in collaboration with:

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Sebelipase alfa for treating lysosomal acid lipase deficiency

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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Date completed 09/12/2015

Source of funding: This report was commissioned by the NIHR HTA Programme as project number HST 15/07/01.

Declared competing interests of the authors

None.

Acknowledgements
None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Riemsma R, Joore MA, Ramaekers BLT, Van Giessen A, Westwood M, Armstrong N, Pouwels X, Worthy G, Stirk L, Severens JL, Kleijnen J. Sebelipase alfa for treating lysosomal acid lipase deficiency: a Highly Specialised Technology Evaluation. York: Kleijnen Systematic Reviews Ltd, 2015.

Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Manuela Joore acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Anoukh van Giessen, Xavier Pouwels and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Marie Westwood acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Johan L Severens critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACAT	Acyl-Cholesterol Acyltransferase
ADA	Anti-drug antibody
AE	Adverse Events
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ApoB	Apolipoprotein B
APRI	Aspartate aminotransferase to Platelet Ratio Index
ARISE	Acid Lipase Replacement Investigating Safety and Efficacy
AST	Aspartate transaminase
BIC	Bayesian information criterion
BIM	Budget impact model
BNF	British National Formulary
BSC	Best supportive care
CAD	Coronary artery disease
CC	Compensated cirrhosis
CDF	Cancer Drugs Fund
CV	Cardiovascular
CE	Cholesteryl Esters
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company Submission
CSR	Clinical study report
CVD	Coronary vascular disease
DBS test	Dried blood spot test
DCC	Decompensated cirrhosis
EMA	European Medicines Agency
ECG	Electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
EU	European Union
EUR	Erasmus University Rotterdam
FA	Fatty Acid
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FC	Free Cholesterol
FCH	Familial combined hyperlipidaemia
FFA	Free Fatty Acid
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
H&E stain	Haematoxylin and eosin stain

HBV	Hepatitus B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitus C virus
HDL/HDL-c	High density lipoprotein/ High density lipoprotein cholesterol
HELLP	Haemolysis; elevated liver enzymes; low platelet count
HeFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
HMG-CoAr	Hydroxymethylglutaryl-coenzyme A reductase
HR	Hazard ratio
HRG	Health resource group
HRQoL	Health related quality of life
HSCT	Haematopoietic stem cell transplantation
HST	Highly Specialised Technologies
HTA	Health Technology Assessment
IAR	Infusion associated reaction
IC	Indirect Comparison
ICER	Incremental Cost-effectiveness Ratio
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LAL/ LAL Deficiency	Lysosomal acid lipase/ Lysosomal acid lipase deficiency
LDH	Lactate dehydrogenase
LDL/ LDL-c	Low density lipoprotein/ Low density lipoprotein cholesterol
LDLR	Low-Density lipoprotein receptor
LIPA	Lysosomal acid lipase gene
LLM	Lipid lowering medication
LOCF	Last observation carried forward
LSD	Lysosomal storage disorder
LYG	Life year gained
LYS	Life Year Saved
MedDRA	Medical Dictionary for Regulatory Activities
MEGE-MRI	Multiecho gradient echo sequence-magnetic resonance imaging
MHRA	Medicines and Healthcare Products Regulatory Agency
MPS	Mucopolysaccharide
MRI	Magnetic resonance imaging
MRU	Medical resource utilisation
MSE	Mean squared error
MTC	Mixed Treatment Comparison
NA	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNT	Number needed to treat
NR	Not Reported
ONS	Office of National Statistics

OS	Overall survival
PAS	Patient access scheme
PDFF	Proton density fat fraction
PedsQL™	Paediatric quality of life inventory questionnaire
PES	Primary efficacy set
PFS	Progression-free survival
PH	Proportional hazards
PLT	Platelet test
PNH	Paroxysmal nocturnal haemoglobinuria
PP /PPS	Per protocol/ per protocol set
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
QOW	Every other week
QW	Weekly
RCT	Randomised Controlled Trial
rhLAL	Recombinant human lysosomal acid lipase
RR	Relative Risk
SAE	Serious adverse event
ScHARR	School of Health and Related Research
SD	Standard deviation
SF-36	Short form 36
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SRBEP	Sterol regulatory element binding proteins
SRT	Substrate reduction therapy
STA	Single Technology Appraisal
SVR	Sustained viral response
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TFHN	Transfusion-free haemoglobin normalisation
TG	Triglyceride
TTF	Time to failure
TTO	Time trade-off
TTP	Time to progression
UDCA	Ursodeoxycholic acid
U/L	Units per litre
UMC	University Medical Centre
WFA	Weight for age
WHO	World Health Organisation
VLDL-C	Very Low Density Lipoprotein Cholesterol

