

Highly Specialised Technology 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:

1. **Second Evaluation Consultation Document (ECD2)** as issued to consultees and commentators
2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
 - **Alexion Pharma UK**
 - **MPS Society**
 - **Willink unit - Central Manchester University Hospitals NHS Foundation Trust**

Please note we received notification of no comments from the Department of Health

3. **Patient expert comments on the evaluation consultation document** from:
 - **Amjad Akhtar** - Patient Expert, nominated by MPS Society
 - **Stuart Lancaster** - Patient Expert, nominated by MPS Society
4. **Comments on the Evaluation Consultation Document from members of the public**
 - **Individual 1**
5. **Proposed Managed Access Agreement (MAA)** - submitted by Alexion Pharma UK
6. **Evidence Review Group Critique (MAA)** from Kleijnen Systematic Reviews

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**

Second 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 9) 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: Wednesday 25 May 2016

Third evaluation Committee meeting: Wednesday 22 June 2016

Details of membership of the Evaluation Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

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 a potentially life-saving treatment for babies with rapidly progressive LAL deficiency, and there is a compelling clinical need. However, the committee was unable to reach a conclusion on the value for money offered by the company's managed access proposal because no associated estimates of costs and benefits were supplied by the company.
- 1.2 The committee is therefore minded not to recommend sebelipase alfa for treating lysosomal acid lipase deficiency. The committee recommends that NICE requests further clarification from the company, which should include:
- updated budget impact and cost–consequence analyses using the list price to show the impact of the committee's preferred cost–consequence and budget impact modelling assumptions
 - updated budget impact and cost consequence analyses to show the impact of the managed access proposal including the committee's preferred cost–consequence and budget impact modelling assumptions, and any financial arrangements that would reduce the cost to the NHS
 - separate budget impact and cost–consequence analyses for each patient group if the managed access proposal has different criteria for different patient groups.

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. 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 progressive LAL deficiency, 1 mg/kg sebelipase alfa is administered by intravenous infusion once weekly. The dosage 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, 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 although the clinical impact of these is not yet known. 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 company estimated the annual cost of treatment for an 11-year-old child to be £491,992 (excluding VAT).

4 Evidence submissions

The evaluation committee (section 8) considered evidence submitted by Alexion Pharma UK, a review of this submission by the evidence review group (ERG; section 9) and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

- 4.1 Rapidly progressive 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 progressive 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 the 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. 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 time. After transplant, people need to have drug 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 receiving 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 as 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 sex-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. The difference between the groups was statistically significant ($p=0.0271$). 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 triglycerides, 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 treatment in babies (reflecting the combined populations of LAL-CL03 and the natural history comparator cohort) and in 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 an 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 alfa 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 alfa 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 less than 1 year could die while in the 'LAL deficiency without CC, DCC or HCC' state. All patients aged less than 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 suggested that it may make sebelipase alfa available in 5 mg vials. In its modelling the company assumed that 5 mg vials would cost the same per mg as 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 after loss of data exclusivity when generic versions may become 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). When applying a discount rate of 1.5% to health benefits, people in the whole modelled cohort 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 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 as babies, 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 (the 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 (the 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 age 1 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, including between 5 and 8 newly diagnosed patients. The company estimated 1 new patient in the 0–1 year age group per year.

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 over 1 year presenting with symptoms, 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 uraemic 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.

- **Adherence 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 adhere to treatment.
- **Drug dose.** The average weekly dose of sebelipase alfa for LAL deficiency presenting in infancy was 2.3 mg/kg in the first year of life (reflecting dose escalation from 1 mg/kg every week to 3 mg/kg every week) and 3 mg/kg every week in subsequent years. 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 5 mg vials (rather than 20 mg vials) 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 20 mg vials were available rather than 5 mg vials. 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 using a 1.5% discount because NICE's [guide to the methods of technology appraisal](#) (2013) 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 20 mg vials.

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 was 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 for total 5-year net budget impact. 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 adherence rates to 100%. This resulted in a 5-year net budget impact of £178,527,667.

Responses to first consultation

4.32 The MPS Society (a group representing patients with LAL deficiency) stated that it considered the ERG's estimates of patient numbers in the budget impact modelling to be too high. It stated that in England there are:

- 7 babies born in the last 5 years with the rapidly progressive form of LAL deficiency
- 2 paediatric patients
- 16 adult patients (10 of whom were diagnosed when they were children).

The company stated that of 31 patients it knows to have been diagnosed with LAL deficiency in the UK, 11 were receiving sebelipase alfa in an ongoing clinical trial (including 4 people who presented as babies); 1 person was receiving sebelipase alfa through a compassionate use programme and a further 19 people had been diagnosed with LAL deficiency but were not receiving sebelipase alfa. The company expected that all people receiving sebelipase alfa in a clinical trial would continue to do so. Of those 20 patients not in a clinical trial the company estimated that, based on a review of patients in the UK, 11 people would already have fibrosis and be eligible to start treatment. If 22 people received sebelipase alfa, the company estimated a 5-year budget impact of £57 million. If all these people continued and adhered to treatment then the 5-year budget impact would be £67 million. The company also stated that it asked 6 consultants in metabolic medicine and 2 consultants in

paediatric hepatology about its assumptions in the budget impact base case in the company submission. These clinical experts suggested lower rates of future diagnosis and treatment than those in the company base case. Their new estimates resulted in fewer patients who would be treated with sebelipase alfa over the course of 5 years than previously estimated by the company. The company stated that the new estimates of diagnosis and treatment rates are commercial in confidence and cannot be reported here.

Company's managed access proposal

4.33 The company submitted a managed access proposal. This defined patient eligibility, starting and stopping criteria and monitoring requirements, which can be summarised as follows:

- Patient eligibility: confirmed diagnosis of LAL deficiency.
- Starting criteria:
 - all babies presenting under 1 year of age
 - patients presenting aged 1–18 years with dyslipidaemia, elevated liver enzymes or symptoms of malabsorption
 - patients presenting over 18 years with liver fibrosis or cirrhosis.
- Stopping criteria: The company noted that the minimum treatment period for defining response has not been determined and lifelong therapy is likely to be needed.
- Monitoring criteria: Outcomes for patients over 12 months should be recorded every 3 months (for example, liver function tests and lipid profile) or 6 months (such as quality of life, which would be captured by the MPS Society). In people who are starting sebelipase alfa aged over 18 years, a liver biopsy should be done every 4 years.

4.34 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 [committee papers](#).

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 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 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 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 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 is 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 LAL-CL03 is now 4 years 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 progressive disease. But because no robust comparative data were available, the committee was unable to determine the variability in response, the 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 profiles, 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 discussed the potential of sebelipase alfa as a 'bridging therapy' in the treatment pathway for LAL deficiency. The committee noted that a clinical expert's evidence submission raised the possibility of using sebelipase alfa to stabilise LAL deficiency presenting in babies of less than 6 months before offering a haematopoietic stem cell transplant (HSCT). The committee noted that HSCT has the potential to treat conditions in which people have an enzyme deficiency, and avoids the need for lifelong regular infusions, 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. Early death was not prevented, perhaps because the babies were too unwell at diagnosis. 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 who had been stabilised on sebelipase alfa was unknown. The committee proposed a research recommendation to compare the benefits of long-term treatment with sebelipase alfa with shorter-term treatment with sebelipase alfa ('bridging therapy') followed by HSCT with curative intent for people with rapidly progressive LAL deficiency which presented when they were babies. Responses to consultation emphasised the practical difficulties of studying this mode of treatment. The committee heard that patients, carers and clinicians would be unwilling to stop an effective treatment to switch to a treatment which has not been shown to be effective and carries a high risk of morbidity and mortality. This would make recruiting to a trial to assess HSCT after sebelipase alfa difficult,

even if this was the sole route to access the treatment under NICE recommendations. The committee concluded that it was not possible to make a recommendation for research into the use of sebelipase alfa as a bridging therapy before HSCT.

- 5.8 The committee noted that the marketing authorisation for sebelipase alfa states that the dosage 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 dosage of sebelipase alfa for babies presenting with rapidly progressive LAL deficiency should be 3 mg/kg weekly, with escalation to 5 mg/kg if there is inadequate response. The committee heard from a clinical expert that in his experience of treating babies with sebelipase alfa, approximately 50% of patients were on a 3 mg/kg dose and 50% were on a 5 mg/kg dose. The committee heard from the company that it is carrying out a clinical trial of the 5 mg/kg dose, but data from this trial are not yet available. The company stated in its submission to NICE that it only included clinical data from babies treated at the dosage stated in the marketing authorisation. The company also noted that it took into account that babies in LAL-CL03 had their dose escalated to 3 mg/kg over the trial period when estimating costs in its economic analyses. The committee further heard that the clinical experts would also consider, in some instances, dose escalation up to 3 mg/kg in some children whose symptoms presented after 6 months and whose LAL deficiency did not respond to the lower dose. The committee reaffirmed that its recommendations could only apply to the dosage covered by the marketing authorisation for sebelipase alfa unless it was directed by the Department of Health to make recommendations for the technology outside the terms of its marketing authorisation. However, the committee stated that it could consider evidence on the use of sebelipase alfa

outside the terms of its marketing authorisation to inform discussions about its licensed use.

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). The committee noted that the company had estimated an annual cost of treatment of £491,992 for an 11 year old. 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, and would increase with time for those diagnosed in childhood. The committee noted that for the population presenting with rapidly progressive LAL deficiency as babies, the company had estimated the costs based on the dosage used for this population in the clinical trial (that is 3 mg/kg, following a period of dose escalation from 1 mg/kg). The committee recalled that it had heard from the clinical experts that they would be likely to use higher doses in clinical practice (see section 5.7). The committee was aware that if some people needed dose escalation above the licensed dose in clinical practice then the annual cost of treatment would be higher than for people receiving the licensed dose. The committee concluded that the average annual cost of treatment calculated by the company for the population likely to receive sebelipase alfa may underestimate the actual cost in clinical practice.
- 5.10 The committee considered the assumptions in the company's budget impact analysis relating to diagnosis, treatment rates and adherence:
- It noted the company's estimate of the incidence and prevalence of LAL deficiency in children aged under and over 1 year and the company's assumption that not all of these patients would be diagnosed. It was

aware that the clinical experts agreed that not all patients would be diagnosed in clinical practice.

- 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 and that treatment would only be likely to be started in clinical practice in people with liver fibrosis (see section 5.3). It noted that the proportion with liver fibrosis was estimated to be around 80% and was closer to the ERG's preferred assumption of treatment rate than the company's.
- The committee considered 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 rates of diagnosis, uptake and treatment continuation and there was a 3-fold difference between the company's and ERG's estimates. During consultation several consultees stated that the ERG's estimated number of people taking sebelipase alfa over 5 years was too high. The company stated that it had consulted further with clinical experts who considered that the company's original estimates of patients who would be diagnosed and receive sebelipase alfa were also too high. The company did not update its base-case results to include the new advice from the clinical experts. The clinical expert at the second committee meeting stated that experience in recruiting for sebelipase alfa clinical trials suggested that the number of people diagnosed and treated with sebelipase alfa over the next 5 years was likely to be closer to the current number of people diagnosed with LAL deficiency than the number of

people predicted by gene mutation studies. The committee was aware that there are 25 people with LAL deficiency under specialised care in England and the company stated that it knew of 31 patients diagnosed with LAL deficiency in the UK. The committee accepted that in the next 5 years the number of people receiving sebelipase alfa was not expected to increase greatly, but it noted the potential for genetic screening for lysosomal storage disorders to identify a greater number in the future. The committee accepted that the number of patients in England who would be likely to receive sebelipase alfa treatment in the first 5 years of use by the NHS is likely to be lower than the estimate in the ERG's budget impact analysis. However, it remained concerned that the company's budget impact model had not fully captured the costs of sebelipase alfa treatment (see section 5.9). The committee concluded that the 5-year budget impact of sebelipase alfa at its list price was likely to fall between the company's estimate of £54 million and the ERG's estimate of £179 million.

Value for money

- 5.11 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.

5.12 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 has a treatment effect, and 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.

5.13 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 5.12). 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. (2012) in modelling NASH 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.

- 5.14 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 5 mg vials 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 5 mg vials were 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. It 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.

5.15 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. The committee was aware from NICE's [guide to the 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 that although sebelipase alfa did extend life expectancy

for babies presenting with rapidly progressive LAL deficiency, it was unclear whether their life expectancy would be restored to near normal. The committee recognised that some people presenting with LAL deficiency later in life would also have reduced life expectancy because of the complications of LAL deficiency. It was unclear how sebelipase alfa would affect the mean life expectancy for the whole population for whom sebelipase alfa is indicated and whether the modelled long-term benefits of reduced complications and improved survival would be achieved. Therefore the committee did not consider that there was a strong case for using a 1.5% discount rate. It concluded that it was more appropriate for the company to include the standard 3.5% discount rate in its base case.

5.16 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 20 mg vials
- a 3.5% discount rate applied to costs and health benefits.

After the committee meeting, the committee asked the ERG to run the model with these assumptions applied. The committee noted that applying these assumptions in a probabilistic analysis 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 there was little 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.

5.17 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 (the range of estimates presented by the company and ERG were between 0 and 20.5 additional QALYs, and the committee's preferred estimate was up to 6.64 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). The committee also recalled that the incremental costs for eculizumab compared with standard care were considerable; these are commercial in confidence and cannot be reported here. 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 to the NHS for elosulfase alfa is lower than that estimated by NICE because elosulfase alfa has a patient access scheme, which provides it at a

discounted cost. This patient access scheme and the associated incremental costs are commercial in confidence and so cannot be reported here). Elosulfase alfa also has a managed access agreement, which contains additional confidential commercial arrangements that further reduce the cost to NHS England.

After considering the company's model, the committee noted that the incremental costs for sebelipase alfa were higher than those for eculizumab and elosulfase alfa. Furthermore, although the company's estimated incremental QALY gains (20.5) for sebelipase alfa 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 the long-term benefits of sebelipase alfa were uncertain because of the limited data available. It heard from clinical and patient experts that this was common to most highly specialised technologies because of the rarity of the conditions and the difficulties in carrying out clinical trials and analyses in small populations. The committee 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 The committee discussed whether there were any subgroups of people for whom sebelipase alfa could be considered to offer greater value for money to the NHS than the whole population covered by its marketing authorisation. It noted in particular the comments received from the patient experts and from consultation that for some people sebelipase alfa is the only treatment option that would allow them to live beyond 1 year.

The committee noted that the company had presented an analysis in which it assessed the costs and benefits for babies with rapidly progressive LAL deficiency only (see section 4.22). The committee noted that although this group would have greater incremental QALYs than the whole population for whom sebelipase alfa is indicated, the incremental costs were also higher. Also, the balance between the QALYs gained with sebelipase alfa and the additional cost for this group was considerably less favourable. The committee concluded that although sebelipase alfa is a potentially life-saving treatment for babies with rapidly progressive LAL deficiency and there is a compelling clinical need for it to be made available for these patients, it could not consider sebelipase alfa good value for money at its list price in this group because the treatment cost was too high in relation to the benefit gained.

- 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 progressive 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, may remove the need for a liver transplant. 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.

Company's managed access proposal

- 5.21 The committee noted that, alongside its consultation responses, the company had submitted a draft proposal for a managed access agreement, but this had not been finalised with NHS England. The committee also noted that the managed access proposal was incomplete and it could only comment on the company's proposals about who would start and stop treatment with sebelipase alfa (see section 5.22) and the data that the company suggested would be collected as part of its registry to address uncertainties in the long-term clinical effectiveness of sebelipase alfa (see section 5.23). The committee also discussed in general terms what it would expect of a complete managed access agreement for it to be taken into account in its evaluation of sebelipase alfa (see section 5.24).
- 5.22 The committee discussed whether the population who would be eligible to start and stop treatment with sebelipase alfa in the managed access proposal was covered by the marketing authorisation for sebelipase alfa

and agreed that it was. It further considered whether the managed access proposal reflected the population that the committee expected would receive treatment in clinical practice based on its discussions of the clinical effectiveness, value for money and budget impact evidence for sebelipase alfa. The committee considered that the statement in the managed access proposal that all babies under 1 year presenting with LAL deficiency and patients over 18 years presenting with liver fibrosis or cirrhosis would start treatment with sebelipase alfa reflected what it had heard about clinical experts' preferences. The committee noted that the criteria for starting treatment in patients presenting between age 1 and 18 years were based on whether patients had markers of dyslipidaemia; liver enzymes associated with liver damage and malabsorption. The committee considered that it was unclear whether the population who would start treatment according to the terms in the managed access proposal would be larger than that estimated in the company's original submission for the committee's evaluation of sebelipase alfa. The committee noted that the managed access proposal allowed a person who had stopped sebelipase alfa to restart again. It also noted that the clinical effectiveness of restarting treatment had not been presented in the company submission and did not appear to have been considered in the economic modelling. The committee was unable to reach a conclusion on the value of sebelipase alfa in the population specified in the managed access proposal because the company had not provided estimated benefits and costs in this group. The committee concluded that it was unclear how the population who would receive and continue treatment with sebelipase alfa according to the managed access proposal related to the population the committee had considered in its evaluation of sebelipase alfa.

- 5.23 The committee discussed the proposed follow-up and monitoring of patients in the company's managed access proposal. The committee noted that the outcomes to be measured included clinical outcomes, surrogate measures for clinical outcomes and quality of life

measurements. The committee noted that apart from people over 18 years there were no direct measures of liver damage in the outcomes listed. The committee stated that non-invasive measures of liver damage (which do not involve a biopsy) are available and that measuring definite clinical outcomes rather than surrogate markers was appropriate. The committee concluded that although the quality-of-life measures included in the managed access proposal were appropriate, the clinical outcome measures chosen were not the most relevant for capturing the clinical effectiveness of sebelipase alfa in preventing long-term complications of LAL deficiency across the whole population.

5.24 The committee considered the terms that should typically be part of a managed access agreement negotiated between the company and all relevant stakeholders. It identified those missing from the proposal for sebelipase alfa, including:

- Restricting the total amount payable by the NHS for the duration of the managed access agreement when there is significant uncertainty about the size of the eligible population.
- A mechanism to prevent the NHS committing itself to providing the technology in the long term when the short-term benefits are found to be less than those seen in clinical trials.
- Collecting meaningful data to strengthen the critical assumptions used in the economic modelling to support review of the technology by the committee at the end of the managed access agreement.
- Further limiting cost in addition to any patient access scheme to bring the balance between costs and benefits into an acceptable range when considering the other important criteria used in the assessment of highly specialised technologies.

It agreed that the committee's decision-making should be informed by data on the cost to the NHS (that is, budget impact data) and costs and benefits that relates directly and transparently to the patient population in

the proposed agreement. The committee concluded that the managed access proposal for sebelipase alfa did not fulfil these criteria.

Conclusion

5.25 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. 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. It considered that the company's managed access proposal did not robustly define the population with the greatest clinical need (for example, babies presenting before 6 months with rapidly progressive LAL deficiency), and no associated estimates of cost and benefits for people with the greatest clinical need had been supplied by the company. Therefore the committee was unable to reach a conclusion on the value for money offered by the managed access proposal. Moreover, the likely total costs to the NHS were unclear both because of lack of information about the size of any population defined by the managed access proposal and uncertainties in the dosing regimens that would be used 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.

Summary of evaluation committee's key conclusions

Evaluation title: Sebelipase alfa for treating lysosomal acid lipase deficiency		Section
Key conclusion		
<p>The evaluation committee was unable to reach a conclusion on the value for money offered by the managed access proposal because no associated estimates of costs and benefits had been supplied by the company.</p> <p>The committee is therefore minded not to recommend sebelipase alfa for treating lysosomal acid lipase deficiency. The committee recommends that NICE requests further clarification from the company</p>		1.1, 1.2
<p>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. 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.</p> <p>The committee concluded that although sebelipase alfa is a life-saving treatment for babies with rapidly progressive LAL deficiency and there is a compelling clinical need for it to be made available for these patients, it could not consider sebelipase alfa good value for money at its list price in this group because the treatment cost was too high in relation to the benefit gained.</p>		5.25, 5.18
Current practice		
<p>Nature of the condition, including availability of other treatment options</p>	<p>Babies with rapidly progressive LAL deficiency have pain, poor feeding, growth failure and severe hepatic disease, and a very short life expectancy of less than a year. Best supportive care does not prevent early death.</p> <p>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 less severe and whose condition is less rapidly progressive, and that the presence of fibrosis would indicate a need for treatment.</p>	5.1, 5.3
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from the clinical experts that, because sebelipase alfa is 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 reactions 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 those in LAL-1-NH01, 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		

<p>Availability and nature of evidence</p>	<p>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 both LAL deficiency and NASH were associated with liver disease progression, although the rate of liver disease progression may be quicker in LAL deficiency than NASH.</p>	<p>5.11</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis</p>	<p>The committee concluded that the structure of the model was broadly appropriate, but it was unclear whether the modelling captured the variability of liver disease progression in LAL deficiency.</p> <p>The committee concluded that it was appropriate to model a long-term treatment effect for sebelipase alfa but that the modelled survival benefit was highly uncertain because there were no data to support the company’s assumption that the long-term consequences of LAL deficiency would be completely prevented by sebelipase alfa.</p>	<p>5.11, 5.12</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee considered that the utility values used by the company for children and adults with LAL deficiency were not plausible because they were higher than the age-dependent UK population norms for people without a chronic health condition. It concluded that there were issues with estimates of utility values identified by both the company and ERG because they had not been derived from people with LAL deficiency. However, on balance, it expected the true utility values were likely to be closer to the ERG’s because it was unlikely that people with LAL deficiency experienced a better quality of life than age-matched people without a chronic condition.</p>	<p>5.13</p>
<p>Cost to the NHS and PSS</p>	<p>The committee accepted that the number of patients in England who would be likely to receive sebelipase alfa treatment in the first 5 years of use by the NHS is likely to be lower than the estimate in the ERG’s budget impact analysis. However, it remained concerned that the company’s budget impact model had not fully captured the costs of sebelipase alfa treatment. The committee concluded that the 5-year budget impact of sebelipase alfa at its list price was likely to fall between the company’s estimate of £54 million and the ERG’s estimate of £179 million.</p>	<p>5.10</p>

Value for money	<p>The committee noted that the long-term benefits of sebelipase alfa were uncertain. 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.</p> <p>The committee concluded that although sebelipase alfa is a life-saving treatment for babies with rapidly progressive LAL deficiency and there is a compelling clinical need for it to be made available for these patients, it could not consider sebelipase alfa good value for money at its list price in this group because the treatment cost was too high in relation to the benefit gained.</p>	5.17, 5.18
Impact beyond direct health benefits and on the delivery of the specialised service	<p>The committee agreed that there would be cost savings and benefits with sebelipase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.</p>	5.20
Additional factors taken into account		
Access schemes	<p>The committee considered a managed access proposal submitted by the company but noted this had not been finalised with NHS England.</p> <p>It agreed that the committee's decision-making should be informed by data on the cost to the NHS (that is, budget impact data) and costs and benefits that relates directly and transparently to the patient population in the proposed agreement. The committee concluded that the managed access proposal for sebelipase alfa did not fulfil these criteria.</p>	5.21–5.24

<p>Equalities considerations and social value judgements</p>	<p>During consultation on the draft scope, a consultee asked whether a definition of early and late-onset 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 was 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. However, the committee did not consider sebelipase alfa at its list price to be good value for money and did not recommend sebelipase alfa within its marketing authorisation.</p>	<p>5.18</p>
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6 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.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology will be considered for review 3 years after publication of the guidance. 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

April 2016

8 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee 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

9 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. Company:

- 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 providing oral and written evidence to the committee.

- 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 providing oral and written evidence to the committee.

