NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Sebelipase alfa for treating lysosomal acid lipase deficiency [ID737]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD2)**

2. **Alexion revised proposal**

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Sebelipase alfa for treating lysosomal acid lipase deficiency

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Alexion	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.	Thank you for your comments. The committee considered in detail all of the comments and evidence provided by the company, and the discussions are presented in Section 5 (Consideration of the evidence) of the FED. We draw your attention in particular to sections of the FED noted below, relating to the specific issues raised.
Alexion	• 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 rational 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.	See sections 5.9-5.11 of the FED.

Consultee	Comment	Response
Alexion	• 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.	See sections 5.27-5.30 of the FED.
Alexion	• 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.	Thank you for your comment. None of these issues relate to protected characteristics, as defined by the Equality Act (2010), and therefore are not considered as equality issues.
Alexion	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.	See sections 5.9-5.11 of the FED.

Consultee	Comment	Response
	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: o all babies presenting under 1 year of age o patients presenting aged 1–18 years with dyslipidaemia, elevated liver enzymes or symptoms of malabsorption o 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.	

Consultee	Comment	Response
Alexion	Section 4.34 No comments.	Noted.
Alexion	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 [cost cap] 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.	See sections 5.9-5.11 of the FED.
Alexion	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	See section 5.10 of the FED.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>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."

<u>Alexion Response:</u>
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)

<table>
<tr><td>Age 0-1 yrs</td><td>Age 1-12 yrs</td><td>Age 13-18 yrs</td><td>Age over 18 yrs</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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Source: MPS Society.</td><td></td></tr>
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Consultee	Comment	Response
	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.	

Consultee	Comment	Response
	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.	
Alexion	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.	See section 5.11 of the FED.

Consultee	Comment	Response
	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.	
Alexion	<u>Section 5.24</u> "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	See section 5.9 of the FED.

Consultee	Comment	Response
	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." <u>Alexion Response:</u> 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.	
Alexion	**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. <u>Section 1.1</u> "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."	See sections 1.1-1.3 and 5.27-5.30 of the FED.

Consultee	Comment	Response
	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.”	

Consultee	Comment	Response
	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 [cost cap], which demonstrates the very significant positive cost savings of the proposed [cost cap] 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.	
Alexion	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	See sections 5.13-5.14 of the FED.

Consultee	Comment	Response
	number of patients diagnosed in England in May 2016 is likely to be [redacted] 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. <u>Section 4.32</u> "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 <u>4</u> 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." <u>Alexion Response:</u> 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	

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	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 [redacted], with [redacted] 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:	

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

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	Age: over 18 [redacted] [redacted] [redacted] [redacted] Total [redacted] [redacted] [redacted] [redacted] Furthermore, with assistance from the MPS Society, Alexion has charted the diagnosis dates of the 22 patients ([redacted] paediatric and [redacted] 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 [redacted] infant, [redacted] children, and [redacted] patients with adult-presentation were diagnosed. **Year of diagnosis of patients with LAL deficiency in England (n=[redacted])** *Graph has been presented but not replicated here* Following data sharing between stakeholders, it is apparent that both the number of current diagnosed patients ([redacted]: [redacted] children and [redacted] 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 [redacted] in Year 1 to [redacted] 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. <u>Section 5.9</u> "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	

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	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 [cost cap] 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 [cost cap] [redacted], while the cost for patients with paediatric or adult presentation, requiring the lower dose, would be capped at around [redacted] (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 [cost cap] [redacted] at the recommended dosing of 3mg/kg every week, the	

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	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 [cost cap] 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	

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	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: [redacted] over 5 years 1-17 years presentation: [redacted] over 5 years 18+ years presentation: [redacted] over 5 years Treatment rates: 0-1 year presentation: [redacted] over 5 years 1-17 years presentation: [redacted] over 5 years 18+ years presentation: [redacted] 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	

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	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical-expert opinion	**Diagnosed**	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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.