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1. SUMMARY

1.1 Background

Lysosomal acid lipase deficiency is an ultra-rare inherited autosomal recessive lysosomal storage disease (LSD). It is characterised by a failure to break down cholesteryl esters and triglycerides in the lysosomes, resulting in a build-up of cholesteryl esters (CEs) and triglycerides (TGs) in vital organs, blood vessels, and other tissues with multi-system manifestations. Lysosomal acid lipase Deficiency (LALD) results in cirrhosis with portal hypertension, liver failure, and early atherosclerosis. The age at onset varies, but LALD is primarily a childhood condition with serious complications frequently occurring at an early age.

1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology

There are no published data on HRQoL in people with LALD. The CS reports the findings of an on-line survey of patients and their families. The survey was conducted by Alexion and distributed through three patient organisations from the UK, Spain and the USA. In addition, HRQoL data from the LAL-CL02 (ARISE) trial were reported, and HRQoL data relating to the effects of chronic liver were presented for diseases considered to be comparable.

Eleven participants took part in the survey (median age 11 years, range 3 to 49 years). Eight (73%) of the participants were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa. The mean age at diagnosis was 5.6 years for children and 33.5 years for adults; for infantile-onset LALD HRQoL is likely to be a secondary consideration to improving survival. The most commonly reported symptom was abdominal pain (91%) of LALD patients; other symptoms mentioned by more than half of the survey sample were fatigue, diarrhoea, nausea, loss of appetite, itchy skin and having a swollen abdomen. Five of the six school age children who participated in the survey were reported as being "able to follow full-time education"; four of these five children were being treated with sebelipase alpha, but it was not clear whether treatment had any effect on their schooling. The mean EQ-5D scores, before treatment with sebelipase alpha, were 0.76 for children (N=8) and 0.34 for adults (N=2); the CS reported small increases in score after treatment (0.84 for children (N=6) and 0.76 for adults (N=1)).

Quality of life data were collected in the sebelipase alfa study LAL-CL02 (ARISE), which included both children and adults (minimum age five years). Study inclusion criteria meant that the HRQoL of participants, at baseline was similar to that expected for an unaffected population. The study included people with substantial pathological liver damage at baseline, [redacted]

1.3 Critique of the decision problem in the company's submission

The remit of the appraisal, as specified in the final NICE scope, is to evaluate the benefits and costs of sebelipase alfa within its marketing authorisation for treating lysosomal acid lipase

deficiency for national commissioning by NHS England. The ERG notes some deviations from the final agreed NICE scope. Briefly, these include:

- The company notes that data are not available for the following four efficacy outcomes for any of the ongoing sebelipase alfa clinical trials: liver synthetic function, liver disease progression, liver transplant, and cardiovascular events.
- The company submission did not include subgroup analyses for infants with very rapidly progressing lysosomal acid lipase deficiency and for people who have had a liver transplant as requested in the scope.

1.4 Summary of clinical effectiveness evidence submitted by the company

The CS presents results from four intervention studies and one historical control study. One of the intervention studies was a placebo controlled randomised trial.

Paediatric (≤ 2 years) patients with LAL Deficiency:

Two studies were included for this population: study LAL-CL03 was a single arm dose escalation study of sebelipase alfa (from 0.35 to 1 mg/kg once weekly IV; up to 3 or 5 mg/kg once weekly IV) including nine patients with follow-up up to 208 weeks; and study LAL-1-NH01 was a retrospective historical control study including 35 patients diagnosed between 1985 and 2012.

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients who survived past 12 months of age in LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics. In LAL-CL03, six of nine sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, one additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival, 95% CI: 0% to 16%).

No other comparative data were presented for this population.

Paediatric/adult (≥ 4 years) patients with LAL Deficiency:

Study LAL-CL02 (ARISE) was a 20-week placebo controlled randomized trial including 36 sebelipase alfa-treated patients (1 mg/kg) and 30 placebo patients.