- 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



May 25, 2016

Meindert Boysen, PharmD, MSc
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence (NICE)
10 Spring Gardens
London, England
SW1A 2BU

**Re: Alexion response to second Evaluation Consultation Document (ECD) for
sebelipase alfa for treating lysosomal acid lipase deficiency**

Dear Dr. Boysen:

Alexion continues to be disappointed that in its second Evaluation Consultation Document (ECD) from April 2016, the National Institute for Health and Clinical Excellence (NICE) Evaluation Committee (the Committee) has not recommended commissioning of sebelipase alfa (Kanuma[®]) for patients in England suffering from lysosomal acid lipase (LAL) Deficiency. However, Alexion agrees with the revised recommendation that a clinical trial with sebelipase alfa as bridging therapy before haematopoietic stem cell transplant (HSCT) is not feasible, and appreciates that the Committee considered and accepted the feedback received from the clinicians, patients, and from Alexion on this proposal.

In addition, Alexion appreciates the opportunity to submit a revised consensus Managed Access Agreement (MAA) for consideration by the Committee. Since the last public meeting in March 2016 for sebelipase alfa, Alexion has worked closely with clinical experts, the relevant patient organisation, and a representative from NHS England (NHSE) to better define the patient population most likely to benefit from treatment with sebelipase alfa as part of a MAA. As a result of these discussions, and in response to NICE's second ECD, we propose a revised consensus MAA that very specifically and narrowly defines treatment start criteria for patients with LAL Deficiency appropriate to each age group (0-1 years, 1-18 years and over 18 years), monitoring criteria and periodicity for monitoring, as well as treatment discontinuation criteria. Importantly, the revised consensus MAA reflects the full input and endorsement of all stakeholders who have contributed to its development, and is intended to ensure access to sebelipase alfa for those patients with LAL Deficiency most in need of treatment, thereby limiting overall costs to the system and enhancing its value for money.

In addition to proposing a revised consensus MAA, we have initiated discussions with NHSE directly regarding proposed commercial terms should the Committee recommend sebelipase alfa for national commissioning. Procedural delays in the progress of our proposed Patient Access Scheme (PAS) have occurred, as well as functional limitations raised by the Department of Health and NICE's Patient Access Scheme Liaison Unit



(PASLU) regarding its capacity to appropriately assess a “complex” PAS for an HST. To ensure that these procedural delays do not negatively impact the Committee’s evaluation of sebelipase alfa, we kindly request the Committee consider our proposed PAS when assessing the revised budget impact and other cost aspects of our overall proposal. Since our discussions about cost containment and risk-sharing proposals are ongoing with NHSE simultaneously, we believe it is appropriate and prudent for the Committee to evaluate our new proposal with these considerable concessions in mind.

Included in our response below, we provide the following documents:

- A revised consensus MAA for use of sebelipase alfa in patients with LAL Deficiency (Attachment A). As noted, the MAA has been discussed in detail with, and approved by, multiple stakeholders including the treating specialists for patients with LAL Deficiency in England, as well as the associated patient group, the MPS Society, and a representative from NHSE.
- An updated budget impact model and cost-consequence model that estimate the impact of the revised consensus MAA (Attachments D and E, respectively);
- The HST patient access scheme (PAS) evidence submission template (Attachment F) and associated appendices; and
- Additional justification why funding sebelipase alfa for LAL Deficiency in England is good value for money and appropriate to help patients most in need.

Since the majority of content from the second ECD for sebelipase alfa is taken directly from the first ECD, our responses below are focused on the sections in the second ECD that are different, most notably the revised consensus MAA and the impact the MAA has on the overall cost to the NHS. The remainder of our responses to the other sections in both ECDs are unchanged, and have been provided in Appendix H as reference.

As always, Alexion remains committed to working with NICE to ensure that patients with LAL Deficiency in England who can benefit most from sebelipase alfa, according to robust clinical criteria defined in the revised consensus MAA, have access to it. As requested, we have marked relevant information in our response Commercial in Confidence (CIC), as appropriate, and ask that every effort be made to ensure this information remains confidential.

Sincerely,

Heidi L. Wagner, J.D.
Senior Vice President
Global Government Affairs



Cc: Carole Longson
Sheela Upadhyaya
Linda Landells
Mary Hughes
Jenna Dilkes
Leanne Wakefield

Attachments:

- Attachment A: Revised Proposed Managed Access Agreement and associated appendices
- Attachment B: Schematic for Proposed Managed Access Agreement
- Attachment C: Stakeholders Consulted in Development of MAA
- Attachment D: Revised Budget Impact Model
- Attachment E: Revised Cost-Consequence Model
- Attachment F: HST PAS Evidence Submission Template and associated appendices
- Attachment G: Checklist of Confidential Information (Appendix H)
- Attachment H: Alexion Responses to First ECD



Alexion’s Response to the Second ECD on Use of Sebelipase Alfa for Treating Lysosomal Acid Lipase Deficiency

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I. Introduction

In the pages that follow, we provide responses to the new sections, or those sections with updated text, in the second Evaluation Consultation Document (ECD) for sebelipase alfa (Kanuma[®]):

- Has all of the relevant evidence been taken into account?

Alexion Response: No; we do not believe that all of the available evidence has been taken into account, including statements provided by the clinical experts and patient groups. Although we acknowledge and appreciate the Committee's removal of the recommendation to study sebelipase alfa as a bridging therapy before haematopoietic stem cell transplant (HSCT), the Committee has not otherwise moved substantively from its statements and recommendations in its first ECD. Alexion provided significant clinical explanation and justification for the treatment of all patients with LAL Deficiency based on the evidence submitted, reviewed, and approved by the European Medicines Agency (EMA). In this response to this consultation, we have further refined the patient population recommended for treatment through a revised consensus Managed Access Agreement (MAA) to better define those most in need of sebelipase alfa treatment (through Start criteria) and the management of their treatment within NHS England (through monitoring and Stop criteria). Details are provided throughout this document.

- Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence?

Alexion Response: No; the clinical summaries are not reasonable interpretations of the clinical data and we provided the justification and rationale to counter the clinical summaries in our response to the first ECD. Alexion also does not agree that the economic considerations are reasonable in the context of a transformative therapy for such a rare and serious disease without other proven safe and effective treatment options. In addition, we have further refined the patient population recommended for treatment with sebelipase alfa through a revised consensus MAA to better reflect those most in need of treatment. As a result, we estimate fewer patients with LAL Deficiency will be treated, thereby reducing the overall annual budget associated with treating these patients. Please see our responses below for more details.

- 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?

Alexion Response: No; the provisional recommendations are not sound and do not provide a suitable basis for use of sebelipase alfa for LAL Deficiency patients of all ages. Rather, the second ECD continues to effectively block access to sebelipase alfa for all patients with LAL Deficiency and does not acknowledge the unmet clinical need that these patients face throughout their lifetime. Although we disagree with the



Committee's view based on current and the best available data in this ultra-rare disease, Alexion has focused its efforts on refining the patient population recommended for treatment through a revised consensus MAA to better reflect those most in need of treatment and to enhance value for money across the treated patient population.

- 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?

Alexion Response: Yes; The Committee's provisional recommendation does not take into account the extremely small number of patients impacted by LAL Deficiency. As a direct result of the extreme rarity of LAL Deficiency, the costs for individual treatment are necessarily higher than for other diseases. Given that the Committee's focus on the costs of treatment seemingly outweighs its focus on clinical value, we believe its recommendation is unjustly biased against patients with this ultra-rare disease.

II. Explanation of Revised Consensus Managed Access Agreement (MAA), Including Proposed Clinical Start, Stop, and Continuation Criteria

Similar to our recent submission for asfotase alfa (Strensiq[®]), we recognise that only one Managed Access Agreement (MAA) has been implemented to date under the HST evaluation process, which was for elosulfase alfa (Vimizim[®]). We have based the revised consensus MAA for sebelipase alfa on the publicly available sections of the elosulfase alfa MAA, and the format we used for asfotase alfa (HST ID758). Please see Attachment A for the revised consensus MAA, and associated appendices, for sebelipase alfa. As noted above, the revised consensus MAA has been fully endorsed by the relevant LAL Deficiency physicians and patient group in England, and represents a consolidated agreement and approach among Alexion, clinical experts, patients, and a representative from NHSE.

Since the majority of our comments to the second ECD are based off the revised consensus MAA, we thought it most useful to first describe the MAA and answer the Committee's questions related to the patient eligibility, starting and stopping criteria, and monitoring requirements, and then discuss the revised budget impact analysis and cost-consequence analysis. Hence, our responses below to sections in the ECD are not in numerical order, but we felt this approach most logical to address the Committees questions.

Response to Company's Managed Access Proposal (Sections 4.33-4.34 and Sections 5.21-5.24)



Section 4.33

“The company submitted a managed access proposal. This defined patient eligibility, starting and stopping criteria and monitoring requirements, which can be summarised as follows:

- Patient eligibility: confirmed diagnosis of LAL deficiency.
- Starting criteria:
 - all babies presenting under 1 year of age
 - patients presenting aged 1–18 years with dyslipidaemia, elevated liver enzymes or symptoms of malabsorption
 - patients presenting over 18 years with liver fibrosis or cirrhosis.
- Stopping criteria: The company noted that the minimum treatment period for defining response has not been determined and lifelong therapy is likely to be needed.
- Monitoring criteria: Outcomes for patients over 12 months should be recorded every 3 months (for example, liver function tests and lipid profile) or 6 months (such as quality of life, which would be captured by the MPS Society). In people who are starting sebelipase alfa aged over 18 years, a liver biopsy should be done every 4 years.”

Alexion Response:

The first draft MAA in response to the initial ECD was produced following discussion between Alexion’s clinical research and medical affairs personnel, with input from the MPS Society (patient organisation), and limited input from a clinical expert advisory panel. Since the last public Committee meeting for sebelipase alfa in March 2016, Alexion has engaged in extensive discussion with clinical experts, the MPS Society, and a representative of NHSE to better define the patient population most likely to benefit from treatment with sebelipase alfa. As such, the revised MAA proposed (Attachment A) reflects input and consensus among these key stakeholders.

Specifically, Alexion consulted with a cross-functional group of experts including adult specialists in inherited metabolic diseases and experts in paediatric metabolic diseases, as well as paediatric hepatologists. Input has also been sought from adult hepatologists through the work of one of the metabolic experts. The adult experts have been able to reflect not only the natural history of disease in patients presenting with clinical symptoms in adulthood, but also the natural history of disease in adults who have been symptomatic since childhood. Data from the MPS Society shows the earliest reported year of diagnosis of a case of LAL Deficiency in England to be 1967. A list of the consultees who contributed to the revised consensus MAA is included in Attachment C.

The revised consensus MAA defines start criteria for different age groups, monitoring criteria and periodicity for monitoring, as well as discontinuation criteria. Please see our responses to Sections 5.21-5.24 in the second ECD below for more details of the development of the clinical criteria in the MAA.



Section 4.34

No comments.

Section 5.21

“The committee noted that, alongside its consultation responses, the company had submitted a draft proposal for a managed access agreement, but this had not been finalised with NHS England. The committee also noted that the managed access proposal was incomplete and it could only comment on the company’s proposals about who would start and stop treatment with sebelipase alfa (see section 5.22) and the data that the company suggested would be collected as part of its registry to address uncertainties in the long-term clinical effectiveness of sebelipase alfa (see section 5.23). The committee also discussed in general terms what it would expect of a complete managed access agreement for it to be taken into account in its evaluation of sebelipase alfa (see section 5.24).”

Alexion Response:

Since the last NICE public meeting in March 2016 for sebelipase alfa, Alexion has worked closely with clinical experts, the MPS Society, and a representative from NHSE to better define the patient population most likely to benefit from treatment with sebelipase alfa as part of a revised MAA. The resulting revised consensus MAA very specifically and narrowly defines treatment start criteria for patients with LAL Deficiency who are appropriate in each age group (0-1 years, 1-18 years and over 18 years), monitoring criteria and periodicity for monitoring, as well as treatment discontinuation criteria. The revised MAA reflects the full input and support of all relevant stakeholders listed in Attachment C.

In addition to proposing a revised consensus MAA, we have initiated discussions with NHSE directly regarding proposed commercial terms should the Committee recommend sebelipase alfa for national commissioning. Procedural delays in the progress of our proposed Patient Access Scheme (PAS) have occurred, as well as functional limitations raised by the Department of Health and NICE’s Patient Access Scheme Liaison Unit (PASLU) regarding its capacity to appropriately assess a “complex” PAS for an HST. In order for these procedural delays not to negatively impact the Committee’s evaluation of sebelipase alfa, we kindly request the Committee to take our proposed PAS and annual patient expenditure into consideration when assessing the revised budget impact and other cost aspects of our submission. Since our discussions about cost containment and risk-sharing proposals are ongoing with NHSE simultaneously, we consider it most prudent for the Committee to evaluate our new proposal with these concessions in mind.

Section 5.22

“The committee discussed whether the population who would be eligible to start and stop treatment with sebelipase alfa in the managed access proposal was covered by the



marketing authorisation for sebelipase alfa and agreed that it was. It further considered whether the managed access proposal reflected the population that the committee expected would receive treatment in clinical practice based on its discussions of the clinical effectiveness, value for money and budget impact evidence for sebelipase alfa. The committee considered that the statement in the managed access proposal that all babies under 1 year presenting with LAL deficiency and patients over 18 years presenting with liver fibrosis or cirrhosis would start treatment with sebelipase alfa reflected what it had heard about clinical experts' preferences. The committee noted that the criteria for starting treatment in patients presenting between age 1 and 18 years were based on whether patients had markers of dyslipidaemia; liver enzymes associated with liver damage and malabsorption. The committee considered that it was unclear whether the population who would start treatment according to the terms in the managed access proposal would be larger than that estimated in the company's original submission for the committee's evaluation of sebelipase alfa. The committee noted that the managed access proposal allowed a person who had stopped sebelipase alfa to restart again. It also noted that the clinical effectiveness of restarting treatment had not been presented in the company submission and did not appear to have been considered in the economic modelling. The committee was unable to reach a conclusion on the value of sebelipase alfa in the population specified in the managed access proposal because the company had not provided estimated benefits and costs in this group. The committee concluded that it was unclear how the population who would receive and continue treatment with sebelipase alfa according to the managed access proposal related to the population the committee had considered in its evaluation of sebelipase alfa."

Alexion Response:

Alexion is pleased that NICE has recognised the strong support amongst clinicians for the treatment of infants, and also of adults with liver fibrosis or cirrhosis. Following the Committee meeting and publication of the second ECD, Alexion has consulted with clinical experts, the MPS Society, and a representative of NHSE to better define the patient population eligible for treatment under a revised MAA.

There was agreement amongst all consultees outlined in Attachment C that the criteria for treating infants should be unchanged from the draft MAA submitted earlier this year and discussed at the last public Committee meeting. These infants present as a medical emergency and initiation of sebelipase alfa is potentially life-saving. Additional discussions with stakeholders have focused on the age 1-18 years patient group, as this population represents a significant unmet medical need, and we understand that the Committee was concerned that the initial criteria for these patients were not sufficiently precise.

The majority of patients with LAL Deficiency present with symptoms during childhood: published literature suggests that 83% of patients present by 12 years of age, with a median age of onset of 5 years.(1) Analysis of data provided to NICE by the MPS



Society for 22 patients diagnosed between 1967 and 2016 who are currently being managed in metabolic centres in England shows the following profile for the age at diagnosis:

Age at diagnosis of patients in metabolic expert centres in England (n=22)

Age 0-1 yrs	Age 1-12 yrs	Age 13-18 yrs	Age over 18 yrs
■	■	■	■

Source: MPS Society.

Progression to liver failure may be rapid in patients with LAL Deficiency. However, children with LAL Deficiency may also present with malabsorption and failure to thrive due to the deposition of lipids in the gastrointestinal tract. The mechanism responsible for causing the malabsorption is the same mechanism that causes failure to thrive in infants who present with rapidly-progressive LAL Deficiency. The mechanism in older children and adults may have a less acute presentation though is nonetheless associated with a negative health outcome and long-term negative health consequences such as growth abnormalities, short stature, and bone issues.

The clinical experts consulted for the revised MAA described malabsorption and failure to thrive as the most common presentation in children with LAL Deficiency. Such children may also already have evidence of liver damage at presentation, and will usually progress to liver damage in the absence of a disease-modifying treatment. Whatever the clinical presentation at diagnosis, the goal in treating children with LAL Deficiency is to prevent them from progressing to liver damage and avoidance of the long-term consequences of uncontrolled lipid accumulation in the liver and other organs as a result of LAL Deficiency. There was consensus among the clinical experts that the life-time risk of liver damage is greater in children presenting with clinical disease than in adults presenting, and that there is a greater heterogeneity in paediatric presentation, resulting in the need for criteria for starting therapy in children that are broader than the criteria for adults. In short, sebelipase alfa therapy should be initiated at a lower threshold of evidence for end-organ disease in children than in adults.

The revised consensus MAA start criteria for children aged 1-18 years are patients who present with one or more of the following:

- Signs and symptoms of malabsorption (>6-month history of diarrhoea or failure to thrive: growth retardation and short stature) (please see the complete MAA in Attachment A for detailed definitions);
- Hepatomegaly with persistently (>3-months) elevated transaminases (ALT 1.5 x ULN for LSD centre reference ranges);
- Signs of liver fibrosis (Ishak score ≥ 1); and/or
- Signs of liver dysfunction – portal hypertension or jaundice or low albumin or prolonged prothrombin time (PT).



The clinical experts were divided on the role of liver transplant in managing patients with LAL Deficiency. In terms of childhood disease, it was felt that liver transplant should not be a barrier to receiving sebelipase alfa as children are more likely to present with gastrointestinal (GI) disease as well as liver disease and there is insufficient data to conclude whether a liver transplant would reverse disease in other organs, particularly the gut.

For patients aged over 18 years, the start criteria require that these patients have evidence of liver fibrosis of Ishak score 3 or above. Unless clinically contraindicated, these adults should have a baseline liver biopsy performed. An Ishak score of 3 or more demonstrates a significant degree of liver damage, with bridging fibrosis visible on biopsy. In patients over 18 years of age, the ongoing accumulation of cholesteryl esters (CEs) and triglycerides (TGs) leading to fibrosis can progress to cirrhosis and ultimately to liver failure and death. As such, treatment in these patients is warranted.

The stakeholder discussions also explored response criteria for those starting treatment. It was agreed that given the potential for presentation in children at different stages of disease, the expectation that for a progressive, genetic disease life-long treatment may be required in all age groups, and given the limited long-term outcomes data available at this time, it was most appropriate to define criteria describing non-responders. Non-response criteria are described for all age groups, including infants. As a result of this change, criteria for restarting treatment are not included in the revised consensus MAA.

Section 5.23

“The committee discussed the proposed follow-up and monitoring of patients in the company’s managed access proposal. The committee noted that the outcomes to be measured included clinical outcomes, surrogate measures for clinical outcomes and quality of life measurements. The committee noted that apart from people over 18 years there were no direct measures of liver damage in the outcomes listed. The committee stated that non-invasive measures of liver damage (which do not involve a biopsy) are available and that measuring definite clinical outcomes rather than surrogate markers was appropriate. The committee concluded that although the quality-of-life measures included in the managed access proposal were appropriate, the clinical outcome measures chosen were not the most relevant for capturing the clinical effectiveness of sebelipase alfa in preventing long-term complications of LAL deficiency across the whole population.”

Alexion Response:

The revised consensus MAA describes a robust regime of regular monitoring in an expert centre and mandated clinical assessments at specified time points to enable assessment of response to treatment. The MAA requires the collection of assessment data in a Registry to enable regular reporting of intermediate outcomes.



Patients with LAL Deficiency may need to be managed under a shared-care approach between metabolic specialists and hepatologists or gastroenterologists, reflecting the symptomatology of each patient. Under the terms of the MAA, which is for a five-year period, treatment with sebelipase alfa may only be initiated under the care of the lysosomal storage disorders (LSD) centres with expertise in using enzyme replacement therapies. Expert input will be required from hepatologists in order to meet the monitoring criteria, particularly the requirement for liver biopsy and Fibroscan[®] in adults. Patients would be required to attend clinic appointments every 6 months at an LSD centre.

Regarding direct measures of liver damage, whilst liver biopsy might be considered the “gold standard” for diagnosing the extent of liver disease, this is challenging in children as it requires a general anaesthetic. The stakeholders who contributed to the revised MAA felt that it was not ethical to mandate a liver biopsy in all children prior to initiating treatment, or as a monitoring tool. There are some clinical presentations where biopsy might be necessary, but, in general, liver biopsy at baseline should not be required in children. In adults, however, liver biopsy at baseline would be required, if clinically feasible.

For all patients, measurement of liver function, both in terms of transaminases and synthetic function, have been incorporated, as well as radiological assessments. These include MRI scanning in adults, and ultrasound scanning in children because, as with liver biopsy, general anaesthetic is usually required for children having MRI scans. It was felt that ultrasound is an effective way of monitoring change in organ size in children, and also allows for Doppler measurement of portal flow to be conducted at the same time.

Moreover, change in liver volume may not correlate with changes in clinical status. The liver may change in volume in response to diet and weight loss, as well as change in size according to fasting status. In addition, as liver disease progresses, liver volume may decrease with change from fibrosis to cirrhosis, and so a smaller liver volume may not be reflective of a beneficial change in liver condition. In contrast, increasing spleen volume is always considered pathological. In the context of liver disease, increasing spleen volume would be reflective of negative change in liver disease, and therefore a greater than 10% increase in spleen volume would be considered reflective of disease progression.

There was extensive discussion with the clinicians on the role of other non-invasive measures of liver function, particularly the role of Fibroscan[®] in assessing response to therapy, and in assessing potential for disease progression. Fibroscan[®] is a relatively new technique and has not been validated in LAL Deficiency. The adult clinicians felt Fibroscan[®] could be a useful adjunct to monitoring response to therapy in the patient population over 18 years of age, but additional research should be carried out to



validate it as a tool in this condition. The recommendation was that in adults, a liver biopsy should be conducted at baseline, with a paired Fibroscan[®]. These should be repeated at the end of the first year of sebelipase alfa therapy to assess responsiveness. Once responsiveness is determined, follow up with non-invasive tests would be appropriate, with further biopsies performed only if clinically indicated (for example, if subsequent Fibroscan[®] suggests increase in degree of fibrosis). Lack of response should not be determined in an adult in the absence of a repeat liver biopsy. There were also concerns raised by the paediatricians on the role of Fibroscan[®] in determining whether to stop treatment with sebelipase alfa in children. Further research and validation of this modality in children with LAL Deficiency is required.

Section 5.24

“The committee considered the terms that should typically be part of a managed access agreement negotiated between the company and all relevant stakeholders. It identified those missing from the proposal for sebelipase alfa, including:

- Restricting the total amount payable by the NHS for the duration of the managed access agreement when there is significant uncertainty about the size of the eligible population.
- A mechanism to prevent the NHS committing itself to providing the technology in the long term when the short-term benefits are found to be less than those seen in clinical trials.
- Collecting meaningful data to strengthen the critical assumptions used in the economic modelling to support review of the technology by the committee at the end of the managed access agreement.
- Further limiting cost in addition to any patient access scheme to bring the balance between costs and benefits into an acceptable range when considering the other important criteria used in the assessment of highly specialised technologies.

It agreed that the committee’s decision-making should be informed by data on the cost to the NHS (that is, budget impact data) and costs and benefits that relates directly and transparently to the patient population in the proposed agreement. The committee concluded that the managed access proposal for sebelipase alfa did not fulfil these criteria.”