Alexion	Revised Budget Impact Analysis – Assumptions **Initial cohort:** A cohort of [redacted] current diagnosed patients (made up of [redacted] infantile-presentation, [redacted] children and [redacted] adults) begin the model in Year 1, including [redacted] infantile-presentation eligible for treatment, [redacted] paediatric-presentation patients who are eligible, and [redacted] adult-presentation patients who are eligible ([redacted] patients eligible in total). **New diagnoses over time:** In the following years, there are [redacted] newly-diagnosed infantile-presentation (calculated based on Meikle et al. (1999) and English age 0-1 population) and [redacted] paediatric/adult-presentation diagnosed patients	See sections 5.13-5.14 of the FED.

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	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 [redacted] new infantile-presentation [redacted] will be assumed to be eligible, and [redacted] ([redacted]+[redacted]) / ([redacted]-[redacted]) = [redacted]/[redacted] = [redacted]) or [redacted] paediatric/adult-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). **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 submission	**Diagnosed**	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(2) Clinical-expert opinion	**Diagnosed**	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(3)Revised-MAA eligible	**Diagnosed**	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treated	Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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 [cost cap] and **£37,405,039** with the [cost cap] (also assuming 85% adherence, some treatment discontinuation, and no incident patients)

Based on the cohort model (using [redacted] patients, of which [redacted] infantile-presentation patients were treated and [redacted] paediatric/adult-presentation patients were treated): **£57,022,836** without the [cost cap] and **£41,352,270** with the [cost cap] (also assuming 85% adherence, some treatment discontinuation, and no incident patients)

In the updated model, based on the new data on [redacted] 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 [cost cap] and **£59,494,518** with the [cost cap] (reduction of 32%). These estimates are summarised on an annual level in the tables below.

Net budget impact over five years, without the proposed [cost cap]

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

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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 [cost cap]

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 [redacted], while the updated model assumes [redacted] newly-treated infantile-presentation [redacted] per year and [redacted] newly-treated paediatric/adult-presentation [redacted] per year.

As reflected in the analysis above, the annual expenditure cap per patient of [redacted] 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.

Alexion

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.

<u>Section 5.15</u>

"The committee discussed the most appropriate discount rate used for costs and health effects. The committee

See sections 5.18-5.20 of the FED.

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	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	

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	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	

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	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	

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	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.	

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	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: Treatment restores people who would otherwise die or have a very severely impaired life to full or near full health;	

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
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Analyses are very sensitive to the discount rate used;
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
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.

<table>
<tr><th colspan="2">Criteria</th><th>Elosulfase alfa MPS Iva</th><th>Eculizumab aHUS</th><th>Asfotase alfa HPP</th><th>Sebelipase alfa LAL-D</th></tr>
<tr><td rowspan="3">1. Treatment restores people to full or near full health</td><td>Addresses underlying cause of disease?</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>Demonstrated survival benefit in trial?</td><td>X</td><td>X</td><td>✓*</td><td>✓**</td></tr>
<tr><td>Large modelled lifetime QALY gain?</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>2. Analyses are very sensitive to the discount rate used</td><td>Difference in lifetime QALY gains between 3.5% and 1.5% (manufacturer estimate)</td><td>7.9</td><td>9.5</td><td>10.8</td><td>10.5</td></tr>
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<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
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<tr><td>3. The long-term health benefits are likely to be achieved</td><td>Length of trial follow-up</td><td>72 weeks</td><td>104 weeks</td><td>Studies 002/003 = 84 months

Studies 006/008 – 60 months

Study 09-10 = 24 months</td><td>52 weeks</td></tr>
<tr><td rowspan="2">4. Does not commit the NHS to significant irrecoverable costs.</td><td>Budget impact***</td><td>Approximately £130.8M in committee papers (p. 17)</td><td>£139.9M in original submission</td><td>£77.5M in original submission to £68.6M based on MAA</td><td>£53.5M in original submission to £87,749,647 without the [cost cap] and £59,494,518 with the [cost cap] based on MAA</td></tr>
<tr><td>Proposed MAA limiting decision to specified time period</td><td>✓</td><td>X</td><td>✓</td><td>✓</td></tr>
</table>
* 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.
</td><td></td></tr>
</table>

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	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 [redacted] infantile-onset patients and [redacted] 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 [cost cap].	See section 5.21 of the FED.