A statistically significant improvement in multiple endpoints was observed in the sebelipase alfa-treated group as compared to the placebo group at the completion of the 20-week double-blind period of the study. The absolute reduction in mean alanine transaminase (ALT) level was -57.9 U/l [redacted] in the sebelipase alfa-treated group and -6.7 U/l (-6%) in the placebo group.

Sixty-five of 66 patients entered the open-label period (up to 130 weeks) at a sebelipase alfa dose of 1 mg/kg once every other week. In patients who had received sebelipase alfa during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels. [redacted] Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period. Consistent with what was observed in sebelipase alfa-treated patients during the

double-blind period, initiation of treatment with sebelipase alfa during the open-label period produced rapid improvements in ALT levels and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Adults (≥ 18 years) with LAL Deficiency:

Study LAL-CL01 was a four week single arm sebelipase alfa study including nine patients divided over three cohorts: 0.35, 1, and 3 mg/kg once weekly IV. Study LAL-CL04 was a 156-week extension including eight adult patients who had completed LAL-CL01.

Changes in serum transaminase levels observed in adults in study LAL-CL01 were consistent with those reported in study LAL-CL02 and were maintained during the extension study LAL-CL04. Initiation of treatment with sebelipase alfa in study LAL-CL01 produced a rapid decline in ALT and aspartate aminotransferase (AST). When patients went off treatment at the end of study LAL-CL01 (interval between dosing of 9 to 28 weeks), both ALT and AST increased. Normalisation of transaminase levels continued during long-term treatment (through Week 104) in the extension study LAL-CL04.

Safety and tolerability

According to the European Medicines Agency (EMA) European Public Assessment Report (EPAR) the most serious adverse reactions experienced by 3% of patients taking sebelipase alfa in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

In addition, three deaths were reported in the sebelipase alfa clinical programme as of the data cut-off across the four primary studies evaluating safety; all patients who died were enrolled in study LAL-CL03. All fatal events were assessed as unrelated to sebelipase alfa treatment by the investigators.

Serious adverse events (SAEs) were reported in 12 (14.3%) of the 84 patients in the pooled safety set. SAEs were more frequent among infants in study LAL-CL03 with the most rapidly progressive form of LAL Deficiency (eight of nine patients, 89%) and were relatively infrequent among children and adults (four of 75 patients, 5%). The most commonly reported types of SAEs were infections (five of 84 patients, 6%). One patient in study LAL-CL02 reported a serious infection (gastroenteritis). The only other SAE reported in more than one patient in the pooled safety set was pyrexia, reported in two patients in study LAL-CL03.

1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted

The main uncertainty regarding the effectiveness evidence is the comparability of baseline characteristics from treated patients and historical control patients, the use of surrogate outcomes and the lack of long-term follow-up.

[redacted]. Given the likely improvements in supportive care over time, results from comparisons between treated patients (LAL-CL03) and historical control patients (LAL-1-NH01) may be biased in favour of sebelipase alfa.

Surrogate outcomes showed a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. These outcomes, on well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition. However, there is no evidence to address long-term and key clinical endpoints (progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death). One of the most important outcomes is slowing the progression of the liver disease and hence delaying or avoiding liver transplant. The duration of the trials providing data presented in the submission was not long enough to look at this outcome. In addition, the long-term safety and efficacy profile of sebelipase alfa is uncertain.

1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on quality of life, cost effectiveness and resource use data for patients with LAL Deficiency or provide utilities, resource use or cost data for the economic model. The company did not identify any economic studies, health state utility data, resource use data nor cost data for LAL Deficiency patients.

