesitate to get in touch. Regards, [redacted] [redacted]
28.	A friend of mine needs this drug in order to live a healthy and pain/problem free life, why should she and others be denied this? Please make this drug available to her through the NHS.
29.	I am writing for [redacted] [redacted], to get the help with her rare disease that could change her life. I would also like to think that although you have more research to do. Let her he your research. She is a beautiful kind caring person you'll meet and by NHS refusing to help she has gone her own way. People will be helping her get this treatment. Please help!
30.	I wish to comment regarding the decision of not funding [redacted] [redacted] [redacted] for her LALD treatment. She is a very valued Nursery Nurse on the on a busy maternity ward, caring for new-born babies, assisting their Mum's with feeding issues and fulfilling a very demanding job. [redacted] works 12 hour shifts, is always incredibly polite, organised and conscientious. However, since her diagnosis with this disease, it has taken some of the 'spark' out of [redacted]. She is coping admirably with daily medication, new diets, travelling to London on a regular basis for treatment and attending regular appointments at the hospital, all of which are a tremendous commitment for a young woman in her early [redacted]'s. [redacted] has let her colleagues know about her ongoing health issues in a quiet,

	mature, sensible and thoroughly professional manner, yet dealing with the information that this disease could cause major complications including a stroke or heart problems. [redacted] understands and is justifiably concerned that her only option if the funding for the treatment is not approved will be to undergo a liver transplant which could potentially be some years down the line. [redacted] has done nothing wrong to warrant this medical condition which was discovered by accident due to feeling unwell at work one day. I cannot understand why funding is given for ongoing treatment for those who have brought illness and disease upon themselves through smoking or alcohol, yet a young woman's life is only going to be resolved by major transplant surgery. I am asking if you would reconsider your decision regarding the funding of this treatment. Yes, I understand there are very few people (less than 50) in the whole UK who have this disease Yes, I understand that the cost of treatment for each person is expensive, and you deem this cost to be TOO expensive to fund HOWEVER, what cost can you put on a person's life and future health and happiness. [redacted] has her whole life ahead of her. Does a young woman have to suspend having a full, happy, normal life due to a rare, life-threatening, and challenging disease that she has developed? I urge you, and encourage you to think again at your decision, without putting a price on a young life.
31.	I believe all patients diagnosed with a rare illness regardless of cost should have the option of receiving treatment especially if they have paid into the system themselves. Clearly there is some disparity with other countries where treatment is available despite the cost. All patients should have fair access to licensed treatment and not have to 'fit' into one of the categories of discrimination as identified on the NICE web site. Penalising someone with a rare disease on the basis of cost alone is discrimination in itself.
32.	I believe that the decision made for the LALD patients' needs to be reconsidered. It is truly disgusting that there is treatment available and they are being declined. As a NHS staff worker, quality of life is a huge component of patient care, to leave someone without their treatment is unjustified and outrageous. Every life is important and I question if this was your daughter/family member, you would think so rash as to decline these people treatment, which in the long term, could save their life. In today's society, we should not live with the worry of not receiving adequate treatment for illnesses/diseases. Everyone pays their taxes, what for? To be told that they have to live with debilitating disease? As a, normally, proud NHS worker I am completely appalled at the decision and I am writing this in hope and as a plea for you to change your mind.
33.	I have read the arguments not to give my daughter and the other 48 adults diagnosed with Lysosomal acid lipase deficiency treatment but instead wait till they require a transplant but surly that is putting more pressure on an already stretched area of the NHS, and the