Alexion Response:

By the use of specific and age-appropriate start criteria, the revised MAA creates a framework for treatment that provides access to those patients considered most at risk from disease and most likely to benefit from treatment with sebelipase alfa. This is predicated on the presence of significant liver disease in adults, and on liver disease or malabsorption in children. The very small number of infants diagnosed annually with LAL Deficiency should all go on to treatment as soon as possible after diagnosis. These start criteria are the result of thoughtful discourse and consensus, and should therefore



reduce the degree of uncertainty about the size of the eligible population and restrict the amount payable by the NHS.

For all infants presenting under the age of 1 year, treatment should continue at least for the duration of the MAA (5 years). To determine lack of response in patients greater than 1 year old, following a minimum 1 year of treatment with a stable dose of sebelipase alfa, the LSD Expert Advisory Group, an established committee of clinical experts representing each of the LSD centres, will assess the patient's medical condition according to defined stop criteria.

Outcomes data for all patients treated under the MAA will be collected in the Global LAL-D Registry. An annual review of the data will be performed in consultation between clinical experts, NICE, NHSE, the patient organisation (The MPS Society), and Alexion. A formal review of the treatment criteria will be conducted at 3 years to enable reconsideration and an exit clause has been proposed if, at the end of the 5 year MAA, the outcomes data do not support long-term treatment of patients with LAL Deficiency.

III. Alexion Comments on Committee's Preliminary Recommendations in Second ECD

Below we provide responses to the Committee's updated recommendations (Sections 1.1 and 1.2) in the second ECD for sebelipase alfa.

Section 1.1

"Sebelipase alfa is a potentially life-saving treatment for babies with rapidly progressive LAL deficiency, and there is a compelling clinical need. However, the committee was unable to reach a conclusion on the value for money offered by the company's managed access proposal because no associated estimates of costs and benefits were supplied by the company."

Alexion Response:

Alexion is pleased that the Committee recognises that sebelipase alfa is life-saving in infants with LAL Deficiency. Given the urgency to treat infants with LAL Deficiency due to the lethal nature of disease at presentation, and the fact that very few infants will be born with LAL Deficiency in England annually, the decision to recommend treatment should not be based solely on cost. Alexion provided evidence regarding the clinical, life-saving benefit of sebelipase alfa treatment in infants with LAL Deficiency. As such, it is difficult to understand what further evidence of value is required in or ethically justifiable in light of regulatory approval by the European Commission (EC) in order to support a decision to fund treatment.

Given the small number of infants expected to have rapidly progressing LAL Deficiency, the estimated overall cost of treating these infants is relatively low and the value for



money relatively high due to the expected survival benefit. This is more fully explained in our revised budget impact and cost consequence models below.

Sebelipase alfa received marketing authorisation from the EC on August 31, 2015, recommending treatment for patients of all ages with LAL Deficiency. As such, the premier regulatory authority in Europe has already made a clear and affirmative judgment based on the evidence produced regarding the risk/benefit for patients of all ages with LAL Deficiency, not just for infants. Alexion also has now submitted a more comprehensive MAA, which has been developed in consultation with leaders from the clinical community, the MPS Society, and a representative of NHSE; the revised consensus MAA has the support and endorsement of the stakeholders described in Attachment C.

Through the development of specific clinical criteria in the MAA, Alexion has been able to establish a more accurate estimate of the overall number of patients in England, of all ages, who should be treated with sebelipase alfa. We have produced a revised budget impact model, as well as revised cost consequence analysis, to illustrate the value for money to the NHS of treating these patients. In addition to clear clinical criteria, Alexion has also committed under the MAA to collect long-term outcomes data through a global LAL-D disease registry. In addition, continued analyses of outcomes from on-going clinical trials will provide further data to clarify the long-term outcomes across the patient population.

Section 1.2

“The committee is therefore minded not to recommend sebelipase alfa for treating lysosomal acid lipase deficiency. The committee recommends that NICE requests further clarification from the company, which should include:

- updated budget impact and cost–consequence analyses using the list price to show the impact of the committee’s preferred cost–consequence and budget impact modelling assumptions
- updated budget impact and cost consequence analyses to show the impact of the managed access proposal including the committee’s preferred cost–consequence and budget impact modelling assumptions, and any financial arrangements that would reduce the cost to the NHS
- separate budget impact and cost–consequence analyses for each patient group if the managed access proposal has different criteria for different patient groups.”

Alexion Response:

The clinical Start criteria developed in the revised consensus MAA define the patients most likely to benefit from treatment with sebelipase alfa. These clinical criteria have formed the basis for the revised budget impact model and cost consequence analyses. Considering that the provisions of the MAA will determine patient access to treatment, the relevant patient population in which the value for money and budget impact should be assessed is the patient population meeting the MAA eligibility criteria, rather than the



broader population that was addressed in Alexion's previous submissions. As such, presented below are budget impact and cost-consequence analyses focused on improving the certainty of both financial expenditure required of, and value for money offered to, the NHS/PSS, by targeting the specific patient population who would be eligible for treatment as defined under the MAA. All stakeholders who have contributed to the development of the MAA agree that the MAA-eligible patient population represents those with the highest need for treatment; as such, the economic analyses should be considered for the entire MAA-eligible patient population, rather than distinguished by the three sub-groups of eligibility criteria that the MAA comprises (please see Attachment A: Revised Proposed Managed Access Agreement for more details).

The budget impact and cost-consequence analyses are provided using the cost of sebelipase alfa both at the publicly-available NHS List Price and also with the application of the proposed PAS, which demonstrates the very significant positive cost savings of the proposed PAS both on the 5-year budget impact and also on lifetime costs of treatment. Alexion also has initiated discussions with NHSE directly regarding proposed commercial terms to achieve cost containment and substantial risk-sharing should the Committee recommend sebelipase alfa for national commissioning.

As context for the economic analyses presented below, which address this MAA-eligible patient population, summaries of previous estimates of net budget impact and value for money are also provided.

IV. Alexion Comments on Provisions in Second ECD Related to Estimated Patient Numbers and Overall Budget Impact

Below we provide comments to the sections in the second ECD for sebelipase alfa that relate to the number of patients expected to be treated and the overall budget impact estimates.

It is important for the Committee to note that the economic modelling in this submission relies on data gathered from centres across England regarding known patients diagnosed with LAL Deficiency. Two sources are used in different ways as follows:

- Limited data for 22 patients in expert metabolic centres in England, who were reported to NICE by the MPS Society in response to the first ECD, have been shared with Alexion in order to be able to quantify the historical rate of diagnosis of new patients with LAL Deficiency and a supposed age distribution across the patient population in England with LAL Deficiency.
- These data, collected in March 2016, have been reviewed alongside the records held by Alexion for patients being treated in England in clinical trials or under compassionate use arrangements. This review suggested that the total number of patients diagnosed in England in May 2016 is likely to be ■ patients overall. It was possible to gather anonymised information about these patients from the



expert clinicians, or from Alexion clinical trials records, including the ages of the children with LAL Deficiency and, importantly, whether the current clinical presentation of each patient would likely meet the proposed MAA criteria for starting treatment with sebelipase alfa.

Thus, subsequent sections of this document may refer to data for either 22 or [REDACTED] known patients in England according to the data available to Alexion for each cohort described above.

Section 4.32

“The MPS Society (a group representing patients with LAL deficiency) stated that it considered the ERG’s estimates of patient numbers in the budget impact modelling to be too high. It stated that in England there are:

- [REDACTED] babies born in the last 5 years with the rapidly progressive form of LAL deficiency
- [REDACTED] paediatric patients
- [REDACTED] adult patients ([REDACTED] of who were diagnosed when they were children).

The company stated that of [REDACTED] patients it knows to have been diagnosed with LAL deficiency in the UK, [REDACTED] were receiving sebelipase alfa in an ongoing clinical trial (including [REDACTED] people who presented as babies); [REDACTED] receiving sebelipase alfa through a compassionate use programme and a further [REDACTED] had been diagnosed with LAL deficiency but were not receiving sebelipase alfa. The company expected that all people receiving sebelipase alfa in a clinical trial would continue to do so. Of those [REDACTED] patients not in a clinical trial the company estimated that, based on a review of patients in the UK, [REDACTED] people would already have fibrosis and be eligible to start treatment. If [REDACTED] people received sebelipase alfa, the company estimated a 5-year budget impact of £57 million. If all these people continued and adhered to treatment then the 5-year budget impact would be £67 million. The company also stated that it asked 6 consultants in metabolic medicine and 2 consultants in paediatric hepatology about its assumptions in the budget impact base case in the company submission. These clinical experts suggested lower rates of future diagnosis and treatment than those in the company base case. Their new estimates resulted in fewer patients who would be treated with sebelipase alfa over the course of 5 years than previously estimated by the company. The company stated that the new estimates of diagnosis and treatment rates are commercial in confidence and cannot be reported here.”

Alexion Response:

Alexion has worked with the clinical community and the MPS Society to refine estimates of incidence and prevalence of patients with LAL Deficiency in England, as well as to project future diagnosis rates based on the history of known patients in England. Clinicians from metabolic, lysosomal storage disorders (LSDs), and liver units with known patients have been surveyed and asked to review those patients according to the clinical criteria defined in the revised consensus MAA. Records for patients who are



already receiving treatment through clinical trial or compassionate use supply have also been reviewed according to the clinical criteria defined in the revised MAA. As such, we have more accurately refined the estimate of eligible patients and this is reflected in the revised budget impact model submitted to NICE. It should be noted and recognised that there is the potential for double-counting as many of these patients are under the care of both a metabolic expert centre and a liver expert centre which may account for the difference between the previously-submitted estimates of the number of diagnosed patients in England with LAL Deficiency by the MPS Society and by Alexion. However, we have taken all reasonable steps, within the confines of patient confidentiality, to avoid duplication in these revised estimates.

Using these combined sources, the overall number of known LAL Deficiency patients being managed in an expert centre in England was found to be ■■■, with ■■■ of these thought to be eligible for treatment under the Start criteria defined in the revised consensus MAA. The summary of data available to Alexion is as follows:

Age	Known LAL Deficiency patients, by age and MAA eligibility			
	Infantile presentation		Paediatric/adult presentation	
	Total Diagnosed	MAA-Eligible	Total Diagnosed	MAA-Eligible
Age: 0-1	■	■		
Age: 1-2	■	■		
Age: 2-3	■	■	■	■
Age: 3-4				
Age: 4-5	■	■		
Age: 5-6				
Age: 6-7				
Age: 7-8				
Age: 8-9			■	
Age: 9-10				
Age: 10-11				
Age: 11-12			■	■
Age: 12-13				
Age: 13-14				
Age: 14-15				
Age: 15-16				
Age: 16-17				
Age: 17-18				
Age: over 18			■	■
Total	■	■	■	■



Furthermore, with assistance from the MPS Society, Alexion has charted the diagnosis dates of the 22 patients (■ paediatric and ■ adults) that were previously identified by the MPS Society survey of metabolic centres and were reported in the previous NICE consultation. These data show that the rate of diagnosis of patients with LAL Deficiency in England has been extremely low and reflects the ultra-rare nature of the disease as stated by Alexion in its submissions. Of note:

- These data do not include the diagnoses of infants prior to the availability of sebelipase alfa as those infants would not have survived without treatment.
- The year with the most diagnoses of patients with LAL Deficiency was 2015, when ■ infant, ■ children, and ■ patients with adult-presentation were diagnosed.

Year of diagnosis of patients with LAL deficiency in England (n=■)



Source: MPS Society

Following data sharing between stakeholders, it is apparent that both the number of current diagnosed patients (■: ■ children and ■ adults) and the likely future number of new cases are significantly lower than the estimates of diagnosed patients in Alexion’s original submission (which ranged from ■ in Year 1 to ■ in Year 5 of the budget impact analysis). As such, it is clear that previously-modelled diagnosis rates, thought to be consistent with an ultra-rare disease that has insidious progression prior to symptoms becoming apparent, should be reduced in line with available real-world data - in particular, lower than both the ERG’s “most plausible” assumption of 20% higher diagnosis rates than Alexion’s original submission (p. 106 of the ERG’s report), and the implied diagnosis rates in the Committee’s Table 1 of the ECD (which reported treated patient counts of 25 in Year 1 to 124 in Year 5). The economic modelling submitted as part of this response to consultation reflects this finding.



Section 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). The committee noted that the company had estimated an annual cost of treatment of £491,992 for an 11 year old. 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, and would increase with time for those diagnosed in childhood. The committee noted that for the population presenting with rapidly progressive LAL deficiency as babies, the company had estimated the costs based on the dosage used for this population in the clinical trial (that is 3 mg/kg, following a period of dose escalation from 1 mg/kg). The committee recalled that it had heard from the clinical experts that they would be likely to use higher doses in clinical practice (see section 5.7). The committee was aware that if some people needed dose escalation above the licensed dose in clinical practice then the annual cost of treatment would be higher than for people receiving the licensed dose. The committee concluded that the average annual cost of treatment calculated by the company for the population likely to receive sebelipase alfa may underestimate the actual cost in clinical practice.”

Alexion Response:

As the Committee notes, given the weight-based dosing of sebelipase alfa, for a given dosing regimen (i.e. 3mg/kg every week for infants less than 6 months of age presenting with rapidly progressing LAL Deficiency, or 1mg/kg every other week for patients presenting as children or adults), treatment costs will be higher for patients commencing treatment in infancy (due to dosing intensity) as well as older/heavier patients (due to heavier weight).

As noted in our response to Section 5.8 below, Alexion can only promote the doses in the marketing authorisation for sebelipase alfa. Alexion is conducting studies in infants in which higher doses are allowed under certain conditions; these trials are ongoing and have not yet been analysed for safety and efficacy.

The variation in possible average annual treatment cost based on dosing regimen or patient weight is the basis for the PAS that Alexion has proposed for sebelipase alfa. Specifically, the proposed annual patient expenditure cap will ensure that average annual treatment costs remain consistent with the clinical benefit and value of sebelipase alfa, and that the potential impact on annual treatment costs of dose escalation for infants or increasing patient age/weight will be mitigated. The value of the cap in terms of expenditure savings increases as patients age and grow. The cost of treating patients with infantile presentation who require the higher dose according to the Summary of Product Characteristics (SmPC) would be capped under the PAS [REDACTED]



██████████, while the cost for patients with paediatric or adult presentation, requiring the lower dose, would be capped at around ██████████ (based on growth charts for the UK from the Royal College of Paediatrics and Healthcare, and the assumptions that (1) LAL Deficiency patients are equally likely to be male as female; (2) patients with infantile presentation grow from the 2nd percentile of weight for age to the 75th percentile over five years; (3) patients with paediatric or adult presentation grow according to the 75th percentile of weight for age; and (4) patients comply with 100% of recommended dosing (a conservative assumption unlikely in long-term clinical practice, but more appropriate in this analysis than previously, given the likelihood of high adherence amongst MAA-eligible patients)). By assuming full financial risk for individual patient costs that exceed the proposed expenditure cap, Alexion is contributing significantly to reduce the annual and lifetime costs of treating patients with LAL Deficiency, thereby ensuring systemic costs to NHSE are contained and also ensuring greater value for money across the more diverse patient population.

Alexion notes the Committee's concerns regarding the potential for additional costs associated with any dose escalation above 3mg/kg in infants treated with sebelipase alfa, based on the testimony of clinical experts. Importantly, it should be noted that because the costs of treating a patient with infantile-onset LAL Deficiency would be capped under the proposed PAS ██████████ at the recommended dosing of 3mg/kg every week, the financial risk posed by potential dose escalation to 5mg/kg every week would be largely mitigated as Alexion would assume the risk for the cost of treatment above the cap level. As such, the PAS would effectively ensure that the overall per patient cost remains consistent with clinical benefit and the value of sebelipase alfa.

Section 5.10

"The Committee considered the assumptions in the company's budget impact analysis relating to diagnosis, treatment rates and adherence:

- 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. It was aware that the clinical experts agreed that not all patients would be diagnosed in clinical practice.
- 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 and that treatment would only be likely to be started in clinical practice in people with liver fibrosis (see section 5.3). It noted that the proportion with liver fibrosis was estimated to be around 80% and was closer to the ERG's preferred assumption of treatment rate than the company's.
- The committee considered 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 rates of diagnosis, uptake and treatment continuation and there was a 3-fold difference between the company's and ERG's estimates. During consultation several consultees stated that the ERG's estimated number of people taking sebelipase alfa over 5 years was too high. The company stated that it had consulted further with clinical experts who considered that the company's original estimates of patients who would be diagnosed and receive sebelipase alfa were also too high. The company did not update its base-case results to include the new advice from the clinical experts. The clinical expert at the second committee meeting stated that experience in recruiting for sebelipase alfa clinical trials suggested that the number of people diagnosed and treated with sebelipase alfa over the next 5 years was likely to be closer to the current number of people diagnosed with LAL deficiency than the number of people predicted by gene mutation studies. The committee was aware that there are 25 people with LAL deficiency under specialised care in England and the company stated that it knew of 31 patients diagnosed with LAL deficiency in the UK. The committee accepted that in the next 5 years the number of people receiving sebelipase alfa was not expected to increase greatly, but it noted the potential for genetic screening for lysosomal storage disorders to identify a greater number in the future. The committee accepted that the number of patients in England who would be likely to receive sebelipase alfa treatment in the first 5 years of use by the NHS is likely to be lower than the estimate in the ERG's budget impact analysis. However, it remained concerned that the company's budget impact model had not fully captured the costs of sebelipase alfa treatment (see section 5.9). The committee concluded that the 5-year budget impact of sebelipase alfa at its list price was likely to fall between the company's estimate of £54 million and the ERG's estimate of £179 million."

Alexion Response:

Alexion notes that the Committee has accepted that the estimates for the number of people likely to be treated with sebelipase alfa previously developed by the ERG significantly exceed the current understanding of the disease prevalence, based on clinical experience and the limited evidence base.

The ERG's overestimation of the number of patients diagnosed and treated, and NICE's subsequent very high estimates of treated patients in Table 1 of the ECD (which reported treated patient counts of 25 in Year 1 rising to 124 in Year 5), appears to have been driven by the unsuitable assumption that the number of patients diagnosed and treated in LAL Deficiency would follow the experience of another unrelated ultra-rare disease. As stated on page 53 of Alexion's Pro-forma Response to the ERG report, the ERG relied upon an arbitrary assumption that the percentage of prevalent LAL



Deficiency patients treated with sebelipase alfa in year 5 should equal the percentage of prevalent PNH patients treated with eculizumab in year 7. This led the ERG to identify “most plausible” continuation and compliance rates that directly contradict the real-world evidence that Alexion provided in response to NICE’s clarification letter, as well as the evidence submitted later in consultation by the MPS Society and the evidence provided in person by a clinical expert.

Since this estimation of patient numbers is so essential to an estimate of budget impact, Alexion reported in its last response that it had consulted with a group of eight UK clinical experts and explored the estimates for patient numbers proposed by Alexion in the original manufacturer submission and by NICE in the ECD. In summary:

- Overall the experts believed that the original Alexion patient numbers were overestimated and that the NICE estimates are not credible.
- Having reviewed the Alexion-proposed BIM projections and the NICE-proposed BIM projections for patient numbers treated, the experts proposed the following for the diagnosis and treatment rates by age of presentation, and proposed to split the age 1+ presentation patients into paediatric and adult to reflect the generally greater severity of disease that presents in childhood.
 - Diagnosis rates:
 - 0-1 year presentation: ██████ % over 5 years
 - 1-17 years presentation: ██████ % over 5 years
 - 18+ years presentation: ██████ % over 5 years
 - Treatment rates:
 - 0-1 year presentation: ██████ % over 5 years
 - 1-17 years presentation: ██████ % over 5 years
 - 18+ years presentation: ██████ % over 5 years

Applying these rates to the prevalence and incidence rates in Alexion’s original submission confirms that clinical experts expected lower numbers of patients diagnosed (and generally lower numbers of patients treated) than were estimated in Alexion’s original submission, as reflected in the table below.

			Year 1	Year 2	Year 3	Year 4	Year 5
Original Alexion submission	Diagnosed	Age 0-1 presentation	█	█	█	█	█
		Age 1+ presentation	██	██	██	██	██
		Total	███	███	███	███	███
	Treated	Age 0-1 presentation	█	█	█	█	█
		Age 1+ presentation	██	██	██	██	██
		Total	███	███	███	███	███
Clinical-expert opinion	Diagnosed	Age 0-1 presentation	█	█	█	█	█
		Age 1+ presentation	██	██	██	██	██
		Total	███	███	███	███	███



			Year 1	Year 2	Year 3	Year 4	Year 5
	Treated	Age 0-1 presentation	■	■	■	■	■
		Age 1+ presentation	■	■	■	■	■
		Total	■	■	■	■	■

However, it should be noted that, per the analysis of confirmed diagnoses of LAL Deficiency in England presented in the response above to Section 4.32, even the clinical experts' predictions of diagnosed patients appear to significantly exceed historical diagnosis rates. Alexion considered the Committee's comments regarding the potential for genetic screening for lysosomal storage disorders to identify a greater number of patients in the future, however it is not expected that this will materially change diagnosis rates in the 5 year period of the budget impact projection.

Further, it is important now to apply the proposed MAA eligibility criteria to the projected numbers of diagnosed patients in order to derive the best estimate of the number of patients who will be treated in England in the first five years. Consequently, on the basis of the data presented in the response above to Section 4.32, Alexion conducted a revised budget-impact analysis, leveraging the best current knowledge of patients diagnosed in England, their eligibility for treatment based on the revised consensus MAA Start criteria as advised by clinicians in the expert centres, and the number of patients likely to be newly diagnosed in future years.

Revised Budget Impact Analysis – Assumptions

- **Initial cohort:** A cohort of ■ current diagnosed patients (made up of ■ infantile-presentation, ■ children and ■ adults) begin the model in Year 1, including ■ infantile-presentation eligible for treatment, ■ paediatric-presentation patients who are eligible, and ■ adult-presentation patients who are eligible (■ patients eligible in total).
- **New diagnoses over time:** In the following years, there are ■ newly-diagnosed infantile-presentation (calculated based on Meikle et al. (1999) and English age 0-1 population) and ■ paediatric/adult-presentation diagnosed patients per year (per the clinical-expert diagnosis rates we received and reported previously, and applied to Alexion initial estimates of prevalence and incidence). Note that this assumption exceeds historic rates of diagnosis reported by the MPS Society and described in Section 4.32 and so is conservative for budget impact.
- **MAA eligibility of newly-diagnosed patients:** The ■ new infantile-presentation ■ will be assumed to be eligible, and ■% ($(\frac{■}{■+■}) / (\frac{■}{■-■}) = \frac{■}{■} = \frac{■}{■}$ %) or ■ paediatric/adult-presentation ■ will be assumed eligible (using the same proportion for eligibility in the future as that amongst the current known cohort of ■ children/adults).
- **Continuation:** In these analyses, treatment continuation rates are assumed to be 100%, as only patients in greatest need of treatment would be eligible under



the MAA. As such, Alexion agrees that in this patient sub-population, continuation rates of 100% are appropriate.

- **Adherence:** Similar to assumptions around continuation rates, Alexion agrees that adherence to treatment within the MAA-eligible patient sub-population would likely be higher than the 85% modelled in Alexion’s previous analyses of the broader LAL Deficiency population. As such, in accordance with the Committee’s request, adherence of 100% is used in the updated budget-impact analysis. However, it should be noted that in long-term clinical practice, adherence of 100% is highly unlikely to occur, and the per-patient annual cost of treatment used in the budget-impact analysis therefore is most likely overestimated.

Revised Budget Impact Analysis – Results

Applying the assumptions above, the number of patients estimated to be treated based on the known cohort of diagnosed patients, projected incident patients and MAA eligibility criteria are presented below (3), accompanied by the estimates from Alexion’s original submission (1) and those previously based on diagnosis and treatment rates specified by clinical experts (2).