A model-based cost-consequence analysis (CCA) is presented to compare the costs, life years and QALYs of sebelipase alfa and best supportive care (BSC) for the treatment of LAL Deficiency from an NHS perspective. Costs and consequences are estimated for a population of 11 years-old over a lifetime horizon. For patients with infant disease onset, a scenario analysis is presented. The Markov model is an adaptation of a model for non-alcoholic fatty liver disease (NAFLD) published by Mahady et al.[2] The model consists of four health states representing different stages of liver disease progression; compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and "LAL Deficiency without CC, DCC, or HCC". Furthermore, it includes a liver transplant tunnel state and an absorbing death state. Adverse events were not included in the cost-consequence analysis. Health outcomes and costs are both discounted at a rate of 1.5%. Patients receiving sebelipase alfa will remain on treatment for their entire lives. In the BSC group, the only treatment option is a liver transplant, which is offered to patients that have progressed to HCC. Health state utilities were retrieved from the economic model by Mahady.[2] Costs were based on literature.[3] The costs of sebelipase alfa depend on dosing scheme (different for infant onset and later onset) and patient weight. The transition probabilities for sebelipase alfa are mostly based on the LAL-CL02[4] data, whereas for BSC transition probabilities retrieved from Mahady et al[2] and Hartwell et al[5] are used. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient compared to BSC and the incremental costs would be [redacted] per patient compared the BSC. In the company's sensitivity analyses this result was most sensitive to discount rate and the transition probabilities to and from the "LAL Deficiency without CC, DCC" and "HCC" health states. In the infants scenario analysis the LAL-1-NH01 study[6] and LAL-CL03 study[7] were used to inform the transition probabilities for the first year. Health state utilities and costs were mostly based on assumptions. This scenario results in 28.6 QALYs gained and incremental costs of [redacted]

A budget impact model submitted by the company estimates the total costs to the NHS of adopting sebelipase alfa in the UK for a period of five years. Two hypothetical scenarios are presented: one where a proportion of patients would receive sebelipase alfa with the remainder receiving BSC, and a second scenario in which all patients would receive BSC. The budget impact model includes two groups of patients. The first group contains patients diagnosed with LAL Deficiency in their first year of life (Age 0-1 presentation group) and the second group includes patients with presentation of symptoms after one year of age (Age 1+ presentation group). Prevalence and incidence are based on various sources of literature and internal modelling by the company. The uptake of sebelipase alfa is determined by diagnosis and treatment rates. Furthermore, the model assumes that several patients will not continue sebelipase alfa treatment or will not comply with prescribed dosing, by using treatment continuation and compliance rates. These rates are based on the company's experiences with other treatments for rare diseases. Applying these rates result in [redacted] of LAL Deficiency patients treated with sebelipase alfa in the first year, to [redacted] of patients treated in the fifth year. The costs of sebelipase alfa are conditional on the availability of a 5 mg vial of sebelipase alfa one year after market access. The net five year budget impact amounts to £53,548,573.

1.7 Summary of the ERG's critique of the value for money evidence and cost to the NHS and PSS submitted

The ERG's critique of the CCA entails the following main points: the health economic search, model structure and estimates for transition probabilities, costs of sebelipase alfa, health state utility estimates, and the handling of uncertainty.

The ERG notes that one limitation of the health economic search is that all Ovid databases were searched in one single strategy. Moreover, the company focused the search strategy on LAL Deficiency only, while it aimed to identify all economic studies that could be used to inform the design of the economic model or provide utilities, resource use or cost data for the economic model. The model structure used in the CCA differs between the comparators as a result of using different sources for transition probabilities (LAL-CL02[4] data for sebelipase alfa and Mahady et al[2] and Hartwell et al[5] for BSC). For sebelipase alfa it is assumed that, based on surrogate endpoints in LAL-CL02, patients cannot progress to the "CC", "DCC", "HCC" health states, and, as a result, cannot receive a liver transplant. In absence of comparative evidence on the clinical endpoints underlying these health states, the ERG questions this model structure. After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market. Furthermore, drug costs were influenced by the foreseen introduction of 5 mg vials of sebelipase alfa one year after market access. This reduces waste and costs associated with sebelipase alfa. The ERG thinks the 5 mg vials of sebelipase alfa should not be incorporated in the cost-consequences analysis because these are not yet available.

The health state utility used in the CCA exceeded the UK general population utility scores.[8] In addition, it was unclear whether the health state utility scores selected by the company were the most appropriate ones for the UK context.

In the probabilistic sensitivity analysis, multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges. In addition, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect.

The ERG's critique on the budget impact model entails three main points. Firstly, the estimation of incidence and prevalence was not transparently reported. As a result, the ERG was not able to assess the quality and the validity of the adjustments made by the company on Scott et al's prevalence rate.[9] Secondly, the estimation of diagnosis, treatment, treatment continuation and compliance rates seem to result in an underestimation of patients receiving sebelipase alfa, when compared to the company's experiences with other treatments for rare diseases. Thirdly, the costs of sebelipase alfa are conditional upon the availability of a 5 mg vial one year after market access.