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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 [cost cap]

	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 [cost cap]

	Scenario	Weighted avg. based

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	<table><tr><th></th><th>Base case</th><th>Infants (LAL-CL03)</th><th>Paeds/adults (ARISE)</th><th>on MAA-eligible patients</th></tr><tr><td colspan="5">Using 20mg vial in all years</td></tr><tr><td>Incremental costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Incremental QALYs</td><td>10.0</td><td>16.5</td><td>10.6</td><td>12.5</td></tr><tr><td colspan="5">Using 20mg vial in all years, and applying the health-utility capping function</td></tr><tr><td>Incremental costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Incremental QALYs</td><td>9.4</td><td>16.1</td><td>9.9</td><td>11.9</td></tr></table> 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 ([redacted] infantile-presentation, [redacted] 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.	
Alexion	**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 [proposed cost cap] 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	See section 5.22 of the FED.

Consultee	Comment	Response
	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 [cost cap] proposed by Alexion. Before the [cost cap] 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 [cost cap], 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).	
Alexion	**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. <u>Section 5.7</u> “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	Comments noted.

Consultee	Comment	Response
	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."	

Consultee	Comment	Response
	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.	
Alexion	**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	See sections 5.27-5.30 of the FED.

Consultee	Comment	Response
	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.	
MPS Society	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	Thank you for your comments. The committee considered the comments received from the patients and carers on their experiences of living with LAL deficiency, and understood that it has a very large impact on some people with the condition. It considered that sebelipase alfa is potentially life-saving in babies with rapidly progressive disease and that there is an important clinical

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	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.	need for this treatment. The committee recognised that the managed access agreement was developed with patient and clinical experts to define the patients who would benefit the most from sebelipase alfa treatment. However, the committee considered that the benefits of treatment remained uncertain, and the cost of sebelipase alfa was exceptionally high. For further details see sections 5.2, 5.4, 5.5 and sections 5.27-5.30 of the FED.
MPS Society	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 additional 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.	Comment noted. The committee discussed the estimated number of people who would have sebelipase alfa and accepted that the

Consultee	Comment	Response
	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 has been presented but not replicated here.* 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 has been presented but not replicated here.* 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 has been presented but not replicated here.* *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.	number of patients in England included in the company's revised budget impact analysis was likely to be an accurate estimate. It understood that the company's estimate was informed by evidence from the MPS Society.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Willink Unit - Central Manchester University Hospitals NHS Foundation Trust (clinical expert)	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.	Thank you for your comment. The committee discussed the impact on the technology on LAL deficiency and the clinical effectiveness of sebelipase alfa. It considered that sebelipase alfa provided clinical benefits for people with LAL deficiency compared with best supportive care, but there was a lack of evidence on the variability in response, whether the treatment effect was maintained and how sebelipase alfa affected long-term clinical outcomes including complications of LAL deficiency and life expectancy. It also considered the cost of sebelipase alfa per person was very high, and it did not consider that the benefits of sebelipase alfa in people with LAL deficiency were sufficient to justify the high cost. Therefore it concluded that sebelipase alfa should not be recommended for people with LAL deficiency. For further details see sections 5.27-5.30 of the FED.
MPS Society (patient expert)	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.	Thank you for your comment. The company presented an updated proposed managed access agreement, which has been considered by the committee. For further details, see sections 5.12 and 5.27-5.30 of the FED.

Nominating organisation	Comment	Response
MPS Society (patient expert)	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.	Thank you for your comment. The committee considered the comments from patient experts on the nature of the condition and recognised that LAL deficiency had a very large impact on some people with the condition. It also concluded that the clinical trial evidence showed that sebelipase alfa had a positive effect in the short term in children and adults with LAL deficiency, but it was very uncertain whether the evidence fully addressed LAL deficiency, whether the treatment effect would be maintained and how sebelipase alfa affected long-term clinical outcomes. NICE must take into account the relative costs and benefits of interventions when making recommendations, but the decisions are not based on evidence of their relative costs and benefits alone. For further details please see section 5.6 of the FED.