	organs these people require are already very sparâ€™s Yes the treatment is expensive but surly in the long term it would be cheaper and put less pressure on a limited NHS service? If other countries are giving their citizens the treatment surely this is enough evidence that it is working. I hope the committee reconsider their decision and give these 49 people the treatment will enable them to lead a healthy and normal life.
34.	I am speaking on behalf of [redacted], a young vibrant woman who has been diagnosed with Lysosomal Acid Lipase Deficiency. She and the other 48 sufferers once again being held to ransom by Pharmaceutical companies who seem to be judge and jury on people's lives. This whole issue is based purely around finance and not what is best for the patient. With only 49 people diagnosed with this condition in the UK we should be allowing them a quality of life. Knowing that life will deteriorate to such an extent that organ transplant is the eventual outcome is surely not a humane way to treat people. I understand that America and Germany offer free treatment. Why are we not doing the same for [redacted] and other sufferers of this terrible condition? They should be allowed fair access to a licenced treatment. Life cannot have a price tag. It is time you stood up to be counted and made the right decision.
35.	As the mother of a little boy [redacted] who has LAL D late onset, & after hearing about this new found treatment & how much of a significant & positive effect the trials have had on patients given Kanuma, the concept of this treatment not being available is absolutely terrifying to me & I beg you to put yourself in the shoes of myself & other parents in the same position. When hearing of [redacted] diagnosis & what that meant for him & us as a family, my whole world was blown apart. I felt absolutely hopeless and devastated. To see [redacted] go from a happy healthy child who had the world at his feet and his whole life ahead of him, who has so many plans for his future and who I truly believe has so much to offer, to this pale, lethargic, weak little boy who suffers from intermittent nausea & is waking me in tears at 2am with diarrhoea & stomach cramps, is heart breaking. I am absolutely petrified to talk about his future with him or with anyone else for that matter, as the uncertainty & not knowing if he will even make it to his 16th/18th birthday, if he'll ever get to pass his driving test, or go to colleague or university or reach any milestone in life that everyone should have the opportunity to experience, leaves me feeling numb inside. If there is just a glimmer of hope to extend his life and give him a better of quality of life then I am willing to do whatever it takes. How can anyone put a price on life? I can only come to you with my own experience of this disease and how it affects us as a family, but this treatment without a doubt is our only real hope and its worth should not measure in numbers. Our children lives have no cost. If you are uncertain whether the effects seen in the clinical trials are sufficient to prevent long-term complications and fully restore life expectancy to that of people without the condition, then if the patients were to lose their battle the funding for that patient would

	cease & not be as large a cost to you anyway, however if it was to extend life expectancy and give a better quality of life to a patient then the funding would not have gone to waste. If we do not at least try with what we know about the disease we are almost condemning children to an early grave and allowing suffering through their short lives? It is unethical to suggest longer term research when clearly we do not have time on our hands, the treatment is already licenced & trials have proven to reduce the effects of the disease which are what cause pain, suffering physically & mentally, and finally premature death. Children are already suffering & who knows what damage is being done whilst waiting for the treatment to become available. As the diagnosis is recent and we have no long term evidence to show the full outcome of LAL D late onset, then how do we know that it will not reach a stage of irreversibility? You have concluded that it is appropriate to model a long-term treatment effect for sebelipase alfa but that the modelled survival benefit is highly uncertain because there is no data to support the assumption that the long-term consequences of LAL D would be completely prevented, but without funding to continue to produce the treatment & availability, how are we ever to show the long term effects? All treatments for all conditions have to start somewhere & with any new found treatment for a recently diagnosed condition it will take time to produce sufficient data & there will always be a risk, there are always no certainties initially. The drug has been licensed and at least 3 specialists from a medical profession have advised me that if available this treatment would certainly be their recommendation for [redacted] late onset LAL D, which speaks volumes... Continued on following comment due to lack of space....
36.	As the mother of a little boy [redacted] who has LAL D late onset, & after hearing about this new found treatment & how much of a significant & positive effect the trials have had on patients given Kanuma, the concept of this treatment not being available is absolutely terrifying to me & I beg you to put yourself in the shoes of myself & other parents in the same position. When hearing of [redacted] diagnosis & what that meant for him & us as a family, my whole world was blown apart. I felt absolutely hopeless and devastated. To see [redacted] go from a happy healthy child who had the world at his feet and his whole life ahead of him, who has so many plans for his future and who I truly believe has so much to offer, to this pale, lethargic, weak little boy who suffers from intermittent nausea & is waking me in tears at 2am with diarrhoea & stomach cramps, is heart breaking. I am absolutely petrified to talk about his future with him or with anyone else for that matter, as the uncertainty & not knowing if he will even make it to his 16th/18th birthday, if he'll ever get to pass his driving test, or go to colleague or university or reach any milestone in life that everyone should have the opportunity to experience, leaves me feeling numb inside. If there is just a glimmer of hope to extend his life and give him a better of quality of life then I am willing to do whatever it takes. How can anyone put a price on life? I can only come to you with my own experience of this disease and how it affects us as a family, but this