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

The CS includes estimates of impacts of sebelipase alfa for LAL Deficiency in (i) lost productivity in patients due to premature death and morbidity, (ii) lost productivity in carers, (iii) respite care and other welfare payments, (iv) out of pocket costs associated with transportation and dietary requirement, and (v) carer's time. The main source of information was the EU-LAL-D Survey.(Appendix 5 CS[1])

The company gives an overview of qualitative accounts of patients and carers on productivity. In addition, quantitative accounts of changes in work hours are provided. The impact of sebelipase alfa on these accounts is unclear. It is mentioned that some LAL Deficiency patients are required to follow a low fat diet, which may be more costly than a regular diet. Furthermore, it is mentioned that family members who accompany patients to the hospital will have travel expenses and may be required to take time off work. Treatment with sebelipase alfa may be also associated with travel expenses to receive treatment as long as administration is not transitioned to home care.

Sebelipase alfa treatment should be supervised by an experienced healthcare professional experienced in the management of patients with LAL Deficiency, other metabolic disorders, or chronic liver diseases.[10] Sebelipase alfa is administered by intravenous infusion with an administration time of approximately two hours. The company states that in England, it is expected that initiation of the infusions and stabilisation of the patient will occur at specialist LSD centres followed by transition to local hospital outpatient clinics or homecare arrangements, as is the case for currently available enzyme replacement therapies. It is anticipated that besides this, no additional infrastructure is necessary. The company also notes that the management of infants is more complex than in older children and adults. Managing infants may require prolonged hospital stay and multi-disciplinary treatment approaches which may impact on resource requirements for the expert centres managing these infants.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health related benefits

A major source of information on the impact of sebelipase alfa on wider societal non-health benefits provided in the MS is the EU-LAL-D Survey.(Appendix 5 CS[1]) The ERG agrees with the company that due to the very low sample size and missing values, the results of this survey must be interpreted with caution. In addition, the survey was performed in various European countries, so does not only reflect the situation in the UK. This adds to the uncertainty of the information from this survey.

In addition to information from the survey, information from the literature is presented. It is unclear to the ERG how the studies mentioned in the MS have been retrieved. As a result, the ERG is unable to assess whether the information is complete, and provides an unbiased reflection of the evidence available in the literature.

The information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is descriptive in nature. No attempt has been made to value the impact in terms of costs. The ERG thinks that, using literature and assumptions, some quantification of wider societal benefits is possible. Presumably, the impact on productivity loss would be highest in terms of costs. Therefore, the ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency.

The ERG thinks it is reasonable to assume that the specialist LSD centres present in the UK will provide the necessary infrastructure to use sebelipase alfa in LAL deficiency patients. The costs of administration of sebelipase alfa in both infants and children older than one year and adults are incorporated in the CCA and the budget impact model.

1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

Strengths: Despite LAL Deficiency being a rare disease, the company presented an impressive series of studies in treated patients and historical controls, including a randomised placebo-controlled trial in 66 patients.

The CS contains details of a recent on-line survey of patients and their families from the USA and Europe which provides relevant information concerning the impact of the disease on patients and their families as well as information on resource use.

Despite the limited evidence available, particularly regarding the long-term consequences of the disease and treatments, the company presented a CCA with a lifetime time horizon along with several sensitivity and scenario analyses.

Weaknesses: Comparative data from treated patients and historical controls may be biased in favour of sebelipase alfa, [redacted] and supportive care will most likely have improved over time. Results from the randomised controlled trial show effects on surrogate endpoints, but no evidence is presented to address long-term and key clinical endpoints, such as progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death. The duration of trials providing data presented in the submission was not long enough to look at

key outcomes such as: progression of the liver disease, avoidance of liver transplant and adverse events.

The CCA and the budget impact model lacked transparency, which made it difficult for the ERG to assess whether the results are complete and valid.

In absence of comparative evidence on long-term and key clinical endpoints, the modelling of the long-term impact of the technology is extremely uncertain.

The calculation of the incidence and prevalence of LAL Deficiency in the UK for the budget impact model lacked transparency. As a result, the ERG was unable to assess the validity of these estimates.