Comments received from members of the public

Role*	Section	Comment	Response
Carer		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	Thank you for your comment. The committee considered the comments from patient experts and their carers and also the available clinical trial evidence. It recognised that LAL deficiency had a very large impact on some people with the condition, and concluded that sebelipase alfa had a positive effect in the short term in children and adults with LAL deficiency, but it was very uncertain whether the evidence fully addressed LAL deficiency, whether the treatment effect would be maintained and how sebelipase alfa affected long-term clinical outcomes. NICE must take into account the relative costs and benefits of interventions when making recommendations, but the decisions are not based on evidence of their relative costs and benefits alone. For further details please see section 5.6 of the FED.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		and has no control over or choice in inheriting. Kind regards A concerned parent	

[redacted], Centre for Health Technology Evaluation
National Institute for Health and Care Excellence (NICE)
10 Spring Gardens
London, England
SW1A 2BU

October 18, 2016

Re: Alexion's Proposal for Sebelipase Alfa

Dear [redacted]

Thank you again for the opportunity to submit to you a revised proposal for sebelipase alfa. As we discussed, the attached summarizes new clinical data illustrating the longer-term benefits of the drug for all patients indicated for treatment. In addition, we have made a significant confidential financial proposal in order to improve the value for money and ensure overall budget certainty for NHS England.

Based on the attached, we respectfully urge you and the Committee to reconsider its recommendation with regard to sebelipase alfa treatment for LAL Deficiency, and allow Alexion the opportunity to negotiate mutually agreeable terms that ensure access to this important therapy.

Finally, given the sensitivities of the information provided in the attached, we assume that this document will remain confidential and have noted commercially confidential information in blue highlight, per normal NICE procedure. Thank you again. We look forward to hearing from you.

Kind regards,

[redacted]

Cc: [redacted]

I. Long-term Clinical Data Update

Alexion is pleased that the Committee recognizes the life-saving benefits and compelling clinical need of sebelipase alfa (Kanuma®) in infants with rapidly progressive LAL Deficiency; however, we are concerned that the Committee has not fully appreciated the long-term data presented, which illustrate the survival benefit for these patients. Specifically, the data show that surviving subjects of clinical trial LAL-CL03 are thriving with normal development. These infants all started the trial before they were 6 months old, and would have been expected to die within the first year of life. However, they are now all over 3 years of age due to therapy with sebelipase alfa. As such, we believe that the long-term benefit of sebelipase alfa in these patients has been appropriately demonstrated. In addition, these severely ill patients with the greatest clinical need for treatment with sebelipase alfa are those included in the proposed consensus Managed Access Agreement (MAA) that was developed in conjunction with expert clinicians and patient groups in England, as well as NHS England.

Moreover, new analysis of long-term sebelipase alfa clinical trial data (up to 78 weeks) in children and adults from LAL-CL02, described in detail below, shows that sebelipase alfa not only addresses the multi-organ consequences of LAL Deficiency, but can also halt or reverse fibrosis/cirrhosis. In light of these data, as well as revised proposed commercial terms addressing the Committee's concerns (also described in detail below), we respectfully request that the Committee reconsider its recommendation with regard to sebelipase alfa treatment for the very few patients identified as eligible for treatment under the consensus MAA.

A. Infants Missing the Vital LAL Enzyme: Survival Beyond Three Years of Age with Normal Development and Significant Weight Improvement

As noted in our initial submission, sebelipase alfa replaces the missing vital LAL enzyme in patients with LAL Deficiency, and has demonstrated a clinically meaningful improvement in the survival of infants deficient of the vital LAL enzyme.

In study LAL-CL03, 9 infants with LAL Deficiency, all of whom were ≤ 6 months of age on the date of their first infusion, were enrolled, treated, and analysed (Primary Endpoint: survival at 12 months of age).

LAL-CL03 demonstrated that sebelipase alfa improves survival in infants presenting with LAL Deficiency, with 67% (exact 95% CI = 29.93%, 92.51%) of sebelipase alfa-treated infants surviving to 12 months of age compared with 0% (0, 16.11%) of untreated patients in a historical control group. Moreover, sebelipase alfa produced clinically meaningful improvements in multi-systemic and life-threatening manifestations of LAL Deficiency, including improvements in growth (WFA percentile), biochemical markers of liver injury, hepatosplenomegaly, haematological abnormalities such as anaemia and thrombocytopenia, and lipid profile. As noted in our earlier submission, three deaths occurred early in the trial and were deemed related to advanced disease highlighting the need for rapid diagnosis and early intervention. One additional death occurred in a 15-month old infant, and was related to the patient's other diseases (Hemoglobin E disease, patent foramen ovale).