			Year 1	Year 2	Year 3	Year 4	Year 5
(1) Original submissi on	Diagnosed	Age 0-1 presentation	■	■	■	■	■
		Age 1+ presentation	■	■	■	■	■
		Total	■	■	■	■	■
	Treated	Age 0-1 presentation	■	■	■	■	■
		Age 1+ presentation	■	■	■	■	■
		Total	■	■	■	■	■
(2) Clinical- expert opinion	Diagnosed	Age 0-1 presentation	■	■	■	■	■
		Age 1+ presentation	■	■	■	■	■
		Total	■	■	■	■	■
	Treated	Age 0-1 presentation	■	■	■	■	■
		Age 1+ presentation	■	■	■	■	■
		Total	■	■	■	■	■
(3)Revis ed-MAA eligible	Diagnosed	Age 0-1 presentation	■	■	■	■	■
		Age 1+ presentation	■	■	■	■	■
		Total	■	■	■	■	■
	Treated	Age 0-1 presentation	■	■	■	■	■
		Age 1+ presentation	■	■	■	■	■
		Total	■	■	■	■	■



For context in interpreting the net budget impact results, summarised below are estimates previously reported throughout the HST appraisal process.

- Original submission: £53,548,573 (assuming 85% adherence and some treatment discontinuation)
- Fact-check response to the ERG's analysis: £63,689,818 (all increase driven by change from 5mg vial to only 20mg vial in Years 2-5, despite a 0.3% reduction due to other changes recommended by the ERG; also assuming 85% adherence and some treatment discontinuation)
- Response to the ECD in March:
 - Based on original prevalence/incidence estimates and clinical-expert-opinion diagnosis and treatment rates: **£41,063,879** without the PAS and **£37,405,039** with the PAS (also assuming 85% adherence, some treatment discontinuation, and no incident patients)
 - Based on the cohort model (using ■ patients, of which ■ infantile-presentation patients were treated and ■ paediatric/adult-presentation patients were treated): **£57,022,836** without the PAS and **£41,352,270** with the PAS (also assuming 85% adherence, some treatment discontinuation, and no incident patients)

In the updated model, based on the new data on ■ known diagnosed patients in England for which we have information regarding eligibility for treatment using the revised consensus MAA criteria, the five-year budget impact estimates with 100% adherence and treatment continuation are **£87,749,647** without the PAS and **£59,494,518** with the PAS (reduction of 32%). These estimates are summarised on an annual level in the tables below.

Net budget impact over five years, without the proposed PAS

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	£11,696,065	£14,442,041	£17,294,166	£20,865,345	£24,362,493	£88,660,111
SA without market access	£241,868	£149,818	£161,372	£172,926	£184,479	£910,463
Net budget impact	£11,454,197	£14,292,222	£17,132,794	£20,692,419	£24,178,014	£87,749,647

Net budget impact over five years, with the proposed PAS

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	£8,352,725	£10,006,166	£11,885,157	£14,034,278	£16,126,656	£60,404,982
SA without market access	£241,868	£149,818	£161,372	£172,926	£184,479	£910,463
Net budget impact	£8,110,857	£9,856,347	£11,723,785	£13,861,352	£15,942,176	£59,494,518

The increase in the estimates relative to the previous cohort model is driven primarily by the fact that the previous cohort model included a closed cohort, while the updated



model assumes █ newly-treated infantile-presentation █ per year and █ newly-treated paediatric/adult-presentation █ per year.

As reflected in the analysis above, the annual expenditure cap per patient of £█ is estimated to significantly reduce the financial risk to the NHS/PSS, yielding a decrease in the net budget impact over a five-year period of 32% under the assumption 100% adherence to treatment. This represents substantial risk-sharing on the part of Alexion by assuming full responsibility for drug costs for an individual patient incurred above the cap level, thereby limiting potential overall net budget impact, particularly as patients grow over time, as well as enhancing the value for money of sebelipase alfa across the patient population treated.

V. Alexion Comments on Sections of the Second ECD Related to the Cost-Consequence Analysis

Below we provide collective responses to the sections of the second ECD that relate to the cost-consequence analysis (CCA) (specifically Sections 5.15, 5.16 and 5.18). In Section 5.16 of the ECD, the Committee notes that in the economic modelling assessing the value for money of sebelipase alfa treatment for LAL Deficiency versus best supportive care (BSC), several “preferred modelling assumptions” should be applied. Alexion responded to these assumptions in our response to the first ECD, noting concerns with the reasoning underlying certainty in particular. These concerns are detailed again below, before assessing the impact of the MAA on the value for money of sebelipase alfa in the treatment of LAL Deficiency.

Section 5.15

“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. The committee was aware from NICE’s guide to the 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 that although sebelipase alfa did extend life expectancy for babies presenting with rapidly progressive LAL deficiency, it was unclear whether their life expectancy would be restored to near normal. The committee recognised that some people presenting with LAL deficiency later in life would also have reduced life expectancy because of the complications of LAL deficiency. It was unclear how sebelipase alfa would affect the mean life expectancy for the whole population for whom sebelipase alfa is indicated and whether the modelled long-term benefits of reduced complications and improved survival would be achieved. Therefore the committee did not consider that there was a strong case for using a 1.5% discount rate.



It concluded that it was more appropriate for the company to include the standard 3.5% discount rate in its base case.”

Section 5.16

“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.”

Section 5.18

“The Committee discussed whether there were any subgroups of people for whom sebelipase alfa could be considered to offer greater value for money to the NHS than the whole population covered by its marketing authorisation. It noted in particular the comments received from the patient experts and from consultation that for some people sebelipase alfa is the only treatment option that would allow them to live beyond 1 year. The committee noted that the company had presented an analysis in which it assessed the costs and benefits for babies with rapidly progressive LAL deficiency only (see section 4.22). The committee noted that although this group would have greater incremental QALYs than the whole population for whom sebelipase alfa is indicated, the incremental costs were also higher. Also, the balance between the QALYs gained with sebelipase alfa and the additional cost for this group was considerably less favourable. The committee concluded that although sebelipase alfa is a potentially life-saving treatment for babies with rapidly progressive LAL deficiency and there is a compelling clinical need for it to be made available for these patients, it could not consider sebelipase alfa good value for money at its list price in this group because the treatment cost was too high in relation to the benefit gained.”



Revised Cost-Consequence Analysis – Assumptions

In the points below, the Committee's preferred assumptions are addressed, along with the evidence supporting them. In some cases, the weight of the evidence does not appear to support the suggested assumptions, and in the case of the ERG's proposed health-utility values, even contradicts them. As such, the incorporation of these assumptions, either in the base case analysis or as sensitivity analyses, is also addressed.

Including the ERG's adjustment of health-related quality of life to UK population norms

As stated on page 72 of the ERG's report, "the ERG implemented a minimum function in the model to ensure the health state utilities in the model would not exceed those of the general population with the same age." The ERG citation for this proposed adjustment is S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11(14):1-160. The age/gender-adjusted general-population utility function which the ERG used to limit the health utility of patients in the CCA analysis of patients with LAL Deficiency was therefore based on a sample of patients aged 45-85 with heart disease, which had to be extrapolated backwards (in age) to the considerably younger LAL Deficiency patient population, which suffers from an ultra-rare liver disease where the average age is approximately 11 years. There is therefore considerable uncertainty around the appropriateness of the utility function applied by the ERG to the LAL Deficiency patient population.

Further, NICE did not require this health utility function to be used in the modelled base cases in their reviews of the all oral HCV regimen submissions; it is therefore unclear why this non-validated approach is deemed relevant in the sebelipase alfa CCA. Nonetheless, in accordance with the Committee's preference, this assumption is included a sensitivity in the ensuing analysis.

The ERG's preferred utility values

Alexion demonstrated in its previous submission that the patients in the LAL-CL02 ARISE trial had quality of life that was no different than a general background patient population. The ERG makes a factual inaccuracy by assuming that the quality of life of the general background patient population is the same as those with HCV in the UK Mild HCV Trial. Specifically, the ERG proposes that the healthiest patient in the CCA has health utility of 0.66, which is contrary to the data in the Alexion trials and those for the general UK population.

However, Section 5.13 of the second ECD states that the Committee "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.” In this statement, it is implied that the Committee’s acceptance of the ERG’s health-utility estimates is motivated by desire for **consistency** with the age-matched general population. However, as mentioned above, use of the ERG’s health-utility estimates yields considerable **inconsistency** with the age-matched general population

For illustration, per the ERG’s implementation of the health-utility cap at the level of the age-matched general UK population, a 100-year-old in the general UK population has average health utility of 0.66. In the Crossan et al. (2) health-utility values, 0.66 is the highest value (associated with the “LAL-D without CC, DCC, or HCC” health state). In effect, assuming that the ERG’s cap function is parameterised correctly, the ERG implies that no patient of any age with LAL Deficiency has health utility higher than a 100-year-old in the general population. Considering that symptoms of LAL Deficiency are minimally pronounced in the “LAL-D without CC, DCC, or HCC” health state, and that Alexion demonstrated that the patients in the LAL-CL02 ARISE trial had quality of life that was no different than a general background patient population, the use of the ERG’s health-utility estimates is highly inconsistent with their own health-utility capping function, and therefore the general population.

As such, in the ensuing analysis, use of Alexion’s original health-utility values is maintained.

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)

Alexion appreciates that the Committee acknowledges the treatment effect of sebelipase alfa, as stated in Section 5.12 of the second ECD: “The committee considered that the evidence from the trials and from the patient experts showed that sebelipase alfa has a treatment effect, and the ERG scenario was not plausible... 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.”

As such, in the ensuing analysis, transition probabilities from Alexion’s original analysis are used. Considering that the patients eligible for treatment based on the proposed MAA have been identified as those with greatest potential to benefit from treatment, potential uncertainty around long-term clinical benefit is likely reduced.

Removing the company’s assumed price reduction of sebelipase alfa at 10 years

It is impossible for Alexion to prove that the price of sebelipase alfa will decrease after the loss of data exclusivity and the introduction of biosimilar competition, as these



events are in the future. However, Alexion believes that on the strength of historical precedent, the likelihood of this scenario being realised is high, much more so than NICE's implicit proposition that the cost of sebelipase alfa will be maintained at its current level over the next 50 years.

The price of all pharmaceutical products in the UK has always declined over time. Price increases are almost never permitted in the UK, and price erosion occurs through competitive pressure, including the introduction of generics or biosimilars, through regional or national procurement exercises, or through mandatory price reductions. Such industry-wide price reductions have been levied frequently in the past, with a 7% price reduction mandated in the 2005 PPRS agreement and a further 6% reduction mandated in the 2009 re-negotiation.

The assumed introduction of a biosimilar of sebelipase alfa is reasonable given current industry experience. The biosimilar market in Europe is quickly becoming established and as more biosimilar manufacturers enter the market, the greater the likelihood of biosimilar competition and pressure on originator prices. While there was initial scepticism that generic competition would occur for orphan drugs, a biosimilar for idursulfase (Elaprase[®]), (Hunterase, Green Cross) has already been introduced in international markets where Elaprase no longer has data exclusivity, and it is clear that biosimilar manufacturers are pursuing interests in orphan drugs.(3)

While the exact impact that this competition will have on sebelipase alfa is unknowable, the 30% estimate used by Alexion in its modelling is a credible estimate and an appropriate base case assumption for the price change. This estimate was based on observed price decreases for biologic treatments in Europe and the US. For example, Table 1 in Mulcahy et al. (2014) (4) presents various estimates of the price reduction for biologics occurring due to biosimilar entry; the US Congressional Budget Office (CBO) (2008) estimate, which is for all biologics, appears most suitable to an orphan drug (others refer to the top-selling biologics), and indicates "20% to 40%, varies by product and increasing over time.(4)

Experience to date in Europe shows significant variance in price differentials between reference products and biosimilars. For example, recent reports of prices for biosimilar infliximab have suggested price reductions of 45% to 72% vs the originator product.(5) In the US, estimates of cost savings from biosimilars range from 12% to 51%.(4) In the UK, NICE has stated that "biosimilars have the potential to offer the NHS considerable cost savings, especially as they are often used to treat long-term conditions".(6)

Experience in haemophilia suggests that these estimates are likely to be true for ultra-orphan products like sebelipase alfa as well. Whilst not technically biosimilars, there are now six recombinant FVIII biologic treatments available for haemophilia A and prices in the UK have fallen significantly as a result of increased price competition; in 2013, prices were 50% lower than in 2007. As such, Alexion continues to believe that



30% is a realistic estimate of price reduction at 10 years, and as stated above, considerably more likely than the suggestion that the cost of sebelipase alfa will be maintained at its current level over the next 50 years. As a result, in the ensuing analysis, the 30% price reduction due to loss of exclusivity at 10 years is modelled.

Continued use of a 20 mg vial

While Alexion acknowledges that the 5mg vial of sebelipase alfa is not yet available, clinical experts have expressed that they intend to administer required dosing of sebelipase alfa as efficiently as possible, which will be facilitated by the availability of the 5mg vial. Alexion would therefore suggest that the Committee give consideration to the potential impact of availability of the 5mg vial on the value for money of sebelipase alfa. However, in the ensuing analysis, it is assumed that only the 20mg vial is available in all years.

A 3.5% discount rate applied to costs and health benefits.

As is stated in Section 5.15 of the second ECD:

“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. The committee was aware from NICE’s guide to the 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 that although sebelipase alfa did extend life expectancy for babies presenting with rapidly progressive LAL deficiency, it was unclear whether their life expectancy would be restored to near normal. The committee recognised that some people presenting with LAL deficiency later in life would also have reduced life expectancy because of the complications of LAL deficiency. It was unclear how sebelipase alfa would affect the mean life expectancy for the whole population for whom sebelipase alfa is indicated and whether the modelled long-term benefits of reduced complications and improved survival would be achieved. Therefore the committee did not consider that there was a strong case for using a 1.5% discount rate. It concluded that it was more appropriate for the company to include the standard 3.5% discount rate in its base case.”

Alexion continues to disagree with the Committee’s conclusion that a 3.5% discount rate should be used in the base-case analysis for sebelipase alfa, on the basis of the evidence provided demonstrating the clinical value of sebelipase alfa, and also for consistency with estimates for eculizumab for atypical haemolytic uraemic syndrome (aHUS) and elosulfase alfa for MPS IVa. Sebelipase alfa meets the criteria for applying the 1.5% discount rate to the same extent as both elosulfase alfa and eculizumab.



In life-limiting diseases such as LAL Deficiency, aHUS, and MPS IVa, discount rates for treatment benefits have a disproportionate impact on the perceived value of the treatment. Recognising this, as noted in Section 5.15 of the second ECD, NICE has issued supplementary guidance on situations in which the Committee has the discretion to apply a lower rate of 1.5% in situations where the discount rate had a material effect on the decision. Specifically, in its Methods of Technology Appraisal, NICE states that a discount rate of 1.5% may be considered under situations where:

1. Treatment restores people who would otherwise die or have a very severely impaired life to full or near full health;
2. Analyses are very sensitive to the discount rate used;
3. Situations for which it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved; and
4. The introduction of the technology does not commit the NHS to significant irrecoverable costs.

NICE has applied this lower rate in two previous evaluations: elosulfase alfa for MPS IVa and eculizumab for aHUS. The Committee’s decision on discount rate for sebelipase alfa is incongruous with previous decisions on this issue, specifically with the previous two completed HST submissions for eculizumab for aHUS and elosulfase alfa for MPS IVa.

It should be recognised that for both treatments for which NICE has applied the 1.5% discount rate, there is uncertainty around these criteria that is inherent in rare/ultra-rare diseases treatments. Fundamentally, it is impossible to know the life-time impact of a drug at the point of marketing approval. Consequently, the Committee’s decision to apply a 3.5% discount rate to sebelipase alfa and a 1.5% discount rate to elosulfase alfa and eculizumab indicates that the Committee believes that there is a material difference in the situation for sebelipase alfa versus elosulfase alfa and eculizumab that could justify treating these medicines differently. This is explored in the table below.

Criteria		Elosulfase alfa MPS Iva	Eculizumab aHUS	Asfotase alfa HPP	Sebelipase alfa LAL-D
1. Treatment restores people to full or near full health	Addresses underlying cause of disease?	✓	✓	✓	✓
	Demonstrated survival benefit in trial?	X	X	✓*	✓**
	Large modelled lifetime QALY gain?	✓	✓	✓	✓



Criteria		Elosulfase alfa MPS Iva	Eculizumab aHUS	Asfotase alfa HPP	Sebelipase alfa LAL-D
2. Analyses are very sensitive to the discount rate used	Difference in lifetime QALY gains between 3.5% and 1.5% (manufacturer estimate)	7.9	9.5	10.8	10.5
3. The long-term health benefits are likely to be achieved	Length of trial follow-up	72 weeks	104 weeks	Studies 002/003 = 84 months Studies 006/008 – 60 months Study 09-10 = 24 months	52 weeks
4. Does not commit the NHS to significant irrecoverable costs.	Budget impact***	Approximately £130.8M in committee papers (p. 17)	£139.9M in original submission	£77.5M in original submission to £68.6M based on MAA	£53.5M in original submission to £87,749,647 without the PAS and £59,494,518 with the PAS based on MAA
	Proposed MAA limiting decision to specified time period	✓	X	✓	✓

* Liese J, Hofmann C, Harmatz P, et al. Efficacy and Safety of Asfotase Alfa in Patients with Infantile Hypophosphatasia Treated for up to 3.5 Years: Results from a Phase II, Open-Label, Uncontrolled Study. Poster preview presented at the Endocrine Society Annual Meeting and Expo, Boston, April 3, 2016.

** Jones SA, et al. Effect of sebelipase alfa on survival and liver function in infants with rapidly progressive lysosomal acid lipase deficiency. *Molecular Genetics and Metabolism*, 2015; Volume 114, Issue 2, S59.

***Budget estimates are cumulative 5-year totals.

As shown above, all four therapies illustrate the following:

- Address the underlying cause of the disease;
- Were estimated to provide substantial lifetime QALY gains;
- Showed large sensitivity to discount rates in lifetime QALY gains;
- Had follow up periods between 1 and 2 years; and
- Had comparable budget impacts, with asfotase alfa and sebelipase alfa having lower estimated 5-year total budget impacts than elosulfase alfa and eculizumab in aHUS.

All but one (eculizumab) proposed a MAA to limit NHS financial exposure to a defined time period and patient population. On the basis of these facts, there appears to be no



material difference between the treatments on the criteria considered that provides clear justification for treating these medicines differently in respect to discount rates.

Owing to the lack of material evidence differentiating the situation of sebelipase alfa from those of elosulfase alfa and eculizumab, and on the basis of the evidence presented of the clinical value of sebelipase alfa treatment, in the ensuing analysis, a discount rate of 1.5% for costs and benefits is therefore used. However, in order to be fully responsive to the Committee's request, as a sensitivity analysis, results using a 3.5% discount rate for costs and benefits are also presented.

Revised Cost-Consequence Analysis – Results

As described in detail above, the revised consensus MAA in Attachment A outlines clinical criteria for treatment of patients who will likely benefit most from sebelipase alfa.

The CCA developed for NICE was parameterised based on the sebelipase alfa clinical trials LAL-CL02 (ARISE) and LAL-CL03 (i.e., baseline disease-severity distributions and transition probabilities between the LAL Deficiency without CC, DCC, and HCC to/from compensated cirrhosis were calculated from the trials). The base case results reflect the impact of sebelipase alfa treatment vs. best supportive care (BSC) in the broader LAL Deficiency population. As a result, the extent to which the CCA base case results reflect the value proposition of sebelipase alfa in the population covered by the Marketing Authorisation depends on the similarity of the MAA clinical criteria for treatment and the clinical profile of patients included in the LAL-CL02 and LAL-CL03 trials.

However, as mentioned above in response to Section 1.2 of the ECD, considering that the provisions of the proposed MAA will determine patient access to treatment, the relevant patient population in which value for money should be assessed is that meeting the eligibility criteria of the proposed MAA, rather than the broader population that was addressed in Alexion's previous submissions, and reflected in the CCA base case results. As such, in the analysis below, Alexion presents CCA results for the infantile-presentation and paediatric/adult-presentation patient groups, which help inform the value for money of sebelipase alfa treatment of LAL Deficiency in the ■ infantile-onset patients and ■ paediatric/adult-presentation known patients in England understood to be eligible for treatment based on the revised consensus MAA criteria.

The revised analyses presented here utilise a 1.5% discount rate in the base case, in accordance with Alexion's belief that this is the most appropriate rate based on NICE's Methods of Technology Appraisal, and to be consistent with the evaluations of elosulfase alfa for MPS IVa and eculizumab for aHUS. Results are also provided using a 3.5% discount rate, although as stated above, owing to the lack of material evidence differentiating the situation of sebelipase alfa from those of elosulfase alfa and eculizumab, and on the basis of the evidence presented of the clinical value of sebelipase alfa treatment, Alexion cautions that a 1.5% discount rate is most



appropriate. Finally, results are presented both at list price, and applying the annual cost cap of £ [REDACTED] proposed in the PAS.

CCA results using a 1.5% discount rate

	Scenario			Weighted avg. based on MAA-eligible patients
	Base case	Infants (LAL-CL03)	Paeds/adults (ARISE)	
Using 20mg vial in all years				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]
Incremental QALYs	20.5	28.6	20.4	23.0
Using 20mg vial in all years, and applying the health-utility capping function				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]
Incremental QALYs	18.8	27.4	18.5	21.4

CCA results using a 1.5% discount rate, and with the annual cost cap of £ [REDACTED] proposed in the PAS

	Scenario			Weighted avg. based on MAA-eligible patients
	Base case	Infants (LAL-CL03)	Paeds/adults (ARISE)	
Using 20mg vial in all years				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]
Incremental QALYs	20.5	28.6	20.4	23.0
Using 20mg vial in all years, and applying the health-utility capping function				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]
Incremental QALYs	18.8	27.4	18.5	21.4

CCA results using a 3.5% discount rate

	Scenario			Weighted avg. based on MAA-eligible patients
	Base case	Infants (LAL-CL03)	Paeds/adults (ARISE)	
Using 20mg vial in all years				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]
Incremental QALYs	10.0	16.5	10.6	12.5
Using 20mg vial in all years, and applying the health-utility capping function				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]
Incremental QALYs	9.4	16.1	9.9	11.9

CCA results using a 3.5% discount rate, and with the annual cost cap of £ [REDACTED] proposed in the PAS

	Scenario			Weighted avg. based on MAA-eligible patients
	Base case	Infants (LAL-CL03)	Paeds/adults (ARISE)	
Using 20mg vial in all years				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]



	Scenario			Weighted avg. based
Incremental QALYs	10.0	16.5	10.6	12.5
Using 20mg vial in all years, and applying the health-utility capping function				
Incremental costs	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]	£ [REDACTED]
Incremental QALYs	9.4	16.1	9.9	11.9

As presented in the final column of the first table (using a 1.5% discount rate), the distribution of patients meeting the MAA eligibility criteria (■ infantile-presentation, ■ paediatric/adult-presentation) gives a weighted average of incremental gain of 23.0 incremental QALYs associated with sebelipase alfa versus BSC across the cohort in the base case. This is reduced to 21.4 QALYs if the ERG “health utility capping function” is applied, limiting the health utility to the age-matched general population’s, albeit in an unvalidated and potentially biased way. There is a very large gain in the infantile-presentation patient population (28.6 QALYs), in addition to a large gain of 20.4 QALYs in the group reflecting the paediatric/adult-presentation patient population (based on the patient characteristics in the ARISE clinical trial).