	treatment without a doubt is our only real hope and its worth should not be measured in numbers. Our children lives have no cost. If you are uncertain whether the effects seen in the clinical trials are sufficient to prevent long-term complications and fully restore life expectancy to that of people without the condition, then if the patients were to lose their battle the funding for that patient would cease & not be as large a cost to you anyway, however if it was to extend life expectancy and give a better quality of life to a patient then the funding would not have gone to waste. If we do not at least try with what we know about the disease we are almost condemning children to an early grave and allowing suffering through their short lives. It is unethical to suggest longer term research when clearly we do not have time on our hands, the treatment is already licenced & trials have proven to reduce the effects of the disease which are what cause pain, suffering physically & mentally, and finally premature death. Children are already suffering & who knows what damage is being done whilst waiting for the treatment to become available. As the diagnosis is recent and we have no long term evidence to show the full outcome of LAL D late onset, then how do we know that it will not reach a stage of irreversibility? You have concluded that it is appropriate to model a long-term treatment effect for Sebelipase alfa but that the modelled survival benefit is highly uncertain because there is no data to support the assumption that the long-term consequences of LAL D would be completely prevented, but without funding to continue to produce the treatment & availability, how are we ever to show the long term effects? All treatments for all conditions have to start somewhere & with any new found treatment for a recently diagnosed condition it will take time to produce sufficient data & there will always be a risk, there are always no certainties initially. The drug has been licensed and at least 3 specialists from a medical profession have advised me that if available this treatment would certainly be their recommendation for [redacted] late onset LAL D, which speaks volumes.
37.	I find it difficult to comprehend that there are treatments and help offered to people who have self-inflicted illnesses or injuries & people who have no value for their own lives or others, yet there is a question over whether to fund a treatment for a life threatening condition that a child is born with and has no control over or choice in inheriting. For LAL D to go untreated it would almost certainly result in a liver transplant which would cost the NHS up to Â£50,000 per patient. The cost of sending out the retrieval team costs several thousand extra, depending on where they have to go & it is expected that you have only a 50% chance of surviving for at least five years after the transplant, not to mention all the after care costs. That's a 50% chance of nearly Â£60,000.00 plus going to waste. Statins costing Â£152.52 per year per patient to reduce the cholesterol levels, nearly Â£3000 over 15 years at best, which has no proof of improving the underlying condition, only a symptom of and so will certainly be a wasted effort to prolong mortality. That only covers the effects on the liver and cholesterol. There are numerous organs which are affected, the spleen, the intestines, cardiovascular complications, care & treatment for fatigue, dietary requirements & advice, medication to ease vomiting & Diarrhoea... What about all these costs? More transplants, treatments, surgeries and after care, all extra

	thousands of pounds we are spending on treatments with a substantially high risk an absolutely no proof whatsoever that it will pro long life or control the condition. Yet we now have a treatment with trials that have shown great improvement to all aspects of the illness, it has shown to reduce the damage caused by the disease & which would have far less distress for the child & parents to have to go through as oppose to transplant & surgeries. Surely the people who have worked hard to produce this treatment and move forward with medical science deserve to know that their efforts have not gone to waste and they have possibly saved multiple lives through this breakthrough medical science, isn't that what medicine and science is all about, moving forward and breaking boundaries? The amount of money that goes to waste on huge risks & what some may view as irrelevant treatments. Methadone for drug users who do not use as an opportunity to get better or save their life but as substitution for drugs they can no longer afford or get access to (Â£15,400,000,000 every year it costs for drugs addiction), cosmetic surgeries such as breast enlargements or rhinoplasty (Up to Â£52.5 million went on breast enlargements and a record Â£10 million was spent on liposuction in 2012-13) as people are not happy with their appearance, treatments for binge drinkers who sustain injuries through aggressive behaviour, drink driving etc. All of this funded on the NHS. Yet, my child & other children with this horrible disease are unable to access a treatment which would save and improve their quality of life; surely you see that this is not the way it should be. My question to the members of the board who are parents is this; How much is your child worth?... Would you think it reasonable if the tables were turned for me to conclude "I'm sorry but I don't think your child's life is worth X amount of money" I beg you to reconsider your decision and look at the bigger picture. [redacted] would give his last penny to help someone out there in need & he has nothing, that's just how he is, please repay him the favour and show him you care as much as he does. Kind regards, [redacted]
38.	I believe that financial support should be given to provide the necessary care that is needed by any young child suffering with this condition. I understand that the financial implications are high, but I fail to understand how a decision may be made to dismiss this petition and rule out support but to fund care for other conditions. If this was my child I would like to think that the country I was born