A recent analysis of the data for infant patients enrolled in LAL-CL03 shows that as of August 28, 2016:

- All 5 subjects have survived beyond 3 years of age and continue to receive sebelipase alfa;(1) and
- The oldest subject has completed the treatment period in the trial (5 years), but remains on sebelipase alfa in France. He will be 6 years of age in early December and has enrolled in school and is living a normal childhood.

In addition to continued survival, infants during the trial have shown:

- Normal personal-social, gross motor, fine motor-adaptive, and language development in all patients;
- Improvements in growth (increase in weight percentile) and improvement in gastrointestinal symptoms, reduction in hepatomegaly and splenomegaly, as well as improvements in their liver enzymes;
- A significant reduction in the need for assisted feeding and transfusions; and
- Ability to transition from intensive 24-hour medical care in the hospital to home without constant medical supervision.

B. Children and Adults Missing the Vital LAL Enzyme: Long-Term Improvement in Markers of Liver Injury, Lipoprotein Risk Profile, and Reversing Fibrosis/Cirrhosis

The phase 3 double-blind, placebo-controlled study LAL-CL02 (ARISE trial) enrolled 66 patients (age ≥ 4 years): 36 patients were randomised to receive sebelipase alfa, while 30 patients received placebo.

As reported in our previous communications to NICE, treatment with sebelipase alfa at 20 weeks resulted in significant improvements in markers of chronic liver injury compared to placebo, reaching the primary endpoint, i.e., ALT normalization (31% vs 7%; p-value = 0.0271). All sebelipase alfa-treated patients had a reduction in ALT. These reductions were also accompanied with statistically significant rapid improvements in LDL-c, HDL-c, non HDL-c, and TG. All sebelipase alfa-treated patients had a mean reduction in liver fat content of 32% while those on placebo showed a 4.2% reduction (p-value <0.0001) in a cohort where 100% had ALT elevation and 31% of patients with biopsies at baseline had cirrhosis.

Once completing the double-blind portion, all patients transitioned over into the open-label portion and received sebelipase alfa.

Since Alexion's initial submission, new, longer-term data from the open-label portion of the CL-02 trial has become available. Importantly, these data, summarized below, show that for children and adults with LAL Deficiency, long-term therapy with sebelipase alfa addresses the multi-organ consequences of the disease, reduce cardiovascular risk and can halt or reverse fibrosis/cirrhosis.(2-4)

- After 76 weeks of sebelipase alfa therapy, nearly all sebelipase alfa-treated patients had rapid and sustained reductions in alanine aminotransferase, including a greater proportion who achieved ALT normalization.
- During the double-blind portion of the study, sebelipase alfa-treated patients had greater improvement in lipoprotein profile (ApoB, ApoA, LDL-P, etc.) compared with placebo, illustrating reduction in cardiovascular risk with sebelipase alfa therapy.

- In addition to the improvements in liver injury markers that were seen after 20 weeks, long-term data showed that there was 1) continued improvement in liver injury markers in a greater number of patients and 2) improved histopathology findings that reinforce longer duration of treatment results in greater reduction in fibrosis, cirrhosis, or cessation of further fibrotic damage (Table 1).
    - Ninety-four percent of the sebelipase alfa-treated patients had stabilization or improvement of steatosis compared to 50% in the placebo group;
    - After 52 weeks of sebelipase alfa therapy, 67% of subjects exhibited at least 1 stage fibrosis regression and 50% demonstrated a 2+ stage fibrosis regression (Figure 1). Overall, after 52 weeks of sebelipase-alfa exposure, patients experienced a mean improvement in Ishak score of 1.58 points (from 3.75 at baseline to 2.17 at week 52), indicating significant reduction in liver fibrosis. The change in fibrosis stage, with continuous sebelipase alfa treatment, demonstrates the impact of active treatment on halting or reversing liver damage as all subjects had fibrosis at baseline.
    - Liver fibrosis has been reported to be the only histologic feature of non-alcoholic fatty liver disease (NAFLD) associated with long-term outcomes.(5-6) In particular, data indicates that fibrosis stages were independently associated with long-term overall mortality, liver transplantation, and liver-related events, based on a longitudinal study of 619 patients diagnosed with NAFLD, with median follow-up of 12.6 years.(6)
    - Given that sebelipase-alfa treatment is associated with significant reduction of fibrosis in a majority (67%) of patients after 52 weeks, and that fibrosis is the main predictor of long-term progression to advanced liver-related events, the 52-week biopsy data from ARISE point to significant long-term benefit of sebelipase-alfa treatment.