The MAA-eligible weighted-average estimate of 23.0 incremental QALYs reflects the patients who would receive treatment under the revised consensus MAA, and is therefore likely to be the most representative of the real world benefit associated with sebelipase alfa in England. In addition, given that the MAA-eligible patients consist of those most likely to benefit from sebelipase alfa treatment, it might reasonably be argued that the degree of certainty of clinical benefit is higher in this group than in the broader LAL Deficiency patient population. Alexion believes that this very large and clinically important QALY gain demonstrates the very significant value of sebelipase alfa in patients described by the revised consensus MAA eligibility criteria.

Value for money of sebelipase alfa versus eculizumab

NICE expressed an interest in understanding how the value for money of sebelipase alfa in LAL Deficiency compared with that of eculizumab in aHUS, which has previously been recommended following NICE HST appraisal. Below, this is explored in light of the PAS and revised consensus MAA proposed for sebelipase alfa. It is important to remember that, despite the fact that both diseases are ultra-rare, aHUS and LAL Deficiency are two very different diseases for which the characteristics of the patient populations are also different. For instance, the majority of patients with LAL Deficiency present with symptoms during childhood (median age of onset of 5 years (1)), while aHUS patients tend to be much older on average at onset (28 years at baseline of aHUS clinical trials C08-002 and C08-003).

Implementation of the MAA is likely to increase the magnitude of the average QALY gain and reduce the uncertainty around that estimate by targeting treatment at those LAL Deficiency patients in whom clinical experts believe there is highest need and greatest potential for benefit.



Based on the criteria defined in the revised consensus MAA, UK clinical experts have estimated the distribution of patients eligible for treatment, and a base case estimate of incremental QALY gains in MAA-eligible patients has been derived using this distribution of patients likely to be treated. This blended estimate of 23.0 QALYs gained is very comparable to that of eculizumab in aHUS (25.04 QALYs gained) and both drugs therefore provide an extremely large and clinically important benefit.

The incremental lifetime patient cost of sebelipase alfa is significantly reduced as a result of the PAS proposed by Alexion. Before the PAS is applied, the weighted-average incremental lifetime cost for the average MAA-eligible patient is £[REDACTED], which is reduced to £[REDACTED] after the application of the PAS, a significant reduction of 55%. The comparable lifetime incremental cost for eculizumab in aHUS was £[REDACTED]. Some of the difference in incremental lifetime cost between eculizumab and sebelipase alfa is explained by the age of patients at treatment initiation, who were much older in the eculizumab in aHUS base case analysis than in the base case for sebelipase alfa (average age at baseline in the aHUS clinical trials C08-002 and C08-003 was 28 years, as mentioned above, compared to the average age of 11.5 years in the LAL-CL02, LAL-CL03, and LAL-1-NH01 studies), and therefore incurred treatment costs for a shorter period over a lifetime horizon.

The higher average annual patient cost also reflects the pricing of sebelipase alfa that was determined in part based on the extremely low patient numbers expected to be treated with sebelipase alfa for LAL Deficiency. It is well recognised in rare/ultra-rare diseases that price and prevalence are correlated and that this is necessary to incentivise research in diseases with very low prevalence. In total, [REDACTED] patients are expected to receive sebelipase alfa in England at Year 5 of the budget impact analysis incorporating the MAA criteria, compared to [REDACTED] for eculizumab in aHUS, and the budget impact estimates are likewise lower for sebelipase alfa (£11.9M vs £28.0M, on average per year over the five-year period of the analysis).

VI. Alexion Comments on Other Sections in the Second ECD with New Text

The following two sections, Section 5.7 and Section 5.8, of the second ECD included new text for which Alexion provides a response below.

Section 5.7

“The committee discussed the potential of sebelipase alfa as a ‘bridging therapy’ in the treatment pathway for LAL deficiency. The committee noted that a clinical expert’s evidence submission raised the possibility of using sebelipase alfa to stabilise LAL deficiency presenting in babies of less than 6 months before offering a haematopoietic stem cell transplant (HSCT). The committee noted that HSCT has the potential to treat conditions in which people have an enzyme deficiency, and avoids the need for lifelong regular infusions, 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. Early death was not prevented, perhaps because the babies were too unwell at diagnosis. 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 who had been stabilised on sebelipase alfa was unknown. The committee proposed a research recommendation to compare the benefits of long-term treatment with sebelipase alfa with shorter-term treatment with sebelipase alfa ('bridging therapy') followed by HSCT with curative intent for people with rapidly progressive LAL deficiency which presented when they were babies. Responses to consultation emphasised the practical difficulties of studying this mode of treatment. The committee heard that patients, carers and clinicians would be unwilling to stop an effective treatment to switch to a treatment which has not been shown to be effective and carries a high risk of morbidity and mortality. This would make recruiting to a trial to assess HSCT after sebelipase alfa difficult, even if this was the sole route to access the treatment under NICE recommendations. The committee concluded that it was not possible to make a recommendation for research into the use of sebelipase alfa as a bridging therapy before HSCT."

Alexion Response:

Alexion agrees with the revised recommendation and agrees that a clinical trial with sebelipase alfa as bridging therapy before haematopoietic stem cell transplant (HSCT) is not feasible for the reasons noted above. Alexion thanks the Committee for considering the feedback received from the clinicians, patients, and from Alexion on this topic.

Section 5.8

"The committee noted that the marketing authorisation for sebelipase alfa states that the dosage 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 dosage of sebelipase alfa for babies presenting with rapidly progressive LAL deficiency should be 3 mg/kg weekly, with escalation to 5 mg/kg if there is inadequate response. The committee heard from a clinical expert that in his experience of treating babies with sebelipase alfa, approximately 50% of patients were on a 3 mg/kg dose and 50% were on a 5 mg/kg dose. The committee heard from the company that it is carrying out a clinical trial of the 5 mg/kg dose, but data from this trial are not yet available. The company stated in its submission to NICE that it only included clinical data from babies treated at the dosage stated in the marketing authorisation. The company also noted that it took into account that babies in LAL-CL03 had their dose escalated to 3 mg/kg over the trial period when estimating costs in its



economic analyses. The committee further heard that the clinical experts would also consider, in some instances, dose escalation up to 3 mg/kg in some children whose symptoms presented after 6 months and whose LAL deficiency did not respond to the lower dose. The committee reaffirmed that its recommendations could only apply to the dosage covered by the marketing authorisation for sebelipase alfa unless it was directed by the Department of Health to make recommendations for the technology outside the terms of its marketing authorisation. However, the committee stated that it could consider evidence on the use of sebelipase alfa outside the terms of its marketing authorisation to inform discussions about its licensed use.”

Alexion Response:

Alexion can only promote the doses in the marketing authorisation for sebelipase alfa. Alexion is conducting studies in infants in which higher doses are allowed under certain conditions. These trials are ongoing and have not yet been analysed for safety and efficacy.

VII. Alexion Comments on the Conclusion in the Second ECD

Section 5.25

“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. 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. It considered that the company’s managed access proposal did not robustly define the population with the greatest clinical need (for example, babies presenting before 6 months with rapidly progressive LAL deficiency), and no associated estimates of cost and benefits for people with the greatest clinical need had been supplied by the company. Therefore the committee was unable to reach a conclusion on the value for money offered by the managed access proposal. Moreover, the likely total costs to the NHS were unclear both because of lack of information about the size of any population defined by the managed access proposal and uncertainties in the dosing regimens that would be used 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.”

Alexion Response:



Sebelipase alfa is the only treatment option that has been approved and demonstrated to substantially improve the survival of infants with rapidly progressive LAL Deficiency, and also to improve the health and clinical outcomes in children and adults with this devastating and ultra-rare disease. As such, it is a treatment that should be made available to patients with LAL Deficiency in England who are most likely to benefit from therapy, as identified in the revised consensus MAA document developed and agreed to by clinical experts, the MPS Society, and a representative from NHSE.

Alexion is concerned that the Committee's recommendation not to fund the small number of patients suffering from LAL Deficiency for which sebelipase alfa is shown to be beneficial, due predominantly to cost, portends a concerning trend by which few, if any, ultra-orphan products will be made available to patients suffering from ultra-rare disease in England. However, in order to address the Committee's concerns about cost and to illustrate value for money to the NHS, Alexion worked directly with key stakeholders to more narrowly define the patients who will benefit most from sebelipase alfa, and to define the patients for which sebelipase alfa represents the greatest value for money to the NHS. We are confident that the revised consensus MAA, combined with our confidential financial risk-sharing proposal, addresses the Committee's cost containment objectives both by limiting the patients eligible for treatment and also by directly limiting/capping the annual per patient and overall costs of treatment to the NHSE.

Further, the potential QALY gains from the use of sebelipase alfa in England are significant and comparable with other technologies approved following HST appraisal. It is, therefore, Alexion's hope that the proposed clinical criteria combined with the proposed financial concessions will encourage the Committee to make a positive funding recommendation for the use of sebelipase alfa in England for patients with LAL Deficiency most in need.

We remain committed to working with NICE and NHSE to ensure that patients with LAL Deficiency in England who can benefit most from sebelipase alfa have timely access to therapy. As always, we remain fully available to answer any additional questions the Committee may have, and look forward to finalising an agreement in support of patients as soon as possible.

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Attachment A: Revised Proposed Managed Access Agreement and Associated Appendices

Please see attached Word document with associated appendices.



Attachment B: Schematic for Proposed Managed Access Agreement

Please see attached Word document.



Attachment C: Stakeholders Consulted in Development of MAA

Below is the list of stakeholders consulted in the development of the proposed MAA:

Clinical Experts

Dr Simon Jones, Consultant in Paediatric Inherited Metabolic Diseases, The Willink Centre, St Marys Hospital, Manchester

Dr Patrick Deegan, Consultant in General Medicine and Metabolic Diseases, Addenbrookes Hospital, Cambridge

Dr Elaine Murphy, Consultant Inherited Metabolic Disease, National Hospital for Neurology and Neurosurgery, London

Professor Nedim Hadzic, Professor of Paediatric Hepatology, Kings College Hospital, London

Dr Saikat Santra, Consultant in Inherited Metabolic Diseases, Birmingham Children's Hospital

Dr Reena Sharma, Consultant Adult Metabolic Medicine, Honorary Senior Lecturer, Salford Royal Foundation NHS Trust, Manchester

Patient Group Representative

Sophie Thomas, Advocacy Support Team Manager, MPS Society

NHS England Representative

Edmund Jessop, Medical Advisor, NHS England



Attachment D: Revised Budget Impact Model

Please see attached Excel spreadsheet.



Attachment E: Revised Cost-Consequence Model

Please see attached Excel spreadsheet.



Attachment F: HST PAS Evidence Submission Template

Please see attached Word document.



Attachment G: Checklist of Confidential Information (NICE Appendix H)

Please see attached Word document.



Attachment H: Alexion Comments to First ECD for Sebelipase Alfa

For reference, we have copied below our responses to the first ECD for the sections that were repeated in the second ECD so the Committee has easy access to our initial responses. As mentioned above, since the text for the below sections of the second ECD were copied verbatim from the first ECD, our responses have not changed. The only exception to that is for Section 4.4 for which we have no comments.

Alexion Comments on Section 2 of First ECD – The Condition (Sections 2.1-2.3)

Sections 2.1 and 2.2

No Comments

Section 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.”

Alexion Response:

Alexion disagrees with the statement that the patients who present after 6 months have a milder course of disease. Though the clinical progression can vary in older patients missing this vital enzyme, the disease is not mild and has been noted in the literature to be progressive (high rates of fibrosis, cirrhosis and significant dyslipidaemia), which places children, adolescents, and young adults at significant risk for disease mortality and morbidity. A review of published literature reveals that of 135 paediatric and adult patients with LAL Deficiency, 51% progressed to fibrosis, cirrhosis, or death within 3 years of symptom onset.(10)

Alexion Comments on Section 3 of First ECD – The Technology (Sections 3.1-3.3)

Section 3.1

No comments.

Section 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.”



Alexion Response:

Alexion disagrees with this statement as the development of antibodies does not necessarily mean that sebelipase alfa will not provide clinical benefit, or put a patient at harm. As noted in the sebelipase alfa SmPC: “The association between the development of ADA to sebelipase alfa and reductions in treatment effect or the occurrence of adverse reactions has not been determined.” Additionally, as noted in our initial submissions, the treatment adverse event profile seen among ADA-positive subjects is consistent with that in the study population (infants, children and adults) in our clinical trials.

Alexion is committed to continuous data collection related to use of sebelipase alfa and the development and impact of the ADA through data collection in the global LAL Deficiency Registry. The Registry will collect data related to long-term efficacy and safety of sebelipase alfa. Of note, in each country where sebelipase alfa is marketed, Alexion provides the sebelipase alfa ADA test free of charge to health care professionals (as noted in the risk management programme associated with regulatory approval).

Section 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 company estimated the annual cost of treatment for an 11-year-old child to be £491,992 per patient (excluding VAT).

Alexion Response:

The figure £491,992 represents the annual cost of treatment for an 11-year-old child based on weight derived from the Royal College of Paediatrics and Child Health indices (2015).

It appears that this value, originally reported in Table D12.12 of Alexion’s initial submission, was mistakenly cited by NICE on page 8 of the “Highly Specialised Technology Evaluation Pre-meeting briefing - Sebelipase alfa for treating lysosomal acid lipase deficiency” document as the average annual treatment cost over 10 years starting at age 11. In actuality, £491,992 is the annual treatment cost for an 11-year-old patient with presentation of LAL Deficiency in child/adulthood.

The misinterpretation seems to be based on NICE’s reading of Table D12.12 in Alexion’s initial submission, where £491,992 is referenced as the annual cost of treatment for an 11-year-old before the 30% price reduction related to loss of exclusivity, which is modelled after 10 years from the start of the model. It appears that NICE interpreted the 10 years referenced as the period over which the annual treatment cost was averaged, rather than as the time assumed until loss of exclusivity (as Alexion intended). The correct average annual treatment cost over 10 years for a patient of age 11 in the first year is £590,023 at NHS List Price. However, it should be noted that



Alexion has proposed a Patient Access Scheme that would cap the cost of treatment for an individual patient in a year to no more than £[REDACTED]. This annual expenditure cap would apply to any patient receiving a dose deemed clinically appropriate by their physician, whether a licensed dose or not. As such, the average annual cost of treatment could be no more than £[REDACTED], and would likely be lower (given that not all patients would require dosing that met the cap). It should also therefore be noted that in NICE's budget impact analysis in Section 5.11, £[REDACTED] (or lower) should be used rather than £491,992 as the average annual treatment cost per patient.

Alexion Comments on Section 4 of First ECD – Evidence Submissions (Sections 4.1-4.34)

Nature of the Condition (Sections 4.1-4.4)

Section 4.1

No comments.

Section 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.”

Alexion Response:

Though the ECD notes that “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”, literature has reported 50% of deaths occurring in those under the age of 21, which represents very significant early mortality amongst patients with LAL Deficiency that the Committee needs to recognise.(1)

Section 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.”

Alexion Response:

One parent of a baby with LAL Deficiency who is currently receiving treatment with sebelipase alfa, and who had tragically previously lost a baby to the disease prior to the option of ERT, gave compelling evidence to the Committee about the family’s experiences. Whilst NICE has recognised some of that father’s experience in the ECD, it has completely failed to recognise the medical emergency that LAL Deficiency in infancy presents. It does not acknowledge the urgent need for the first licensed treatment for LAL Deficiency, which addresses the root cause of the disease, to be routinely commissioned for the very small number of such affected families in England.

Section 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.”

Alexion Response:

No comments.

Clinical Evidence (Sections 4.5-4.11)

Section 4.5

No comments.

Section 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.”



Alexion Response:

As noted in our response to Section 1.2 above, survival is poor via HSCT, with the median age at death of 8.6 months.

Section 4.7

No comments.

Section 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).”

Alexion Response:

The LAL-CL03 study is ongoing and as of January 2016, 5 of the patients have survived beyond 24 months of age. This information has now been published by Jones et al, Molecular Genetics and Metabolism 117 (2016) S63.(11) Subsequent data review has shown that all 5 patients are still alive and have survived to 36 months of age as of March 1, 2016. These infants had shown improved feeding and growth and continue to meet developmental milestones. These data highlight the significant maintenance effect of continued treatment in these infants and the anticipated ability to restore full life expectancy. The oldest patient is now 5 years and 2 months and is still doing well.

Sections 4.9 to 4.11

No comments.

Economic Evidence (Sections 4.12-4.25)

Section 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.”

Alexion Response:

It should be acknowledged that NAFLD and NASH were identified by clinical experts as the diseases most analogous to LAL Deficiency.

Sections 4.13 to 4.19

No comments.

Section 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.”

Alexion Response:

Alexion’s assumption of a price decrease after 10 years is due loss of data exclusivity, as noted in our initial submission. Alexion suggests rephrasing the second sentence in Section 4.20 above to the following: “The company noted that it will be making sebelipase alfa available in 5 mg vials, and it was assumed that they will have an equivalent price per mg to the 20 mg vials currently available.”

Sections 4.21 to 4.23

No comments.

Section 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 uraemic 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.”

Alexion Response:

In the seventh bullet point in Section 4.24, Alexion suggests correcting the first and second sentences to read, “The average weekly dose of sebelipase alfa for patients presenting with LAL deficiency in infancy was 2.3 mg/kg every week in their first year of life (reflecting dose escalation from 1 mg/kg every week to 3 mg/kg every week) and 3



mg/kg every week in subsequent years. The dose for LAL Deficiency presenting at 1 year or over was 1 mg/kg every other week.”

Section 4.25

No comments.

Economic Review Group Review (Sections 4.26-4.31)

Section 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.”

Alexion Response:

The ERG’s concern that the infant studies are “not comparable and may be subject to bias” is not based on evidence. No data for this conjecture that supportive care has improved over time was provided by the ERG. In fact, the opposite has been stated by local UK experts. Specifically, in recent discussions with a local UK expert who specialises in diagnosing infants with LAL Deficiency, he reiterated that there have been no major improvements in care for these patients, and even with the best supportive, and/or aggressive care, the outcome of an untreated infant with LAL Deficiency will be death in infancy. It is neither ethical nor appropriate to take an alternative approach to studying a fatal disease in infants as a concomitant control would not be appropriate. The rarity of the disease also means that historical controls must go back a long way in time. This approach was agreed with both the EMA and FDA for regulatory purposes and should be accepted by NICE.

Alexion has conducted difficult yet robust clinical trials in infants with ultra-rare disease for whom mortality was previously almost 100%. The Committee should recognise the societal benefits of research in such challenging clinical situations and cannot assume positive outcomes for BSC without evidence to support that assertion and in the face of expert opinion to the contrary. Alexion has taken a scientifically robust approach to provide a comparative control from natural history data and strongly believes that patients with ultra-rare disease should not be disadvantaged because their condition has not previously been well-studied.



The ERG's own Figure 4.1 titled "Monthly weight gain by date of first chart review" does not support the assertion and instead supports (the ERG's comment) that there "seems to be no obvious trend (in weight gain in the month of first diagnosis) over time. On page 38 of the ERG's report, the ERG concludes: "Nevertheless, on the basis of failure to thrive, the prognosis for patients in study LAL-CL03 appears similar to the prognosis for patients in study LAL-1-NH01 without sebelipase alfa." The outcomes of the comparable LAL-1-NH01 patients selected by the ERG (n=25) still result in death for all the infants and there is no evidence of improvement over time.

The patient subpopulation (N=21 or N=25) in the historical control from study LAL-1-NH-1 includes patients who were enrolled in 2010 and 2011, and therefore represents current BSC practice. Given the rarity of LAL Deficiency, the LAL-1-NH-1 trial allowed cases to be as far back as 1985; however, when BSC is compared between those patients before 2005 to those after 2005, there is no difference in outcomes [before 2005: median age of death: 3.6 months; after 2005: median age of death: 2.7 months]. Therefore, it is clinically appropriate to use the data presented in LAL-NH01 as the historical control arm for LAL-CL03.

Although not included in Alexion's initial submission, recent personal communication with an investigator in the LAL-CL03 study reveals that "the severity of patients included in the study should also be compared to analysis of siblings' survival where available." Specifically, this investigator stated "In at least two of my patients, results with the same supportive treatment have been growth failure followed by death (including one sibling treated with BMT)." This example disproves the ERG's belief in the improvement in BSC in the current clinical environment.

Finally, recent communication with another lysosomal storage disease expert in the UK illustrates that the mainstay of supportive care that is needed for these ill infants is primarily related to malabsorption and growth failure. This expert notes that no major improvements have occurred with feeding and formula and that it is factually inaccurate to assume a substantial improvement in supportive care in the time interval between LAL-CL03 and LAL-1-NH01 study.

Section 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.”

Alexion Response:

With regard to the ERG being uncertain of the “long-term safety and efficacy profile of sebelipase alfa”, the totality of available clinical evidence for sebelipase alfa was included in Alexion’s initial submission to NICE to show the beneficial clinical endpoints of the drug. The EMA (and FDA) reviewed this evidence and approved sebelipase alfa for “long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency” (Kanuma SmPC, 2015; (12)).

A recent analysis of the infusions given in CL02, CL04 and CL06 representing approximately 4,900 infusions in 105 subjects (ages of 3 and 59 years of age) highlight the ongoing safety profile of sebelipase alfa. . Most adverse events have been mild to moderate in severity. Few treatment emergent adverse events (TEAEs) have been serious and few have been related to treatment. Three subjects (3%) have had related or possibly study drug–related serious TEAEs, all of which were infusion associated reactions (IAR). No subject who has tested positive for ADA has experienced a severe TEAE or serious TEAE or discontinued treatment due to a TEAE; TEAEs in ADA-positive subjects have been consistent with TEAEs in the overall population.(13)

As noted earlier, given the rarity of the disease, clinical trials that directly assess the ability to stop progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events, or death were not feasible. The marketing authorisation for sebelipase alfa was reviewed and approved by clinical experts with experience with lysosomal storage disorders and liver disease who found the clinical data to provide sufficient evidence of long-term benefit for patients with LAL Deficiency. Alexion’s submission to NICE included these same data, illustrating the key clinical endpoints (ATL, LDL-C, and liver fat content reduction) that have significant clinical relevance to the impact of sebelipase alfa in the treatment of LAL Deficiency. These data were deemed appropriate for regulatory review and represent the only and longest term data (for both untreated and treated patients) available globally for this ultra-rare disease.

It is unclear what NICE means by “long-term safety and efficacy” and what evidence is expects in the context of an HST conducted in the year of new drug licensing, particularly for an ultra-rare disease. NICE should ensure that unrealistic ideals for a long-term evidence base do not bias against the very small number of patients who have the first prospect ever for a safe and effective treatment for LAL Deficiency.

Section 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.



Alexion Response:

Sources of efficacy data

With regards to the ERG's assertion that "different sources of data were used to determine transition probabilities for people receiving best supportive care or sebelipase alfa", the ERG failed to acknowledge that Alexion used a comparison of trial data for sebelipase alfa versus natural history data for BSC as is common in modelling ultra-rare diseases, and as is common in modelling liver-related disorders like HCV. It also failed to acknowledge that in sensitivity analyses, Alexion compared sebelipase alfa versus BSC using head-to-head data from the trials.

Selection of health-utility values

With regards to the ERG's assertion 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", ERG dismissed the work of the clinical experts at EMA (and FDA) who have reviewed this evidence and approved sebelipase alfa for "long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency".(Kanuma SmPC, 2015; (12))

The ERG stated that they "considered that the way the company had identified utility values used in its model had not been transparently described", but failed to note that Alexion derived the health utility values directly from Mahady et al. (14), the one published NAFLD cost-effectiveness model available for the submission. In the absence of any published LAL Deficiency utility values, clinical experts identified NAFLD as the closest analogue to LAL Deficiency, and Alexion took utility values from the single NAFLD model available for submission. This was described transparently in our submission and associated responses.