	and raised in, and work hard to contribute to, would not turn their back on my child who needs this care. Please let your response be favourable for this little boy and many more like him. He deserves this treatment to help his illness, just like anyone else suffering with a condition.
39.	I was diagnosed with LALD last September at [redacted] hospital in [redacted]. Where they informed me that a drug will becoming available. To hear that the drug Kanuma has been declined due to funding and more research needed I believe this is inhumane. I as a patient also work as a nurse on special care baby unit at [redacted] hospital caring for the new born babies. My future plans ahead was converting to a trained nurse and specialising in neonatal transitional care. On hearing the news of the drug being declined I feel my future is being taken away from me. As all I can see ahead of me is ill health without the drug. I have been struggling with the bowl problems and tiredness with holding down a full time job. I am already taking tablets every day to try and reduce my cholesterol and am also on a low fat diet. As a [redacted] year old not being able to socialise with food and drink is life changing in itself. I am absolutely devastated that this drug is not going to be available for me as I am struggling already. There is nothing more frustrating when you know there's a medication that can let me live a normal healthy life and someone is making the decision that me and 47 others cannot have it. It is a massive disgust to live in the UK and work for the NHS and not be cared for as a patient yourself. If I don't get this treatment, the amount of appointments and tests I have each month, taking tablets, treatment I will need for my symptoms, this will all add up! When I hear about money being spent on obesity , alcoholics, cosmetic surgery , this is very upsetting for me as it wasn't my choice to become ill and there's nothing I can do about it myself. I wish you to please re think your decision and how it will affect me and the 47 other patients!! Thank you for your time. [redacted] [redacted]
40.	My daughter was diagnosed with LALD Sept 2015. As a family we were devastated by this news after researching and discovering that this genetic disease is a multi-system disease which is life limiting. It took us a few months to even digest the news. As parents we had the added devastation that it was genetic and that myself and my husband had passed this to our daughter. But there was hope we were told that treatment was available in America and 2016 would be available in the UK. As a family it's those words we have clung to whilst my daughter has tried to carry on her young life dealing with her symptoms having numerous hospital appts and working full time. Receiving the telephone call to say the treatment has been rejected by NICE I cannot actually put into words how devastating that is to us. My daughter who would lead a healthy life if she received this drug is now destined to have her bright future taken away and is heading for a life of ill health and premature death. I am begging as a parent to all involved in this life changing decision to reconsider. I understand the cost of the drug has played a factor in the decision. How much is my daughter's life worth can you really put a price on her. Thank you for reading my supporting comment.
41.	This drug should be made available for those who need it, where it can improve their quality of life. Funny how our Government can provide weapon of death for wars BUT can't give its citizens drugs for saving lives.
42.	It is vital that if a treatment is available that it be provided to those that need it. Withholding such treatment sentences those with this disease to a bleak future. One little boy I know ([redacted]) desperately needs this treatment to improve his quality of life and increase his lifespan. He's an amazing little boy; he's doing well at school, has lots of friends, loves football, and is loved by all that know him. His parents are desperate to get this treatment for their only son, in hope of him having a normal future. I really hope the treatment is