Table 1: Long-Term (76-Week) Results from Sebelipase Alfa Trial CL-02 (ARISE): 97% of Patients had Rapid and Sustained Reduction in ALT

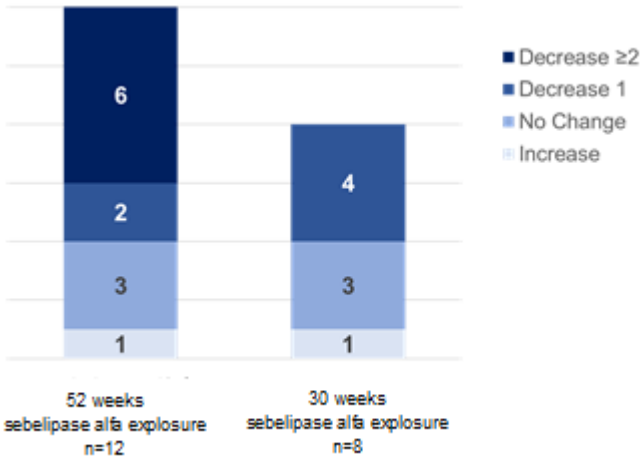
SA exposure	ALT			AST		LDL-c Mean % Change	HDL-c Mean %Change	Non HDL-c Mean %Change	Mean TG %Change
	% with ALT Reduction	Normalize	Mean % change	Normalize	Mean % change				
20 weeks SA*	100%	31.0%	-53.3	42.0%	-44.4	-28.5	18.9	-27.9	-25.4
52 weeks SA**	97%	47%	-52.8	58.0%	-43.5	-29.8	24.4	-29.0	-22.6
76 weeks SA***	98%	51%	-56.1	65%	-50.7	-27.5	22.9	-26.5	-16.7

SA = sebelipase alfa; *SA arm only (n=36)

** Original sebelipase alfa arm and placebo arm entered the open label portion and each arm received total 52 weeks of sebelipase alfa

*** Original sebelipase alfa arm and placebo arm entered the open label portion and each received total 78 weeks of sebelipase alfa)

Figure 1: Reversal of Liver Fibrosis (Change in Ishak Score in ARISE)



In summary, new long-term data illustrate that treatment with sebelipase alfa results in significant clinical benefit for all individuals with LAL Deficiency:

- For the infant population, natural history documented survival of less than 12 months. With sebelipase alfa therapy, survival to 3 years of age or beyond is accompanied by normal development milestones and social development.
- For children and adults, in addition to the improvement in key multi-system disease markers during the double-blind portion of the study, long-term therapy with sebelipase alfa is associated with regression or stabilization of liver fibrosis or cirrhosis.

II. Ongoing Data Collection

The Committee requests that Alexion "define a full data analysis plan to ensure that the data collected in the revised managed access agreement and global registry will provide sufficient information to address the uncertainties associated with the long-term benefits of sebelipase alfa." In 2016, Alexion engaged in discussions with the regulatory authorities around the world to ensure that the Global LAL Deficiency registry can meet the Post Marketing Commitment (PMC) and Post Authorization Measure (PAM). Given the recent agreement and endorsement of the registry revisions with these health authorities, the required protocol amendments are currently being rolled out to active sites as well to the new sites.