The ERG uses health utilities from an inappropriate HCV population (the UK Mild HCV Trial), though these patients are sicker than NAFLD patients owing to comorbidity burden. In the UK Mild HCV Trial, 53% (104/196) of enrolled patients were infected via intravenous drug abuse; 31% had "unknown" source of infection, per Wright et al. (15), Table 8, page 16. Mahady et al. (14) use some HCV health utilities in their estimates, but use those at the higher end of the health utility spectrum in HCV indicating a healthier population infected through the blood supply and not risky behaviour; this avoids confounding NAFLD quality of life with the large comorbidity burden associated with some HCV patients (e.g., HIV, HBV, psychiatric disorders, intravenous drug use); excess rates of these comorbidities are not present in the LAL Deficiency patient population.

Further, the ERG states that "the ERG used the health state utilities as reported by Crossan et al.", but the ERG misquotes the HCV health utilities that they cite in Crossan et al.(2) For example, they use 0.66 (page 73) for the "LAL-D without CC, DCC or HCC' state", when this state is a mix of mild and moderate fibrosis. The ERG misquotes the



DCC and HCC health utilities from Crossan et al., using a value of 0.49 (page 73) instead of 0.57, which appears on page 66 of Crossan et al.(2)

Magnitude of health-utility values vs. general population

The ERG recommended capping the utility values in the model so that they would not exceed those of the general population, implementing a minimum function in the model to ensure the health state utilities in the model would not exceed those of the general population with the same age. For its utility-capping function, the ERG cites Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11(14):1-160.(16) The use of the capping function proposed by the ERG raises several concerns:

- Ward et al. (16) is a well-known published manuscript assessing cost-effectiveness of statin use in patients age 45 to 85. LAL Deficiency is an ultra-rare liver disease where the average age is *about 11 years old*. The utility function applied by the ERG is not applicable to the LAL Deficiency patient population, given that LAL Deficiency starts at such a young age, and the linear relationship between age and health utility has not been validated in extrapolation back to paediatric patients.
- NICE did not require this health utility function to be used in the modelled base cases in their reviews of the all oral HCV regimen submissions to NICE by Gilead and AbbVie. It therefore seems inconsistent to apply this non-validated approach to the review of LAL Deficiency, particularly because it is an ultra-rare disease .

Importantly, and as elaborated upon in Alexion's response to Section 5.14, in light of the capping function proposed by the ERG, the appropriateness of Crossan et al. (2) health-utility values becomes highly implausible. Per the ERG's health-utility capping function, 0.66 is the average utility of a 100-year-old in the general UK population; however, citing Crossan et al. (2), the ERG proposes 0.66 as the highest health-utility value for a LAL Deficiency patient of any age. Alexion demonstrated that the patients in the LAL-CL02 ARISE trial had quality of life that was no different than a general background patient population; more generally, it seems highly unlikely that patients with limited evidence of fibrosis would have health-utility no higher than a 100-year-old in the general population.

Selection of discount rate

The discount rate of 3.5% for costs and benefits suggested by the ERG is inappropriate according to the NICE guidelines for highly specialised technologies (HSTs). The NICE guide to the methods of technology appraisal 2013 states the following:

"In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal



Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved.”(Section 6.2.19 of the NICE Methods Guide to the methods of technology appraisal. NICE. April 2013. <http://publications.nice.org.uk/pmg9>, Last accessed September 30, 2015.)

For sebelipase alfa, the ERG model assumes a discount rate of 3.5% for both costs and benefits, implying that the ERG does not accept that sebelipase alfa meets the criteria in the NICE Methods Guide. As is presented criterion-by-criterion in Alexion’s response to Section 5.16, sebelipase alfa does meet these criteria, and as a result, should be evaluated using an annual discount rate of 1.5%.

Impact of loss of exclusivity and vial size on annual treatment costs

The assumptions around the effect of loss of data exclusivity and vial size are addressed in this document in Alexion’s response to Section 5.15.

Section 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.”

Alexion Response:

The ERG conclusion that sebelipase alfa provides no additional benefit at all over palliative care is in direct contradiction to the findings of the Committee for Orphan Medicinal Products at the EMA, the FDA, clinical expert opinion, the clinical data and basic medical reason.

There are three assumptions which lead to the ERG’s conclusion in the ECD that “Sebelipase alfa was associated with no additional QALYs compared with best supportive care.” These assumptions are as follows:

1. Equal probability of transiting from 'LALD without CC, DCC or HCC' to 'CC' for both comparators, using the annual probability of 3.2% obtained through the survival analysis;



2. Probability of transiting from 'CC' to 'LALD without CC, DCC or HCC' based on FIB-4 scores for both comparators; and
3. All other transition probabilities based on Mahady et al. (14) (equal for both comparators).

Each of these assumptions by the ERG does not have a logical basis given the available data for sebelipase alfa and current clinical opinion of the natural history of LAL Deficiency.

The first assumption: "Equal probability of transiting from 'LALD without CC, DCC or HCC' to 'CC' for both comparators, using the annual probability of 3.2% obtained through the survival analysis" does not appear logical, given the data available. Without justification, the ERG is relying on a probability calculated with *only BSC-treated patient data* to parameterize the sebelipase alfa arm, instead of using the available on-treatment data from the clinical trials for sebelipase alfa patients as was done in the company model. It would be logical to use the trial observations for sebelipase alfa-treated patients once they started receiving sebelipase alfa, instead of exclusively BSC-treated patients as the ERG suggests.

The second assumption regards the: "Probability of transiting from 'CC' to 'LALD without CC, DCC or HCC' [should be] based on FIB-4 scores for both comparators." Alexion explored use of FIB-4 scores for parametrizing this transition for both comparators in several sensitivity analyses presented in Table D12.23 of Alexion's initial submission. However, given the limited sample size available in the trials data for calculating the probability of disease regression, and that there is no clinical evidence of disease regression for patients with progressive liver disease treated with best supportive care, in the base case, it was deemed that transition probabilities for NAFLD/NASH were most appropriate for the best supportive care comparator. Given that the sebelipase alfa trials provide the only data available for parametrizing sebelipase-alfa transition probabilities, in the base case, FIB-4 scores using a CC threshold of 1.45 were used for sebelipase alfa. It should be noted that in all of the sets of transition probabilities calculated using different CC thresholds than 1.45 for FIB-4 and the Forns index (shown in Table D12.7 of Alexion's initial submission), none of the placebo patients in the ARISE trial improved from 'CC' to 'LALD without CC, DCC or HCC', while sebelipase alfa-treated patients improved on all FIB-4 thresholds tested. When using the APRI liver score, 1/3 of placebo patients improved compared with 6/7 sebelipase alfa-treated patients.

The third assumption is that both sebelipase alfa-transition probabilities and BSC-transition probabilities from CC to DCC or HCC should come from natural history data. For sebelipase alfa-treated patients, the trials contain 2,691 [cumulative] weeks of treatment; during these 51.75 years of patient-study time, there were no observed instances of patients on sebelipase alfa transitioning to DCC or HCC. While the degree of uncertainty surrounding short-term trials data may be questioned, the ERG's proposal



to ignore the trials data is unscientific, and calls into the question the rationale for performing a health-economic assessment.

Other issues noted in Section 4.29 were addressed in the comments to the prior section (Section 4.28).

Section 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 [REDACTED] 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.”

Alexion Response:

Alexion sought on multiple occasions, through our responses to NICE and the ERG, to make our budget impact calculations transparent. In Alexion’s responses to NICE’s clarification questions, further detail regarding the incidence and prevalence calculations were provided. Subsequently, in Alexion’s fact-check proforma of the ERG’s analysis, a step-by-step description of the calculations was provided in response to Issue 18; as was noted in this response, allelic frequencies used in the Hardy-Weinberg calculations described to calculate prevalence rates were derived from analysis of large genomic databases, and such analysis is confidential to Alexion and beyond the scope of Alexion’s submission to NICE. Further, the prevalence rates calculated were provided to the ERG, so were available for the ERG to perform sensitivity analyses upon, as the ERG did in its report.

Additionally, the ERG states that the 100% mortality rate for BSC-treated patients in their first year of life was not incorporated into the model, contrary to the description in our initial submission. This is factually inaccurate. As reflected in cells W10:AA31 of the “Patient Calcs” sheet in the budget impact model, the 100% mortality rate was included in the main calculations of the number of prevalent BSC-treated patients progressing through the model, as described in Alexion’s initial submission. The ERG incorporates this rate in an additional calculation relating to non-drug medical costs, which while



appropriate, makes minimal difference to results of the model (yielding a -0.3% change in budget impact in Alexion's base case modified to use the 20 mg vial in all five years).

The third bullet point should also be corrected as follows: "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 paroxysmal nocturnal haemoglobinuria." Please note that proportion of patients with LAL Deficiency treated with sebelipase alfa amounting to ■■■ of the proportional of PNH patients treated with eculizumab is commercial in confidence.

Finally, while Alexion acknowledges that the 5mg vial of sebelipase alfa is not yet available, clinical experts have expressed that they intend to administer required dosing of sebelipase alfa as efficiently as possible, which will be facilitated by the availability of the 5mg vial. Alexion would therefore suggest that consideration be given to the potential impact of the 5mg vial on the value for money of sebelipase alfa, specifically as a sensitivity analysis in the budget-impact analysis.

Section 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."

Alexion Response:

The summary above is incorrect. The ERG's suggested change to the application of infant mortality and use of recalculated non-drug costs yields a *decrease* in the total net budget impact from £53,548,573 (averaging £10.7M annually) in Alexion's base case to £53,372,077 (averaging £10.7M annually), a -0.33% change rather than an *increase* as this section suggests. This is described specifically in Issue 17 of Alexion's fact-check of the ERG's report, submitted to NICE: "The ERG should clarify its suggested changes,



and the impact of these on budget impact, by (1) specifying where additional incorporation of the 100% BSC mortality rate is required beyond its incorporation in the original model and (2) that the ERG proposes non-drug direct medical costs based on a patient's first five years of life (including the half-cycle starting the CCA model) rather than a patient's first full five years of life (excluding the half-cycle starting the CCA model), and that these changes collectively yield a -0.33% change in net budget impact (£53,548,573, as reported in the CS, to £53,372,077)."

The change of material importance suggested by the ERG is to assume use of a 20 mg vial for all of the five-year period of the BIM, rather than use of a 5 mg vial in years 2-5. This change, when implemented *alone* in Alexion's initial analysis, yields total net budget impact of £63,866,314 (averaging £12.8M annually). Implementing the two changes above, in addition to the use of the 20 mg vial in all years of the BIM, yields a total net budget impact of £63,689,818 (averaging £12.7M annually).

In addition, the ERG's proposed adjustments to diagnosis, treatment, continuation, and compliance rates are based on arbitrary assumptions and conflict with real-world evidence regarding continuation and compliance rates. The adjustments that the ERG considers "most plausible" are determined on the basis that they yield a proportion of LAL Deficiency patients treated with sebelipase alfa in year 5 that is similar to the proportion of PNH patients treated with eculizumab, another ultra-orphan drug, in year 7. The assumption that the two diseases would have a similar proportion of patients treated at different timepoints is arbitrary. Further, the ERG assumes that diagnosis and treatment rates should be adjusted in order to align with eculizumab for PNH (although this arbitrarily assumes similarity between the diseases), but proposes continuation and compliance rates inconsistent with eculizumab for PNH, when these rates are arguably more likely to be similar across the diseases (given that both sebelipase alfa and eculizumab have limited adverse-event profiles, and are delivered via the same route of administration - IV infusion). As such the ERG's proposed adjustments yielding five-year net budget impact of £178,527,667 (averaging £35.7M annually) lack a credible basis. It therefore comes as little surprise that, as is addressed in Sections 5.10 and 5.11, the ERG's adjustments are viewed by clinical experts in LAL deficiency as yielding significant overestimates of the number of patients expected to be treated.

UK clinical experts do not expect to treat █% of prevalent LAL Deficiency patients with sebelipase alfa within 5 years and recently advised Alexion that they would expect less than █% of total prevalent patients to be treated by year 5 (see response to Section 5.10).

Alexion Comments on Section 5 of First ECD – Consideration of the Evidence (Sections 5.1-5.21)

Nature of the Condition (Sections 5.1-5.3)



Section 5

“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.”

Alexion Response:

As noted in the comments below, Alexion disagrees that the Committee considered all of the clinical evidence available for use of sebelipase alfa in patients of all ages with LAL Deficiency.

Section 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.”

Alexion Response:

Alexion has submitted with this response a draft Managed Access Agreement (MAA) (see Attachment A) that describes the severe symptoms of LAL Deficiency in patients of all ages that should indicate routine commissioning of ERT with sebelipase alfa. These objective criteria have been developed with significant input from clinicians and a patient representative. This approach will enable NICE and NHS England to define clearly those patients at greatest risk from their disease and for whom treatment with sebelipase alfa is likely to offer the greatest benefit and the best value for money to the NHS in England. Alexion is keen to discuss this proposal with NICE and is confident



that an agreement can be reached to enable access to treatment for patients facing a bleak future without sebelipase alfa.

Section 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.”

Alexion Response:

It is difficult to conclude whether the patients giving evidence to NICE are individuals with “typical” or “more severe” disease as these are terms without real relevance in ultra-rare disease where patient numbers are very small. Progressive liver disease with lipid accumulation is the most common insidious sign of LAL Deficiency uncovered during clinical assessment. Additionally, on further investigation it is evident that patients have more than one organ system involved. All of the patients/carers who took the time to participate in the NICE HST process were able to describe improvements in their or their child’s signs and symptoms following treatment with sebelipase alfa and so all represent patients who could significantly benefit from sebelipase alfa if it were available in England.

Section 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.”

Alexion Response:

As noted in our response to Section 5.1 above, Alexion has included a proposed MAA (Attachment A) that describes the severe symptoms of LAL Deficiency in patients of all ages who are missing this vital enzyme and should receive routine commissioning of sebelipase alfa.

Impact of the New Technology (Sections 5.4-5.8)

Section 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.”

Alexion Response:

NICE has not fully recognised the significant clinical benefits experienced by the patients who have contributed to the ECD decision, and the innovation that sebelipase alfa represents in LAL Deficiency, and must now engage with all stakeholders who are willing to work to develop a framework for England to provide this effective new treatment to the very small number of patients affected by LAL Deficiency in England.

Section 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.”

Alexion Response:

A baby presenting before 6 months with rapidly progressive LAL Deficiency represents a medical emergency and a very challenging clinical situation even for experienced healthcare teams. We are fortunate to have the world-leading centre-of-excellence in caring for these babies in England at Manchester Children’s Hospital. At the time of data cut-off for survival analysis, 26 January 2016, 5 of the 5 patients had survived beyond 24 months and these data were recently presented at a global congress (Jones et al, *Molecular Genetics and Metabolism* 117 (2016) S63; (11)). Subsequent data review has shown that all 5 patients are still alive and have survived to 36 months of age as of March 1, 2016. These infants had shown improved feeding and growth and continue to meet developmental milestones. These data highlight the significant maintenance effect of continued treatment in these infants and the anticipated ability to restore full life expectancy. The oldest patient is now 5 years and 2 months and is still doing well.

Section 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.”

Alexion Response:

The clinical trial LAL-CL02 was not designed to capture these events (liver fibrosis, cirrhosis, transplant, CV events, or death) as it was not a feasible study design. The significant improvements in lipid parameters observed in LAL-CL02 (the phase 3 trial) and concomitant improvement in liver parameters, illustrate the ability of sebelipase alfa to replace the vital LAL enzyme and re-establish lipid homeostasis metabolism in the patient. In an untreated LAL Deficiency patient, the ongoing accumulation of substrate causes steatosis and initiates the clinical pathway of fibrosis and cirrhosis affecting liver function. Sebelipase alfa hydrolyses the accumulated substrate stopping this pathway and addresses the underlying cause of disease.

Alexion is committed to collecting long-term data on the impact of sebelipase alfa treated patients via the Alexion global LAL Deficiency Registry. Please see response to Section 6.10 for additional information on the registry.

Value for Money (Section 5.11-5.19)

Section 5.11

“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.”

Alexion Response:



Alexion welcomes the Committee's conclusion that the structure of the model is broadly appropriate. As noted in Alexion's initial submission, "According to clinical experts, NAFLD (and its progressive form, NASH) is the best model analogue for LAL Deficiency. [...] These diseases provide insights into prediction of liver disease progression in LAL Deficiency as there are some commonalities in the progression from fibrosis to CC to HCC or liver transplant." While there may be variability in liver disease progression in LAL Deficiency versus NASH/NAFLD, Alexion relied upon the most appropriate analogue model structure, based on expert opinion.

Section 5.12

"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."

Alexion Response:

While Alexion agrees with the Committee's conclusion that contrary to the ERG's suggestion, sebelipase alfa has a treatment effect, we are concerned that this significantly understates the clinical efficacy of the treatment. Alexion's initial submission included data submitted to the European Medicines Agency (EMA) for marketing authorisation, on the basis of which EMA approved sebelipase alfa for "long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency" (Kanuma SmPC, 2015; (12)). The marketing authorisation for sebelipase alfa was reviewed and approved by clinical experts with experience with lysosomal storage disorders and liver disease, who found the clinical data to provide evidence of long-term benefit for patients with LAL Deficiency. Alexion's initial submission included these same data, illustrating the key clinical endpoints (ATL, LDL-C, and liver fat content reduction) that have significant clinical relevance to the impact of sebelipase alfa in the treatment of LAL Deficiency. These data were deemed



appropriate for regulatory review and represent the longest term data (for both untreated and treated patients) available globally for this ultra-rare disease.

The complexity and rarity of a disease like LAL Deficiency precludes a traditional outcomes-based clinical trial design. The study size and duration for the sebelipase alfa clinical trials, which were discussed and agreed to with EMA and the US Food and Drug Administration (FDA), align with addressing the root cause of the disease, the rarity of the disease, and the rate of disease progression. The extreme rarity of LAL Deficiency precludes performing studies of the size and duration that would be required to directly assess the impact of sebelipase alfa on clinical events associated with progressive liver disease (e.g., decompensated cirrhosis or liver-related mortality). As stated in Alexion's initial submission (p. 174), "The epidemiologic gold standard for staging liver fibrosis is biopsy, but due to small numbers of patients, it is not possible to estimate transition probabilities from biopsy data. In infants, biopsy is not performed owing to risk to the infant's tenuous health status. In LAL-CL02, biopsies were collected in fewer than half of the patients. Biopsy required consent for paediatric patients, thus the sample in which biopsies are available is non-random. Furthermore, repeat biopsies are required to assess progress or regress. This resulted in a potentially unrepresentative set of only 10 placebo patients and 16 sebelipase alfa patients with repeat biopsies in the double-blind phase of LAL-CL02."

NICE's *Interim Process and Methods of the Highly Specialised Technologies Programme* document notes (p. 8) that, with respect to ultra-orphan drugs, it is necessary to "recognise the particular circumstances of these very rare conditions" which may include the limited "nature and extent of the evidence". While all efforts possible were made to include available evidence from the sebelipase alfa clinical trials in the parametrization of the cost-consequence analysis, the uncertainty in long-term live-disease progression is unavoidable, given the nature of the trials, which per NICE's guidelines, should not preclude an ultra-orphan drug from equal consideration for a positive recommendation.

Alexion has proposed both a PAS and an MAA in order to help address the uncertainties that exist in the evidence base, and to ensure that sebelipase alfa can provide good value for money for the NHS in treating patients with this severe and progressive disease that is associated with early mortality and where there is such urgent need for the first licensed treatment.

Section 5.13

"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 5.12). 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.”

Alexion Response:

The conclusion reached above that utility values from Crossan et al. (2) are most appropriate appears to be based on a misunderstanding of the ERG’s proposed adjustments to the utility values used in the cost-consequence model. Further, the combination of the health-utility cap function that the ERG proposes and the Crossan et al. (2) health utilities conflicts with clinical characterization of the disease, and generally appears internally inconsistent.

The ERG proposed two adjustments to the treatment of health utility values in the model: (1) a cap on health utility at the level of the age-matched general UK population and (2) use of health utility values from Crossan et al. (2) rather than from Mahady et al. These adjustments are independent; that is, the conclusion that LAL deficiency patients should not experience health utility higher than the age-matched general UK population does not imply that health utility values for liver-disease health states from Crossan et al. (2) are more appropriate than those from Mahady et al. (14) However, in the statement that NICE “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,” it seems that both adjustments are accepted, although only the first is justified on the basis of it being “unlikely that people with LAL deficiency experienced a better quality of life than age-matched people without a chronic condition”.



This misunderstanding has significant impact on results of the cost-consequence analysis. In Alexion's base case, incremental QALYs associated with sebelipase-alfa treatment vs. best supportive care were estimated at 20.48. Application of the cap on health-utility values at the level of the age-matched general UK population yields incremental QALYs of 18.76. If Crossan et al. (2) health-utility values are used in addition to the cap, incremental QALYs fall to 14.75.

It should be noted that, per the ERG's implementation of the health-utility cap at the level of the age-matched general UK population, use of Crossan et al. (2) health utility values appears to lead to internal inconsistency. The ERG's cap function predicts health utility of 0.66 for a 100-year-old in the general UK population. In the Crossan et al. (2) health-utility values, 0.66 is the highest value (associated with the "LAL-D without CC, DCC, or HCC" health state). In effect, assuming that the ERG's cap function is parametrized correctly, the ERG implies that no patient of any age with LAL Deficiency has health utility higher than a 100-year-old in the general population. Considering that symptoms of LAL Deficiency are minimally pronounced in the "LAL-D without CC, DCC, or HCC" health state, this seems highly implausible.

Therefore, in the absence of additional explanation of the appropriateness of using Crossan et al. (2) health-utility values rather than those from Mahady et al. (14), Alexion believes NICE's preferred modelling assumptions using in Section 5.17 should be revised.

Section 5.14

"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.”

Alexion Response:

Alexion acknowledges that there is uncertainty around if and when biosimilar competition might occur, although we do not agree with the assumption that there will be no price erosion over time, and believe that amongst the sources of uncertainty that the Committee considers, such price erosion should reasonably be considered based on published evidence. Such evidence includes:

- Table 1 of Mulcahy et al. (2014) (17), which presents various estimates of the price reduction for biologics occurring due to biosimilar entry in the U.S. Amongst these, the US Congressional Budget Office (2008) (18) estimate, which is for all biologics, indicates price erosion of "20-40%" which varies by product and increases over time.
- Prices for biosimilar infliximab have suggested price reductions of 45-72% vs the originator product.(Generics and Biosimilars Initiative (2015) (5))
- In the US, estimates of cost savings from biosimilars range from 12-51%.(Mulcahy et al. (2014) (17))

While Alexion acknowledges that the 5mg vial of sebelipase alfa is not yet available, clinical experts have expressed that they intend to administer required dosing of sebelipase alfa as efficiently as possible, which will be facilitated by the availability of the 5mg vial. Alexion would therefore suggest that consideration be given to the potential impact of the 5mg vial on the value for money of sebelipase alfa, specifically as a sensitivity analysis in the budget-impact analysis.

Section 5.16

“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.”

Alexion Response:

Using the copy of the ERG’s CCA model received on December 16, 2015 (entitled “Appendix 6 - CCA of Treatment with Sebelipase Alfa for LALD_v2_ERG base case.xlsm”), Alexion attempted to replicate the ERG’s calculation of the results reported above, using the Committee’s preferred modelling assumptions. The individual impact of the Committee’s five preferred changes from Alexion’s original analysis are presented in the table below.