Areas of uncertainty: There is no mention in the CS of possible stopping rules for sebelipase alfa. In fact the company assumes treatment will be administrated for the full lifetime of the patient (CS, Section 2.3, page 31). However, given the many differences between patients it cannot be assumed that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

Although, there is considerable follow-up in some of the sebelipase alfa studies, with nine patients having received sebelipase alfa treatment for up to 208 weeks and eight patients receiving up to 156 weeks of treatment, this is only a fraction of the expected lifetime treatment with sebelipase alfa. Therefore, the long-term safety and efficacy profile of sebelipase alfa remains uncertain.

The availability of a 5 mg vial after one year of market access is considered uncertain. Also, after 10 years of market access, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market.

1.11 Summary of exploratory sensitivity analyses undertaken by the ERG

1.11.1 Summary of exploratory analyses for the cost consequences analysis

The ERG preferred base case resulted in a substantial decrease of the incremental QALYs; from 19.2 QALYs in the company base case to 0.0 QALYs in the ERG base case, indicating no additional benefit for sebelipase alfa. This decrease was mainly due to the use of alternative transition probabilities; removing inconsistent assumptions regarding the model structure and use of sources for model input estimation. In addition, the use of alternative utilities had a substantial impact on the incremental QALYs. The incremental costs estimated by the company [redacted] were lower than the incremental costs estimated in the ERG base case ([redacted]). This could mainly be explained by removing the 30% cost reduction after 10 year. Moreover, there was substantial uncertainty regarding the incremental costs (95% confidence interval showed a range of approximately [redacted].

The infant scenario presented by the company showed incremental costs and QALYs of [redacted] and 28.6, respectively. In the infant scenarios performed by the ERG using the

1.5% discount rate, the incremental costs were relatively similar while the incremental QALYs were approximately halved.

1.11.2 Summary of exploratory analyses for the budget impact analysis

The ERG performed additional analyses on (1) incidence and prevalence rates, (2) diagnosis and treatment rates and (3) treatment continuation and compliance rates due to the uncertainty surrounding these estimates in the company's budget impact model

The ERG performed analyses on incidence and prevalence rates in the Age 1+ presentation group. The results show that a 50% increase of the prevalent population will increase the five year net budget impact to £90,541,337. The incidence rate does not strongly influence the five year budget impact.

The ERG performed sensitivity analyses on diagnosis and treatment rates in the Age 1+ presentation group by increasing and decreasing these rates with 10% or 20% in the sebelipase alfa with market access scenario. In these analyses the five year net budget impact ranged from £23,439,245 to £126,845,898 and the number of treated patients in the fifth year of the budget impact model varied from [redacted] to [redacted].

The ERG performed sensitivity analyses on treatment continuation and compliance rates. These rates were increased and decreased with 10% or 20% in the sebelipase alfa with market access scenario. In these analyses the five year net budget impact ranged from £36,137,359 to £206,367,686 and the number of treated patients in the fifth year of the budget impact model varied from [redacted] to [redacted].

The company stated that approximately [redacted] of the PNH patients are on eculizumab treatment.[11] Based on this information, the ERG thinks that the scenario where treatment rates are increased by 10%, diagnosis rates increased by 20% and both treatment continuation and compliance rates are set on 100% may be the most plausible because it provides [redacted] of treated patients with sebelipase alfa. This scenario results in a five year net budget impact of £178,527,667 which is more than three times higher than the company's base case five year net budget impact.

1.11.3 ERG exploratory analysis for the wider societal benefits

The ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency. In the searches the ERG conducted to retrieve additional information for the CCA, the study by Scalone[12] was identified. This study reports on productivity loss due to chronic hepatic diseases. Productivity loss corresponded to on average 6.8 days/patient-month by patients and caregivers, and 14.4 days/patient-month for transplant patients. The ERG performed the productivity loss calculations in two ways: based on the human capital approach (HCA) and the friction costs method (FCM). The ERG used a friction period of three months, hence time horizon does not impact these calculations. The lifetime HCA calculation resulted in productivity loss of £268,856, and the FCM resulted in £2,226.