Data analyses for the Registry have been planned to address regulatory questions and will be prioritized to address the following topics on all patients in the registry:

- Evaluate the long-term, prospective clinical outcome of sebelipase alfa in adult and pediatric patients with LAL Deficiency;
- Progression of liver and cardiovascular diseases;
- Changes in anthropometric assessments;
- At a minimum, liver assessments will include liver biopsies, imaging, deterioration of liver synthetic function, clinical progression to end stage liver disease, receipt of liver transplantation, and death;

- Cardiovascular assessments: incidence rates of stroke, MI, and death;
- Additional evaluations will include dosing regimens and reasons for any dose modifications; and
- Collect safety data including any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies).

Patients who are treated in England under the MAA will be invited to enroll in the LAL Deficiency Global Registry and their data stored in the Registry database. Alexion will do a data analysis for all patients treated under the MAA on an annual basis. With the very small numbers of patients in England expected to receive and benefit from treatment, statistical significance of efficacy end points are unlikely to be achieved. In addition to the registry data, Alexion expects to be able to provide descriptive statistics for the criteria outlined in the MAA and will provide these to NICE and NHS England as requested.

III. Financial Proposal

In addition to the new long-term clinical data, including reversal of liver damage, described above that support the life-saving and life-improving effects of sebelipase alfa, Alexion proposes below significantly revised commercial terms in response to the Committee's concerns. Although Alexion maintains the appropriateness of our original terms given the severity of disease, the transformative nature of sebelipase alfa and the extremely low prevalence of LAL Deficiency in England and globally, we feel strongly that those patients identified under the MAA should be granted access to sebelipase alfa as the first and only treatment option available that replaces the vital missing enzyme in these patients.

As you are aware, LAL Deficiency is a devastating and ultra-rare disease, so the overall patient population is very small relative to other rare and even some ultra-rare diseases. In addition, there are a limited number of patients who would be eligible for sebelipase alfa treatment under the consensus MAA, which restricts treatment to those who would benefit most from therapy. Alexion estimates fewer than [redacted] would be treated in England over the five-year term of the agreement. Nonetheless, given the Committee's concerns regarding the costs of sebelipase alfa, Alexion proposes revised commercial terms in a good faith effort to ensure even greater value for money and financial certainty for the NHS when providing sebelipase alfa to patients in need.

Improved Value for Money and Proposed Confidential Per Mg Price Decrease

To ensure even greater value for money, Alexion proposes a confidential [redacted] reduction in the per milligram (mg) list price of Kanuma to [redacted] per mg or [redacted] per 20mg vial, resulting in a revised cost range of ~[redacted] to [redacted] for patients with infantile presentation (regardless of whether they receive dosing of 1 mg/kg or 3 mg/kg every week and of ~[redacted] to [redacted] for patients with pediatric presentation, with an estimated average patient cost of ~[redacted]. In addition, given the weight-based nature of dosing of sebelipase alfa, Alexion has proposed to cap or limit the annual per patient expenditure to [redacted], which results in a combined effective discount of [redacted] across the treated patient population on an average weighted basis.

We believe these reductions significantly enhance the high value proposition for sebelipase alfa, with average costs at or even below the price of other highly-specialized technologies currently funded in England.

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Guaranteed Budget Certainty and Proposed Five-Year Overall Budget Cap

Alexion feels strongly that the consensus MAA provides upfront certainty to NICE and NHS England that only those patients that would benefit most would have access to sebelipase alfa treatment. In addition, Alexion proposes to ensure overall budget certainty by rebating back fully the costs incurred by NHS England in excess of [redacted] over the five-year term of the agreement, beginning January 1, 2017, which reflects the proposed [redacted] price reduction (proposed above) applied to our May 2016 budget impact model estimate of [redacted]. This represents a modest NHS England commitment of approximately [redacted] annually in return for a highly innovative therapy that replaces the vital missing enzyme and provides substantial QALY gains of 28.6 for infantile-presentation and 20.4 for pediatric/adult presentation.

Together, these four cost containment mechanisms – 1) confidential discount on list price; 2) annual per patient cost cap; 3) consensus MAA, which restricts patient access; and 4) overall five-year budget cap -- provide meaningful savings and value to NHS England as well as ensure budget predictability by controlling both the cost of and access to treatment.

IV. References

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