Changes (cumulative down rows)		QALYs			Incr. Costs
		SA	BSC	Incr.	
-	Alexion's base case cost-consequence analysis	39.7	19.2	20.5	£ [REDACTED]
[1]	Removing the company’s assumed price reduction of sebelipase alfa at 10 years	19.2	39.7	20.5	£ [REDACTED]
[2]	Continued use of the 20 mg vial after the first year of the model	19.2	39.7	20.5	£ [REDACTED]
[3]	Including the ERG’s cap on health-related quality of life to the general UK population level	19.0	37.7	18.8	£ [REDACTED]
[4]	Use of the ERG’s preferred utility values	13.7	28.5	14.7	£ [REDACTED]
[5]	Use of a 3.5% discount rate applied to costs and health benefits.	10.0	17.2	7.2	£ [REDACTED]

Of note, Alexion calculated 17.22 QALYs for sebelipase alfa and 10.02 for best supportive care, yielding 7.20 incremental QALYs associated with the use of sebelipase alfa vs. best supportive care. It is unclear what difference exists between the ERG’s calculation and Alexion’s.

As detailed in the response to Section 5.16 above, Alexion believes that use of 1.5% as the annual discount rate (on costs and benefits) is appropriate for the evaluation of sebelipase alfa rather than the 3.5% used by the Committee. Per row [4] in the table above, setting the discount rate to 1.5% rather than 3.5%, but otherwise accepting the Committee’s preferred modelling assumptions, increases incremental QALYs from 7.2 to 14.7. Further, per the response to Section 5.14 above, in the absence of additional explanation of the appropriateness of using Crossan et al. (2) health-utility values rather than those from Mahady et al. (14), Alexion does not see a sound basis for the use of health-utility values from Crossan et al. In the table above, row [3] reflects that, when only accepting the ERG’s health-utility capping function amongst QALY-related changes



to assumptions preferred by the Committee (i.e., those other than removal of the 30% price reduction at 10 years and the use of the 5mg vial), the incremental QALY gain is 18.8. Alexion believes that justification has been provided for using the 1.5% discount rate and Mahady et al. (14) health-utility values (rather than those from Crossan et al. (2)), and as such, that the appropriate incremental QALY gain to consider is 18.8.

Section 5.17

“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.”

Alexion Response:

In making its decision the Committee highlighted the relative costs and QALY gains of highly specialised technologies previously evaluated by NICE. In particular, the committee draws a comparison with elosulfase alfa and suggests that sebelipase alfa does not provide the same level of health gain and is more costly. Alexion contests this assessment.

The cost of sebelipase alfa is comparable with elosulfase alfa; indeed, based on the manufacturer estimates, the budget impact of sebelipase alfa is expected to be lower than for elosulfase alfa (£15m vs £29m in Year 5).

The QALY gains are also similar. Using estimates from the manufacturer submissions gives a gain of 20.5 QALYs for sebelipase alfa vs 18.18 QALYs for elosulfase alfa. NICE highlighted that using the Committee’s preferred assumptions the QALY gain for sebelipase alfa is 6.64 QALYs, whereas the comparable figure for elosulfase alfa was 10.03. However, it is very important to recognise that the difference between the NICE estimates for the two products is accounted for almost entirely by the fact that NICE applied a 1.5% discount rate on QALY gains for elosulfase alfa, but a 3.5% discount rate for sebelipase alfa. As stated in Section 5.16, Alexion believes that the decision to apply different discounts rates between these two products is unreasonable in light of the evidence and in doing so, NICE has failed to act fairly. Further, as detailed in Section 5.14, the justification that NICE provides for relying on the ERG’s preferred health-utility values (from Crossan et al. (2)) only justifies the use of a health-utility capping function, not the use of Crossan et al. (2) values. Importantly, if the capping function and Crossan et al. (2) utility values are used, the implication is the highly implausible fact that no patient in the model, regardless of age or degree of fibrosis (or lack thereof), could have health utility higher than a 100-year-old in the general population. Correcting these two assumptions amongst those preferred by NICE yields incremental QALYs of 18.8, substantially higher than those calculated by the ERG in review of elosulfase alfa.

If equal discount rates of 1.5% are appropriately applied to both products, then the magnitude of health gain is very similar (both for NICE estimates and manufacturers) and the total budget impact for sebelipase alfa is likely to be comparable, if not lower. If plausible health-utility values are used (and capped at the age-matched general



population level), the health gain is much higher for sebelipase alfa. Furthermore, Alexion has proposed a managed access agreement – as did BioMarin – that will manage the clinical and financial uncertainty about which the Committee has expressed concern. As such, Alexion believes that patients with LAL Deficiency should have the same access to sebelipase alfa as patients with MPS IVa have to elosulfase alfa.

Section 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.”

Alexion Response:

No comments.

Impact of the Technology Beyond Direct Health Benefits and on the Delivery of the Specialised Services (Section 5.20)

Section 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.”

Alexion Response:



In patients with rapidly progressing infantile LAL Deficiency, the societal impact of the disease—and societal benefit of sebelipase alfa—is likely to be qualitatively greater than for most highly specialised technologies (HSTs). The impact on parents' and families' quality of life of experiencing the birth and subsequent death of a child with a terminal disease is extreme. The constant need for hospitalisation and the emotional toil of the situation represent a substantially greater burden on parents' ability to live a normal life, including their ability to participate in the economy, than for other HSTs.

In these infantile patients with rapidly progressing LAL Deficiency, the societal benefit of sebelipase alfa for the patient themselves is also likely to be disproportionately high. Providing patients with the opportunity for a full life, with all that entails, both economically and humanistically, is a benefit of almost unquantifiable magnitude. NICE should therefore recognise that for rapidly progressing infantile LAL Deficiency the societal benefit of sebelipase alfa is substantially greater than for other HSTs.

There is also a tremendous health impact of LAL Deficiency for children and adults. Specifically, the lipid accumulation as a result of LAL Deficiency can lead to liver cirrhosis, liver failure, other systemic complications such as an enlarged spleen, anaemia and blood platelet deficiency and probably atherosclerosis, in addition to frequent abdominal pain, fatigue, diarrhoea, nausea, loss of appetite, itchy skin, and swollen abdomen. Data show that more than 1 organ is affected by LAL Deficiency in approximately 87% of patients and that within 3 years of the beginning of symptoms, approximately 50% of the children and adults with LAL Deficiency progress to liver complications such as fibrosis or cirrhosis, or require a liver transplant. Of those with LAL Deficiency, 50% of deaths occur in those under the age of 21.(1)

The MPS Society's response to the Evaluation Committees second consultation document.

The MPS Society was very disappointed that the Evaluation Committee's second recommendation was to continue to deny patients diagnosed with LAL D access to treatment. This is despite acknowledging the compelling clinical evidence and patient experiences that has been presented throughout this process.

We are aware that further information has been requested from the company in relation to budget impact and cost consequence analysis, as the committee were unable to reach a conclusion on the value for money. (1.1, 1.2) and that the emerging theme throughout the review was the continued reference to the cost of the treatment and the committee's inability to balance treatment effect against the current cost put forward by the company. The Society and some clinicians have raised this with the company and hope that a mutual resolution between all parties will be taken forward.

However, even though this was a large area of concern raised by the committee, it is important not to lose sight of what is in the patient's best interests. Results presented so far clearly show positive outcomes clinically, on burden of disease and on quality of life, which is dramatically improved. It is important to note the position that clinicians are currently in, particularly the paediatricians who have a duty to treat and protect children to prevent where possible the death of that child.

For infants this treatment is lifesaving and most children are having a good quality of life and are meeting developmental milestones (sitting, walking, saying their first words, celebrating their first birthday and other birthdays, starting school and riding a bike). Yes, we do not know what the longer term outcomes are for these children but would withholding treatment be a breach of an individual's right to life and in the case of children could this be seen as neglect? As adults and professionals responsible for the wellbeing of all children surely the welfare and best interests of a child should be our first concern. We understand that a duty to treat is not absolute but if a treatment gives a positive outcome, is not burdensome and is beneficial to a patient, should a right to life be denied? Davis 1994 concluded "unless the child is in the process of dying, continued survival is always on balance a benefit to the child, so that if treatment is not burdensome it should always be given" (quoted by Sarah Elliston 2007; The best interests of the child in Healthcare)

The committee has acknowledged that in clinical practice, most clinicians would want to treat all diagnosed infants and that the treatment of the late onset population would be based on clinical assessment. It is recognised that not all late onset patients would require treatment straight away if at all. Following a request from NICE the company have set up a MAA working group of Specialist Clinicians, Hepatologists, The MPS Society and NHS England to draft a set of guidelines to set out the start, stop and monitoring criteria for the assessment and treatment of all eligible patients. It is my understanding that the company are submitting this as part of their submission.

A further concern that has been raised by the committee throughout this process is the potential number of unidentified patients that could be diagnosed with LAL D. The MPS Society has tried to evaluate the numbers of patients across England and the evaluation of our findings are attached.

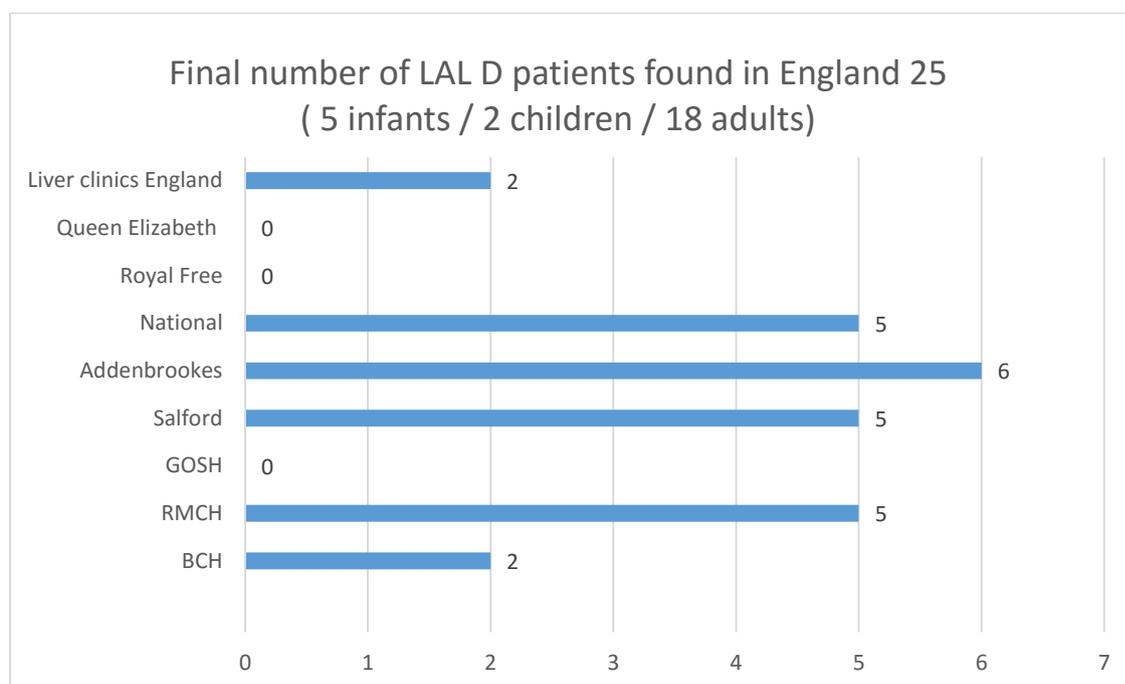
Review of the incidence of LAL D across England.

The MPS Society has contacted the 8 specialist centres to ascertain exact number of patients with LAL D known throughout England. In addition to this we contacted 19 specialist liver centres across England (identified by either known shared care cases or centres listed on the British Liver foundation website) to try to establish other known patients across England.

Unfortunately despite repeated attempts to make contact, we only heard back from 9 of the 19 centres contacted. Out of these 9 centres, 6 had known LAL D patients (2 of the remaining centres had not heard of LAL D before my contact). All but 2 of these patients appear to be shared care with one of the specialist centres.

Below is a table outlining the estimated numbers of LAL D patients in England. Any overseas treated patients through the clinical trial have been excluded. Since the last ECD, a further infant has been diagnosed and is being enrolled on the clinical trial. This child has been included in the table below.

Table 1; Estimated known LAL D patients in England (MPS Society May 2016)



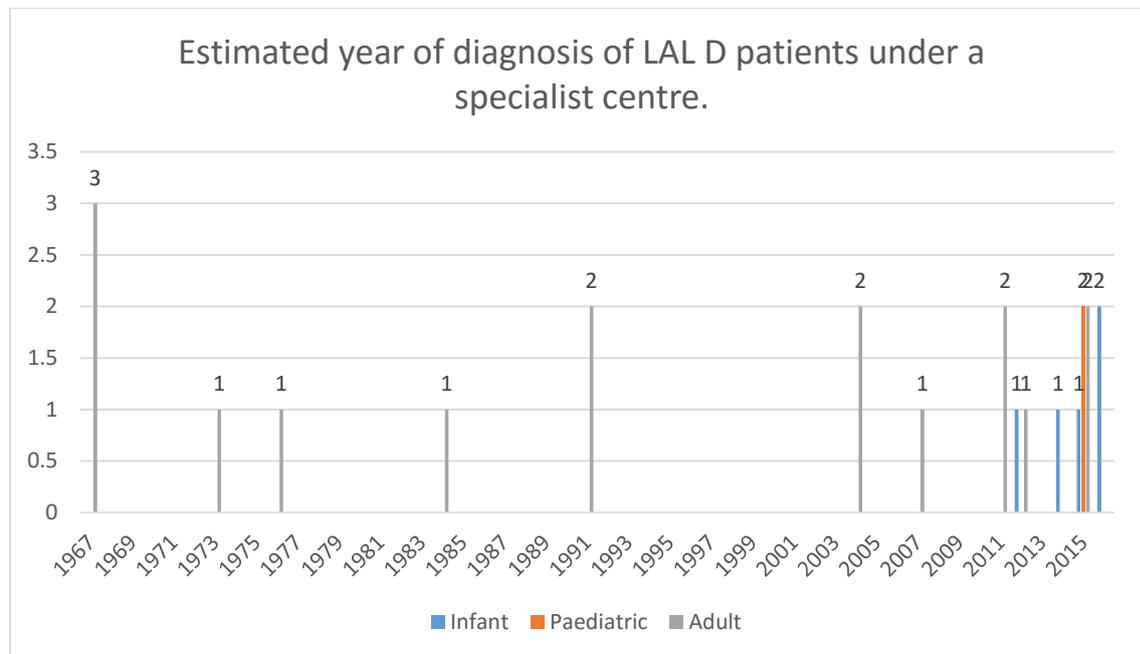
From our analysis there are currently;

- 7 children (5 infants and 2 children) under the care of the specialist paediatric centres.
- 16 adults under the care of the specialist adult centres.
- 2 adults under the care of a liver unit and not shared with any adult specialist centre.

In total 25 confirmed LAL D patients have been found across England.

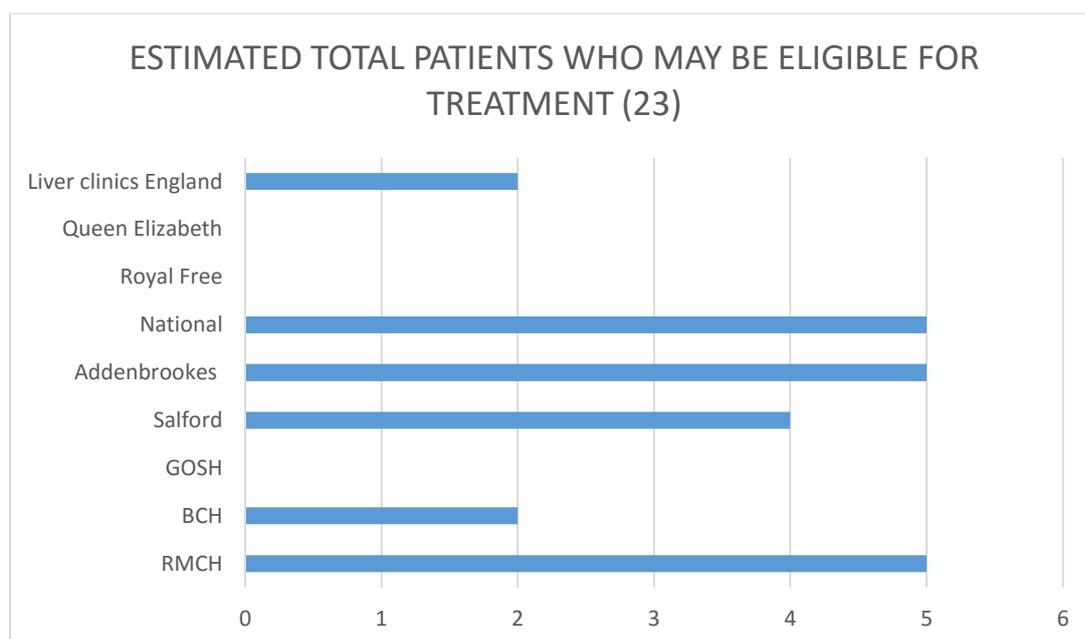
From the information shared from the specialist centres we have been able to chart the estimated diagnosis rate of patients with LAL D (please see table below). As you can see the incidence of LAL D is very low. A further example of this condition being one of the ultra-rare diseases.

Table 2 Estimated year of diagnosis for LAL D patients across specialist centres in England (MPS Society, May 2016).



Out of the 25 identified patients, The MPS Society has estimated that approximately 23 patients may be eligible for treatment (please see table below).

Table 3. Estimated patients who are or may be eligible for treatment (MPS Society; May 2016)



*However it is important to note the following;

- One of the infant patients has just undergone an HSCT, so long term use of the treatment may not be required.
- One of the adult patients is only on treatment compassionately until a suitable liver is found for transplant.
- Some of the adult specialist centres have indicated that some patients may not be eligible for treatment. These are not patients who have been transplanted so the MPS Society felt that we could not exclude them from our analysis.

It is therefore accepted that the Society's estimated numbers could be further reduced based on eligibility and patient compliance as referred to in the draft MAA.

In conclusion

Given the low incidence of LAL D patients found across England and looking at the rate of diagnosed cases over 40 years, patient numbers are relatively low in comparison to other rare diseases. Even for the infant population it is estimated between 1-3 cases per year would be identified, which falls in with recent identified cases.

Reported by

Sophie Thomas

Advocacy Support Team Manager

The MPS Society

References

Sarah Elliston; 2007, The best interests of the child in healthcare; Oxon; Routledge & Cavendish.

Dear Dr Jackson,

Regarding the 2nd ECD for Sebelipase (April 2016), I provide our response for the consultation. As clinicians and HCPs treating infants with the severe form of LALD and having older children with late onset disease not on therapy, we are very disappointed by the April ECD which gave a negative recommendation for Sebelipase. In the document you state 'Sebelipase alfa is a potentially life-saving treatment for babies with rapidly progressive LAL deficiency, and there is a compelling clinical need.' The main reason given for not funding this is cost of the drug.

We understand that discussions on the cost of this and other drugs in this situation cannot be held directly with NICE – and so I am not sure of the point of this process continuing with clinical and Patient involvement.

We have continued to provide input into the development of the draft MAA, and hope that at the June meeting we can have further discussion about how this may work. This should be a process aimed however at improving patient outcomes rather than reduction of cost.

I would urge again a formal review of the process for evaluating high cost drugs for rare diseases by NICE.

Regards

Simon

Dr Simon Jones
Consultant in Paediatric Inborn Errors of Metabolism,

Dear Sir /Madam

I was disappointed that NICE continue to deny access to this life saving treatment. I feel as parents we are stuck between Nice and Alexion. I also feel that Alexion were ill prepared and information should have been more transparent.

The Ethics should be that these children need the Medicine and it should be approved.

There is too much politics behind the scenes and I feel both parties need to resolve this as it is dragging on and as parents we could do without this hanging over our heads .

Both parties need to come to a middle ground as they are aware that without this enzyme replacement therapy these kids will not survive.

Kind regards

Amjad Akhtar
Patient Representative

I Stuart Lancaster (Patient expert) wish to respond with the with the following comments to the Evaluation Committee's Preliminary Recommendations regarding Sebalipase Alpa:

I am a patient on the on-going Clinical Trial of Sebalipase Alpa since 2011 & my current trial phase ends March 2017.

I would be absolutely devastated if this treatment were to be no longer made available at the end of my trial purely based on financial costs. The thought of returning to the days of pre-treatment would be dreadful. When I was diagnosed with LAL Deficiency there was no specific treatment so when the Clinical Trial was made available to me it was like a light at the end of a very black tunnel.

My health is stable, I feel extremely well, happy & also feel that I'm improving all the time. **I have had my quality of life returned to me which I had lost prior to treatment.** The thought of a return to my state of health prior to treatment with Sebalipase Alpa would be an unthinkable & devastating prospect, unbearable pain, nausea, unable to eat without nausea alongside the mental & emotional stress of living with a condition like LAL Deficiency. To some these factors up my quality of life would take an enormous downturn.

Having felt the enormous impact physically, emotionally & mentally of receiving Sebalipase Alpa, it would be totally unethical & unkind to withdraw it purely on financial costing. I feel that all persons with this condition should have the right to receive treatment but at the very least myself & other persons that have reaped the benefits of Sebalipase Alpa through Clinical Trials deserve the right to continue being treated.

At present I am very optimistic about my future but if a decision to not fund this treatment was made I would be very fearful & be placed under extreme stress once again as my health would surely deteriorate.

Surely when so much good has been done by Sebalipase Alpa it cannot be undone again by withdrawing it's availability from myself & others.

Dear Sir / Madam

In your response you stated that you were uncertain whether the effects seen in the clinical trials are sufficient compared to the cost of the treatment. I as a parent of a child not receiving treatment fail to see how this is a comparison when the drug has already proven to extend an individual's life expectancy and give a better quality of life to patients currently receiving this treatment through the clinical trial. How can giving these quality's be a waste of funding? how can we at not least try, condemning instead, children to an early grave and allowing suffering through their short lives.

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 specialist from a medical profession have advised myself that if available this treatment would certainly be their recommendation for my sons late onset LAL D. Does clinical opinion not count in Society today?

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.

Kind regards
A concerned parent

**The contents of this document have been
omitted as they are confidential**



in collaboration with:



Maastricht University

ADDENDUM TO:
Sebelipase alfa for treating lysosomal acid lipase deficiency

ERG critique of cost-effectiveness model submitted 25th May 2016

Cost-consequences analyses

The proposed changes, by the company, to the cost-consequences analyses (CCA) are described and accompanied with a response from the ERG in Table B1. In summary, the ERG regarded that the company did not provided any new data nor any new arguments justifying a revision to the ERG base case. Hence, the ERG base case remains unchanged. The updated company's base case (conditional upon the changes in Table B1) and the ERG base case with and without the annual cost cap of ██████ proposed in the PAS are presented Tables B2-B5.