	approved.
43.	My granddaughter has LALD and finding out her and the other 47 patients have been declined treatment I feel very angry and discussed. It is not only that [redacted] is our granddaughter, myself, my husband, my daughter and granddaughter has put in so many years working for the NHS. Part of me understands the situation the NHS is in, but I plead with you to take this into consideration.
44.	I wish to beg you on behalf of [redacted] [redacted] & his loving family to approve this new treatment. Anyone who knows [redacted] know him as a happy little boy who lives, eats & sleeps football, it's his dream. His parents also have a dream; that is to have a healthy son with a bright future ahead of him. Please give him that chance because all our children deserve a good future & some kids will never have that but here we are with a promising new treatment that SHOULD be available no matter the cost, how much would you say the health of your children or grandchildren would be? Priceless? that's right and that's exactly what [redacted] is, please don't play God, do the right thing & give these kids areal chance at having a future, thank you for your attention.
45.	Every patient should be giving the right to receive treatment if it's available! LALD is a lifelong disease and a patient will have a lifetime of problems which can also be life threatening. We all pay our taxes and what is the point if it's not being used on positive things. The amount and time the company have spent on testing the drug and finding a drug to help these patients then I believe you should take the time to fund this treatment else professionals work is wasted and 48 patients will suffer. I myself know someone diagnosed with LALD and she ([redacted] [redacted], Plymouth Devon) has already been rejected and one of the reasons was because the condition LALD has minimum research and history. What do you expect when there are only 48 confirmed cases in the UK? By giving [redacted] this treatment there will be plenty of research and data to collect which will help more people. This treatment will also allow her to live her life without the stress and worry she's had to put up with being diagnosed with this rare condition. Just take a moment and think if this was your family member would your decision be different.
46.	LALD is a lifelong disease that can have a lifetime of problems ... nobody should be ignored with this disease and everyone as well as the NHS should be doing everything they can to help those individuals who have been diagnosed with this disease. This disease is misunderstood and without treatment can be life threatening! Everyone should have the right to treatment when it is available. A very close friend of mine has been diagnosed with this disease and I find it appalling that the NHS is not going to fund the life changing treatment she needs. She has worked for the NHS for years now and helped and cared for hundreds of patients, yet she cannot receive the help she desperately needs ... I am disgusted!
47.	I feel that all patients who pay National Insurance should have fair access to treatment and transplants should be a last resort especially if a treatment is available
48.	All patients should have fair access to this licensed treatment in order to have a fit and healthy life. Without the treatment in time the patient's health will deteriorate. Each case will have to be taken into consideration individually and because of the expense of the treatment the patient's age should be a factor
49.	LALD is a debilitating and lifelong disease. A sufferer can have a lifetime of problems that without treatment can be life threatening. LALD is not well understood in the public eye but that does not mean that the disease should be ignored. What happened to Human

	Rights? How can some individuals be picked to receive treatment and others are refused funding? ALL humans should have the right to treatment; it is inhumane to leave a person to suffer. I personally know somebody diagnosed with LALD. This has turned her whole life around at the age of 23. No 23 year old should have to watch everything they eat and drink and spend majority of their time feeling ill and constantly worried of what the future holds for them. She has worked for the NHS for several years and for her to be denied lifesaving treatment is insulting. I sincerely hope that this decision is reconsidered.
50.	Can't believe the NHS isn't funding for this treatment; she works for the NHS as well and so does her mother. The funding of the treatment could change her life and help her in so many ways it's so worth it .I hope everyone makes the right decision! Wish [redacted] the best of luck and I hope and pray she gets the treatment she needs x
51.	Evidence suggests Sebelipase Alfa increases life expectancy in patients living with the disease so should be made ready available to patients.
52.	I feel that if someone is in need of treatment it should be available to make their lives better for them. Especially when they have worked and paid their taxes and national insurance contributions.
53.	To whom it may concern, Overview of child: Born [redacted], to parents whom are not related. Poor feeding from day 1; went from breastfeeding to bottle cow and gate to Neocate a very fatty milk. As that is what the health professionals asked us to do. At an outpatients appointment at [redacted] hospital on 8-1-2016 an abdominal examination sparked concern. An enlarged liver and spleen where detected. A transfer to [redacted] children's hospital, a week in there several blood tests daily, bone marrow tested, scans, x-rays all concluded to Wolman's which was diagnosed on 15-1-2016. I a parent of a child with Wolman's believe the NHS should approve the ERT treatment. Mainly because since my baby was diagnosed in January we had no hope as the internet suggested death was to come as my child had hit the 3 month mark when diagnosis was made. This has been the case for many children unfortunately. Luckily we got transferred to [redacted] Children's over the weekend, this meant we reached it on Monday and started treatment that Wednesday. From the time of the transfer and being admitted my child deteriorated a lot he was dehydrated and looked horrific (I will attach pictures for reference if permitted). From having the first enzyme 6 weeks ago to now there is a big difference to my child. He is more energetic, happy, content and sleeps well unlike before as we were advised by previous dieticians to wake him 2 hourly to give feeds as he was not gaining weight.