Table B1: Company suggested changes to the CCA and response from the ERG

Company rationale and suggested change	ERG response
<i>A 3.5% discount rate applied to costs and health benefits</i>	
<p>For both treatments for which NICE has previously applied a 1.5% discount rate there is uncertainty around the criteria that is inherent in rare/ultra-rare diseases treatments. It is impossible to know the life-time impact of a drug at the point of marketing approval. The Committee’s decision to apply a 3.5% discount rate to sebelipase alfa and a 1.5% discount rate to elosulfase alfa and eculizumab indicates that the Committee believes that there is a material difference in the situation for sebelipase alfa versus elosulfase alfa and eculizumab that could justify treating these medicines differently.</p> <p>Alexion believes that the evidence provided demonstrates the clinical value of sebelipase alfa, and is consistent with estimates of value for eculizumab for atypical haemolytic uraemic syndrome (aHUS) and for elosulfase alfa for MPS IVa. Alexion asserts that sebelipase alfa therefore meets the criteria for applying the 1.5% discount rate to the same extent as both elosulfase alfa and eculizumab.</p> <p>Suggested change to company base case: Maintain discount rate of 1.5% and add a sensitivity analysis using a 3.5% discount rate (consistent with the ERG approach)..</p>	<p>As described in the ERG report: <i>“The NICE Technology Appraisal Methods Guide specifies that a rate of 1.5% may be considered by the Appraisal Committee if it is highly likely that the long-term benefits will be achieved”</i></p> <p>As mentioned in the response to the factual inaccuracy check, <i>“The appropriate discount rate is for the [appraisal] committee to decide.”</i> Hence, the ERG agrees with the company’s approach that analyses based on both discount rates should be presented (as done in the original ERG report).</p> <p>Change to ERG base case: None</p>
<i>Including the ERG’s adjustment of health-related quality of life to UK population norms</i>	
<p>As stated on page 72 of the ERG’s report, “the ERG implemented a minimum function in the model to ensure the health state utilities in the model would not exceed those of the general population with the same age.” The age/gender-adjusted general-population utility function which the ERG used to limit the health utility of patients in the CCA analysis of patients with LAL Deficiency was therefore based on a sample of patients aged 45-85 with heart disease, which had to be extrapolated backwards (in age) to the considerably younger LAL Deficiency patient population, which suffers from an ultra-rare liver disease where the average age is approximately 11 years. There is therefore considerable uncertainty around the appropriateness of the utility function applied by the ERG to the LAL Deficiency patient population.</p>	<p>As stated in the ERG report: <i>“The health state utility used in the economic model by the company did exceed the UK general population utility scores,8 e.g. in the economic model approximately 90% of the patients are still expected to be alive at age 65 with a utility of 0.92 whereas the UK general population utility for persons aged 65 is expected to be 0.784. Despite requested (clarification question B611), the company did not provide a plausible justification for the seemingly implausible high health state utility nor any scenario analyses using alternative health state utilities (e.g. age dependent utilities). Therefore, the ERG implemented a minimum function in the model to ensure the health state utilities in the model would not exceed those of the general population with the same age.”</i></p> <p>The company is incorrect in stating that this function reflects “patients aged</p>

Company rationale and suggested change	ERG response
<p>Suggested change to company base case: Incorporate the health utility capping function as provided by the ERG (consistent with the ERG base case).</p>	<p><i>45-85 with heart disease</i>". As quoted above from the ERG report, this function reflects the UK general population and ensures that the health state utilities in the model would not exceed those of the general population with the same age. Hence, the ERG regards this approach as appropriate, as also already stressed in the response to the factual inaccuracy check.</p> <p>Change to ERG base case: None</p>
<p><u>ERG's preferred utility values</u></p>	
<p>In proposing the use of Crossan et al. (2015) (2) health utilities, the ERG proposes that the healthiest patient in the sebelipase alfa CCA has health utility of 0.66, which is contrary to the data in the Alexion trials and those for the general UK population.</p> <p>Alexion demonstrated that the patients in the LAL-CL02 ARISE trial had quality of life that was no different than a general background patient population, so the use of the ERG's health-utility estimates is highly inconsistent with their own health-utility capping function, and therefore the general population.</p>	<p>As stated in the ERG report: <i>"It was unclear why the utilities from Mahady et al were considered most appropriate [by the company]. Additionally, it was unclear how the health state utilities were calculated if multiple sources are reported by Mahady et al, as was the case for all but one health state utility. To salvage this issue, the ERG used the health state utilities as reported by Crossan et al. These health state utilities were measured using the EQ-5D for hepatitis C patients and in part measured in the UK. Here it is assumed that the utilities for the different health states would be similar for different liver diseases irrespective of the initial cause. Please note that this latter assumption is also applicable to the health state utilities reported by Mahady et al as these were primarily retrieved from hepatitis C populations."</i></p> <p>Moreover, the company's suggestions that the <i>"Committee's acceptance of the ERG's health-utility estimates is motivated by desire for consistency with the age-matched general population"</i> seem to be based on a <u>misinterpretation of the ECD</u>. In the 2nd ECD it is stated that: <i>"the true utility 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."</i></p> <p>The company implies that health state utility data are available in the following quotes: <i>"health utility of 0.66, which is contrary to the data in the Alexion trials"</i> and <i>"Alexion demonstrated that the patients in the LAL-CL02 ARISE trial had quality of life that was no different than a general background patient population"</i>. The ERG did however not receive any data supporting these</p>

Company rationale and suggested change	ERG response
<p>Suggested change to company base case: None, use of company's original health-utility values is maintained.</p>	<p>statements from the company. The ERG would, however, welcome utility data from the company's trials given the lack of utility data from people with LAL deficiency.</p> <p>Change to ERG base case: None</p>
<p><u><i>The company's inclusion of a treatment effect for sebelipase alfa in its transition probabilities</i></u></p>	
<p>As stated in Section 5.12 of the second ECD: "The committee considered that the evidence from the trials and from the patient experts showed that sebelipase alfa has a treatment effect, and the ERG scenario was not plausible... 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."</p>	<p>The ERG agrees with the notion from the 2nd ECD that the ERG base case is "extremely conservative" (section 5.12). However, as noted by the AC this follows from the ERG's view (see section 5.3.3.5 of the ERG report for more details):</p> <p><i>"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"</i></p> <p>Moreover, the AC <i>"equally considered there were no data to validate the company's assumption that sebelipase alfa would stop further disease progression."</i></p> <p>The ERG maintains its view that there is no evidence to link the results from the clinical trials to improvement in liver disease progression and as stated in the ERG report:</p> <p><i>"the ERG did not find any plausible justifications to use different sources and assumptions for the probabilities to develop "CC", "DCC" and "HCC" nor for the probability to transit back "LALD without CC, DCC or HCC" (from "CC")"</i></p> <p>The ERG believes, it is the company's responsibility to provide plausible assumptions and/or arguments to support a treatment benefit. In the current assessment this is not provided and the ERG consequently does not have any other option than (unwillingly) make the conservative assumption of no treatment benefit. Although the ERG could not find any plausible method to model the potential treatment benefit, the ERG agrees with the AC that the approach the ERG inevitably uses, is extremely conservative. Therefore, the ERG explored (in the exploratory analyses of the ERG report; Table 6.2) the impact of assuming a treatment benefit using a hazard ratio of 0.5.</p> <p>Explorative scenario 1: <i>"Exploring the benefit of sebelipase alfa if for sebelipase alfa 1) the transition probability from "LALD without CC, DCC, or HCC" to "CC" would be reduced by 50% and; 2) the transition probability from</i></p>

Company rationale and suggested change	ERG response
	<i>“CC” to “LALD without CC, DCC, or HCC” would be increased by 50%”</i>
<p>Suggested change to company base case: None, transition probabilities from the company’s original analysis are used.</p>	<p>Change to ERG base case: None, an explorative scenario analysis was presented in the original ERG to explore the impact of assuming a treatment benefit using a hazard ratio of 0.5.</p>
<p><u><i>Removing the company’s assumed price reduction of sebelipase alfa at 10 years</i></u></p>	
<p>It is impossible for Alexion to prove that the price of sebelipase alfa will decrease after the loss of data exclusivity and the introduction of biosimilar competition, as these events are in the future. However, Alexion believes that on the strength of historical precedent, the likelihood of this scenario being realised is high, much more so than NICE’s implicit proposition that the cost of sebelipase alfa will be maintained at its current level over the next 50 years.</p> <p>The price of all pharmaceutical products in the UK has always declined over time. Price increases are almost never permitted in the UK, and price erosion occurs through competitive pressure, including the introduction of generics or biosimilars, through regional or national procurement exercises, or through mandatory price reductions.</p> <p>While the exact impact that these potential developments will have on sebelipase alfa is unknowable, the 30% estimate used by Alexion in its modelling is a credible estimate and an appropriate base case assumption for the price change.</p>	<p>As stated in the ERG report: <i>“After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price, a generic version of the drug would enter the market.”</i></p>
<p>Suggested change to company base case: The 30% price reduction due to loss of exclusivity at 10 years is modelled.</p>	<p>Change to ERG base case: None</p>
<p><u><i>Continued use of a 20 mg vial</i></u></p>	
<p>While Alexion acknowledges that the 5mg vial of sebelipase alfa is not yet available, clinical experts have expressed that they intend to administer required dosing of sebelipase alfa as efficiently as possible, which will be facilitated by the availability of the 5mg vial in the near future. Alexion would therefore suggest that the Committee give consideration to the potential</p>	<p>As stated in the ERG report: <i>“The ERG thinks the 5 mg vials of sebelipase alfa should not be incorporated in the cost-consequences analysis because these are not yet available.”</i></p>

Company rationale and suggested change	ERG response
impact of availability of the 5mg vial on the value for money of sebelipase alfa.	
Suggested change to company base case: Assume that only the 20mg vial is available (consistent with the ERG base case).	Change to ERG base case: None

Table B2: CCA results (deterministic)^{a,b}

Company base case using a 1.5% discount rate		
	Costs	QALYs
BSC	£46,748	18.97
SA	████████	37.73
Increment	████████	18.76
Company base case using a 3.5% discount rate		
	Costs	QALYs
BSC	£32,560	13.93
SA	████████	23.33
Increment	████████	9.40
ERG base case using a 1.5% discount rate		
	Costs	QALYs
BSC	£44,744	19.38
SA	████████	19.38
Increment	████████	0.00
ERG base case using a 3.5% discount rate		
	Costs	QALYs
BSC	£29,166	12.93
SA	████████	12.93
Increment	████████	0.00
Exploratory analysis conditional on ERG base case using a 1.5% discount rate and assuming a treatment benefit using a hazard ratio of 0.5 (see description of scenario 8; section 6.1 of the original ERG report for more details)		
	Costs	QALYs
BSC	£44,744	19.38
SA	████████	20.91
Increment	████████	1.53
Exploratory analysis conditional on ERG base case using a 3.5% discount rate and assuming a treatment benefit using a hazard ratio of 0.5 (see description of scenario 8; section 6.1 of the original ERG report for more details)		
	Costs	QALYs
BSC	£29,166	12.93
SA	████████	13.70
Increment	████████	0.77

^aFor comparability with the results reported by the company, the deterministic analyses are presented. See original ERG report (Table 6.1) for the probabilistic results of the ERG base case.

^bThe base case was based on a cohort aged 11 years of whom 84% had no cirrhosis and 16% did have cirrhosis at baseline (infant scenario is presented separately).

Table B3: CCA results for infant subgroup (deterministic)^{a,b}

Company infant scenario using a 1.5% discount rate		
	Costs	QALYs
BSC	£52,112	0.04
SA	████████	27.47
Increment	████████	27.44
Company infant scenario using a 3.5% discount rate		
	Costs	QALYs
BSC	£52,112	0.04
SA	████████	16.17
Increment	████████	16.13
ERG infant scenario using a 1.5% discount rate ^c		
	Costs	QALYs

BSC	£52,422	0.14
SA	██████████	13.92
Increment	██████████	13.78
ERG infant scenario using a 3.5% discount rate ^c		
	Costs	QALYs
BSC	£52,422	0.14
SA	██████████	9.05
Increment	██████████	8.91

^aFor comparability with the results reported by the company, the deterministic analyses are presented.

^bThe infant scenario was based on a cohort aged 0 years of whom 100% had no cirrhosis at baseline.

^cThis scenario includes the correction of the company's half-cycle correction and assuming alternative utility values (see description of scenarios 6 and 7; section 6.1 of the original ERG report for more details)

Table B4: CCA results with the annual cost cap of ██████████ proposed in the PAS (deterministic)^{a,b}

Company base case using a 1.5% discount rate		
	Costs	QALYs
BSC	£46,748	18.97
SA	██████████	37.73
Increment	██████████	18.76
Company base case using a 3.5% discount rate		
	Costs	QALYs
BSC	£32,560	13.93
SA	██████████	23.33
Increment	██████████	9.40
ERG base case using a 1.5% discount rate		
	Costs	QALYs
BSC	£44,744	19.38
SA	██████████	19.38
Increment	██████████	0.00
ERG base case using a 3.5% discount rate		
	Costs	QALYs
BSC	£29,166	12.93
SA	██████████	12.93
Increment	██████████	0.00
Exploratory analysis conditional on ERG base case using a 1.5% discount rate and assuming a treatment benefit using a hazard ratio of 0.5 (see description of scenario 8; section 6.1 of the original ERG report for more details)		
	Costs	QALYs
BSC	£44,744	19.38
SA	██████████	20.91
Increment	██████████	1.53
Exploratory analysis conditional on ERG base case using a 3.5% discount rate and assuming a treatment benefit using a hazard ratio of 0.5 (see description of scenario 8; section 6.1 of the original ERG report for more details)		
	Costs	QALYs
BSC	£29,166	12.93
SA	██████████	13.70
Increment	██████████	0.77

^aFor comparability with the results reported by the company, the deterministic analyses are presented.

^bThe base case was based on a cohort aged 11 years of whom 84% had no cirrhosis and 16% did have cirrhosis at baseline (infant scenario is presented separately).

Table B5: CCA results for infant subgroup with the annual cost cap of [REDACTED] proposed in the PAS (deterministic)^{a,b}

Company infant scenario using a 1.5% discount rate		
	Costs	QALYs
BSC	£52,112	0.04
SA	[REDACTED]	27.47
Increment	[REDACTED]	27.44
Company infant scenario using a 3.5% discount rate		
	Costs	QALYs
BSC	£52,112	0.04
SA	[REDACTED]	16.17
Increment	[REDACTED]	16.13
ERG infant scenario using a 1.5% discount rate ^c		
	Costs	QALYs
BSC	£52,422	0.14
SA	[REDACTED]	13.92
Increment	[REDACTED]	13.78
ERG infant scenario using a 3.5% discount rate ^c		
	Costs	QALYs
BSC	£52,422	0.14
SA	[REDACTED]	9.05
Increment	[REDACTED]	8.91

^aFor comparability with the results reported by the company, the deterministic analyses are presented.

^bThe infant scenario was based on a cohort aged 0 years of whom 100% had no cirrhosis at baseline.

^cThis scenario includes the correction of the company's half-cycle correction and assuming alternative utility values (see description of scenarios 6 and 7; section 6.1 of the original ERG report for more details)

Budget impact model

Company rationale and suggested change	ERG response
<u>Initial cohort calculation</u>	
<p>In Alexion's previous budget impact model (BIM), the initial cohort of patients was calculated based on diagnosis rates (and treatment rates, to derive treated patients) applied to 1 incident patient in the age 0-1 presentation group and to a prevalent population of 244 individuals in the age 1+ presentation group.</p> <p>Suggested change: The number of known patients in England has been used to represent the number of prevalent patients in the first year of the revised BIM (i.e. █ patients, of which █ are infant patients). All infant are assumed to receive treatment. To determine the number of paediatric/ adult patients receiving treatment in the first year of the revised BIM, the following methodology was used: <i>"Clinicians from metabolic, lysosomal storage disorders (LSDs), and liver units with known patients have been surveyed and asked to review those patients according to the clinical criteria defined in the revised consensus MAA."</i></p>	<p>The company based the number of diagnosed patients in the first year of the budget impact model on a survey of experts from metabolic expert centre and a liver expert centre. However, the methodology to retrieve data from the different centres was not clearly described. The ERG is consequently not able to assess the validity and reliability of the provided estimates.</p> <p>Change to the ERG base case: The ERG agrees with the company's amendments and amended the ERG base case accordingly.</p>
<u>New diagnoses over time</u>	
<p>While the revised BIM starts from an initial cohort of known patients, it continues to account for newly-diagnosed patients over time, some of whom will be eligible for treatment according to the revised consensus MAA.</p> <p>Suggested change: The number of newly-diagnosed patients equals:</p> <ul style="list-style-type: none"> • Age 0-1 presentation: Based on the Meikle (1999) (1) estimate of incidence of LAL Deficiency in infants of 1:704,000. • Age 1+ presentation: In Alexion's original submission, it was estimated that there would be 244 prevalent age 1+ presentation patients in Year 1 and 269 in Year 5 of the BIM. English clinical experts opined that █ would be diagnosed in Year 1 (█ x 244 = █) and █ would be 	<p>In the company's response to the second ECD meeting response, the company explains that eight UK clinical experts have been consulted and that the following diagnosis rates are the most plausible:</p> <ul style="list-style-type: none"> - Diagnosis rates: <ul style="list-style-type: none"> o 0-1 year presentation: █ over 5 years o 1-17 years presentation: █ over 5 years o 18+ years presentation: █ over 5 years <p>The ERG notes that the methodology (e.g. how did the UK clinical experts come to a consensus concerning treatment rates) used to obtain the diagnosis rate estimates is not described in the company's response to the second ECD meeting.</p>

Company rationale and suggested change	ERG response
<p>diagnosed in Year 5 ($\blacksquare \times 269 = \blacksquare$). This implies that diagnosed patients increase by \blacksquare ($(\blacksquare - \blacksquare) / 4 = \blacksquare$) on average in each of the four years after Year 1.</p>	<p>In order to calculate the number of diagnosed patients in the Age 1+ presentation group, the diagnosis rates obtained from the experts survey were applied to the prevalent and incident LAL-D patients as calculated in the company's original BIM. Therefore, the same critique apply to these calculations, i.e. the calculations are still unclear to the ERG, which hampers the possibility to assess the validity of the incidence and prevalence rates (see ERG report, pages 95-96; the ERG tested the influence of varying incidence and prevalence rates on the budget impact, see ERG report, page 102). Because the incident and prevalent patient population is an important element for determining the number of diagnosed patients, the ERG is not able to assess whether the number of diagnosed patients per year is representative of the UK setting. A post-marketing monitoring research is needed in order to obtain more precise estimates of prevalence, incidence and diagnosis rates for the LAL-D patients population because, currently, uncertainty remains around these estimates.</p> <p>The ERG agrees with the number of diagnosed patients in the Age 0-1 presentation group.</p> <p>Change to the ERG base case: The ERG implemented the company's amendments in its base case analysis. Furthermore, the ERG presents sensitivity analyses which illustrate the influence of a bigger or smaller LAL-D patients population on the company's revised BIM. The company's revised BIM is used for these analyses since the ERG agrees with all other amendments of the company, resulting in an ERG base case analysis which is equivalent to the company's revised BIM (the ERG was able to reproduce the company's revised BIM). In these sensitivity analyses, the prevalent population (based on the company's original BIM) is increased or decreased by 50%. Results will be presented without the annual per patient cost cap (Table B8).</p>
<p><u>MAA eligibility of newly-diagnosed patients</u></p>	
<p>The \blacksquare new infantile-presentation \blacksquare will be assumed to be eligible, and $\blacksquare\%$ ($(\blacksquare$ paediatric + \blacksquare adult) / (\blacksquare known patients - \blacksquare infantile presentation) = $\blacksquare / \blacksquare = \blacksquare\%$) or \blacksquare paediatric/adult-</p>	<p>The ERG agrees with the proposed amendments even though a thorough description of the methods used to obtained the treatment rate estimates for the paediatric/adult patient population would have</p>

Company rationale and suggested change	ERG response
<p>presentation [REDACTED] will be assumed eligible (using the same proportion for eligibility in the future as that amongst the current known cohort of [REDACTED] children/adults).</p> <p>Suggested change: The treatment rate for the Age 0-1 presentation group (infantile patients) is [REDACTED] and the treatment rate for the Age 1+ presentation group (paediatric and adult patients) is [REDACTED].</p>	<p>been desirable. For example, the company does not provide the number of experts who participated in the survey and whether the experts agreed on which patients should receive treatment based on MAA eligibility criteria. This information would have been useful to investigate whether MAA eligibility criteria will be correctly implemented (and respected) across different metabolic, lysosomal storage disorders (LSDs), and liver units.</p> <p>Change to ERG base case: None for treatment rate of infants. Treatment rate of the paediatric/adult patients will be set at [REDACTED].</p>
<p><u>Treatment continuation and adherence rates</u></p>	
<p>Similar to assumptions around continuation rates, Alexion now assumes that adherence to treatment within the MAA-eligible patient sub-population would likely be higher than the 85% modelled in Alexion's previous analyses of the broader LAL Deficiency population. As such, in accordance with the Committee's request, adherence of 100% is used in the updated budget-impact analysis. However, it should be noted that in long-term clinical practice, adherence of 100% is highly unlikely to occur, and the per-patient annual cost of treatment used in the budget-impact analysis therefore is most likely overestimated.</p> <p>Suggested change: Compliance (adherence) rate is set at 100% in the company's updated budget impact analysis for both presentation groups (infant and paediatric/adult patients)</p>	<p>The ERG agrees with the proposed amendment.</p> <p>Change to ERG base case: None</p>
<p><u>Inclusion of the proposed annual per-patient expenditure cap</u></p>	
<p>Given the significant delays in reviewing the patient access scheme (PAS) submitted by Alexion for consideration, we are working directly with NHSE on the confidential commercial terms outlined in our proposed PAS for sebelipase alfa. However, the risk-sharing arrangement proposed through the imposition of an annual patient expenditure cap remains the same, and we continue to put forth this per patient expenditure limit as a cost</p>	<p>As the PAS does not seem to be finalised yet, the ERG will present ERG base case results with and without applying the annual [REDACTED] cost cap per patients.</p> <p>Change to ERG base case: As for the CCA, the ERG will present BIM results with and without applying the annual [REDACTED] cost cap per patients.</p>

Company rationale and suggested change	ERG response
<p>containment and risk-sharing mechanism for NICE, the Committee, and NHSE to consider in our discussions.</p> <p>Suggested change: An individual annual patient cost cap of [REDACTED] is used in the modelling.</p>	
<i>Other changes</i>	
<p>As summarized in Issue 17 of Alexion’s fact-check of the ERG’s report, the ERG suggested a change to the application of infant mortality and use of recalculated non-drug medical costs, which yielded a combined -0.33% change in five-year cumulative net budget impact. These changes were accepted by Alexion in the revised BIM.</p> <p>In addition, in Years 2-5 of the BIM, the 20 mg vial of sebelipase alfa is used rather than the 5 mg vial, <u>as recommended by the Committee</u>, as the 5 mg vial has not yet been commercialized.</p> <p>Suggested changes: Non-drug medical costs have been recalculated according to the ERG methodology and only 20mg vials are used in the budget impact model.</p>	<p>The ERG agrees with the proposed amendments.</p> <p>Change to ERG base case: None</p>

Table B6: Net budget impact over five years, without the proposed PAS (company’s revised BIM)

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	£11,696,065	£14,442,041	£17,294,166	£20,865,345	£24,362,493	£88,660,111
SA without market access	£241,868	£149,818	£161,372	£172,926	£184,479	£910,463
Net budget impact	£11,454,197	£14,292,222	£17,132,794	£20,692,419	£24,178,014	£87,749,647

Table B7: Net budget impact over five years, with the proposed PAS(company’s revised BIM)

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	£8,352,725	£10,006,166	£11,885,157	£14,034,278	£16,126,656	£60,404,982
SA without market access	£241,868	£149,818	£161,372	£172,926	£184,479	£910,463

Net budget impact	£8,110,857	£9,856,347	£11,723,785	£13,861,352	£15,942,176	£59,494,518
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Table B8: Sensitivity analyses based Net budget impact over five years, without the proposed PAS (company's revised BIM)

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
Number of prevalent patients decreased by 50%(122 prevalent patient in year 1, ■ in year 5; results in ■ additional patients per year)	£11,454,197	£13,478,035	£15,444,526	£18,070,176	£20,549,854	£78,996,788
Company base case: Net budget impact (244 prevalent patient in year 1, 269 in year 5)	£11,454,197	£14,292,222	£17,132,794	£20,692,419	£24,178,014	£87,749,647
Number of prevalent patients increased by 50%(366 prevalent patient in year 1, ■ in year 5; results in ■ additional patients per year)	£11,454,197	£15,106,410	£18,821,063	£23,314,663	£27,806,174	£96,502,506