	I feel that we are so lucky and blessed to be the last person allowed onto the trial. Because if there was no trial and we had to go through the lengthy process of asking the NHS to give him the drug under special circumstances. It would have been too late. I really don't know what to write to make the NHS change their mind. As the next child diagnosed may not be as lucky as mine. Also what will happen to us if the trial finishes and there's no ERT available on the NHS for us and other children. Why would the NHS make a child suffer when there is treatment available? Please help us help our children the next generation. Thank you
54.	To the people at NICE Back ground of child: He was on born [redacted]. Parents are not related in any way. Son has been in and out of hospital every week since birth. From birth he lost a lot of his birth weight around 10%, which took 7 weeks to get back to his birth weight. He was breastfed at start then started formula milk Cow and Gate which made him vomit and have diarrhoea after every feed. Then he was put on Neocate LCP which contains a large quantity of fat. On 08-01-16 he had an outpatients appointment at [redacted] General Hospital in which the Specialist Paediatric Doctor realised he had an enlarged liver and spleen. She then got us transferred to [redacted] Children's Hospital. They started several tests and took loads of bloods daily. They tested his kidneys, liver, bone marrow, lungs and several other things. There was no sign of anything until 18-01-16 when he was diagnosed with Wolman's disease. We got transferred to [redacted] Children's Hospital where he would undergo lifesaving treatment called Enzyme replacement Therapy which is a drug trial and saves many children's lives. We were scared that we will lose our first child. As for the night before his first Enzyme treatment he deteriorated a lot but now 6 weeks later after weekly infusions he looks absolutely wonderful. He's much happier, he plays, talks, giggles, Thanks to all the treatment he is getting. If it was not for the ERT treatment our son would have been dead by now. I cannot thank the company enough for making this drug available to us on trial. It has changed our sons and our lives. It would be much better if the drug would be prescribed in UK as it will save thousands of lives. There are children that are dying before they cannot get this treatment or drug. The one thing I would only ask for would be to get this ERT prescribed in the UK. I am not just speaking for myself but for all the people out in this country please give us the ERT.

	There is a lot of money getting wasted on plastic surgery, breast enlargements and laxatives and many other unnecessary things, which are given out to lazy, self-obsessed and selfish people who are causing you to question the ERT being available on NHS because of high cost. People can live without getting plastic surgery and enlargements done on their bodies but without ERT people would die. Once again I would be grateful if the ERT could be available to everyone in UK. You cannot put a price on your child. ERT WILL SAVE LIVES and is needed in the UK on the NHS. You say in your evaluation that ERT is ok in the short term but Bone Marrow Transplant is more long term as it is cost effective. But where is the evidence to say these young babies and children are strong enough for such evasive surgery; without the risk of losing their life whilst in surgery. When they can have ERT and live a happy fulfilling life. Please just think with all the children in mind and how you can save their lives with your decision.
55.	I think this drug should be on the NHS, every year money is given to help children around the world but why not for this drug, please we need this drug to help my 5 months old nephew and other children who suffer from the same illness. Anyone who has children you wouldn't want their child to go through that and you would do everything in your power to help your child so please please allow the ERT on the NHS.
56.	To whom it may concern, Overview of child: Born [redacted], to parents whom are not related. Poor feeding from day 1; went from breastfeeding to bottle cow and gate to Neocate a very fatty milk. As that is what the health professionals asked us to do. At an outpatients appointment at [redacted] hospital on 8-1-2016 an abdominal examination sparked concern. An enlarged liver and spleen where detected. A transfer to [redacted] children's hospital, a week in there several blood tests daily, bone marrow tested, scans, x-rays all concluded to Wolman's which was diagnosed on 15-1-2016. I a parent of a child with Wolman's believe the NHS should approve the ERT treatment. Mainly because since my baby was diagnosed in January we had no hope as the internet suggested death was to come as my child had hit the 3 month mark when diagnosis was made. This has been the case for many children unfortunately. Luckily we got transferred to [redacted] Children's hospital over the weekend, this meant we reached it on Monday and started treatment that Wednesday. From the time of the transfer and being admitted my child deteriorated a lot he was dehydrated and looked horrific (I will attach pictures for reference if permitted). From having the first enzyme 6 weeks ago to now there is a big difference to my child. He is more energetic, happy, content and sleeps well unlike before as we were advised by previous dieticians to wake him 2 hourly to give feeds as he was not gaining weight. I feel that we are so lucky and blessed to be the last person allowed onto the trial. Because if there was no trial and we had to go

	through the lengthy process of asking the NHS to give him the drug under special circumstances. It would have been too late. I really don't know what to write to make the NHS change their mind. As the next child diagnosed may not be as lucky as mine. Also what will happen to us if the trial finishes and there's no ERT available on the NHS for us and other children. Why would the NHS make a child suffer when there is treatment available? Please help us help our children the next generation. Thank you