2. BACKGROUND

2.1 Introduction

This chapter presents an overview of lysosomal acid lipase deficiency (LALD) and its management. The content of this chapter is based on relevant literature, information provided by clinical advisors to the Evidence Review Group (ERG) and information presented in the background sections of the company's submission (CS).[1 13] For additional information on the aetiology, epidemiology, health impact, prognosis and management of LALD, please see the CS (pages 39-73).

2.2 Description of health problem

2.2.1 Lysosomal acid lipase deficiency

Lysosomal acid lipase deficiency is an ultra-rare inherited autosomal recessive lysosomal storage disease (LSD). It is characterised by a failure to break down cholesteryl esters and triglycerides in the lysosomes, resulting in a build-up of cholesteryl esters (CEs) and triglycerides (TGs) in vital organs, blood vessels, and other tissues with multi-system manifestations.[1, 13] LALD results in cirrhosis with portal hypertension, liver failure, and early atherosclerosis.[1] The age at onset varies, but LALD is primarily a childhood condition with serious complications frequently occurring at an early age. In a review of 135 childhood and adult cases, the median age at first onset was five years, with 83% presenting at 12 years of age or younger.[14] In this study, 87% of people with LALD experienced manifestations in more than one organ and 79% of these were 19 years of age or younger.[14] A further observational study reported that the median age at the first report of disease related abnormalities was 5.8 years, with 81% of cases (n=48) being younger than 18 years.[15] Infants presenting with LALD experience rapid disease progression, characterised by malabsorption, growth failure, and liver failure with a reported median age of death of 3.7 months.[16]

2.2.2 Epidemiology

The CS reports published estimates of the prevalence of LALD ranging from 1:40,000 to 1:300,000 or 1:400,000.[9, 17, 18] Infantile presentation of LALD is rarer with a reported incidence estimate of approximately 1:704,000 births.[19] The CS estimated the prevalence of LALD in England to be 1:99,000.[1]

2.2.3 Aetiology

LALD is caused by mutations in the *LIPA* gene located on chromosome 10q23.2-q23.3. Affected individuals are typically either homozygous or compound heterozygous for *LIPA* gene mutations. In late onset LALD, presenting in children and adults, many cases are associated with a common mutation and patients may have some residual enzyme activity.[20] The most commonly occurring mutation is the exon 8 splice site mutation, c.894G > A (E8SJM), which is found in more than 50% of children and adults with LAL Deficiency.[21] In LALD which presents in infants, there are many different mutations that can result in complete loss of enzyme function.[22]

2.2.4 Pathogenesis

Lysosomal acid lipase (LAL) is a critical component of lipid metabolism, which breaks down LDL-derived neutral lipids (cholesteryl esters and triglycerides). LDL-cholesterol is taken up by hepatocytes. LAL in the lysosomes (cell organelles containing hydrolytic enzymes) breaks down the LDL-cholesterol to free cholesterol and free fatty acids. In LALD, absent or reduced enzyme activity results in an accumulation of cholesteryl esters and triglycerides in the lysosomes and low levels of intracellular free cholesterol. Low levels of free cholesterol cause up-regulation of endogenous cholesterol production by HMG-CoA reductase and of endocytosis via LDL receptors, as well as increased synthesis of apolipoprotein B (ApoB) and markedly increased production of very-low-density lipoprotein cholesterol (VLDL-C).[1, 21]

2.2.5 Clinical features

As noted above, infantile onset is the most severe form of LALD, with early and severe symptom onset observed at a median age of one month. Infantile onset disease is characterised by rapid progression with a median age at death of 3.7 months[16] and almost 100% mortality within six months.[1] Accumulation of cholesteryl esters and triglycerides in the liver, intestines and adrenal glands results in hepatosplenomegaly, liver dysfunction, diarrhoea, vomiting, anaemia, failure to thrive, adrenal calcifications and liver fibrosis and cirrhosis.[23-27] Early death in infants with LALD is largely attributable to severe failure to thrive and/or rapidly progressing liver disease.[21]

Childhood and adult LALD is also associated with a significant morbidity burden and early mortality. Liver pathology is the dominant presentation, with 86% of LALD patients having liver manifestations.[14] The CS reports study data indicating that approximately 50% of paediatric and adult LALD patients progresses to fibrosis, cirrhosis or liver transplant within three years of presentation.[28] This is supported by baseline data from a phase 3 trial in which 44% of LALD patients (n=66) had a history or evidence of medically important chronic liver disease at baseline, including cirrhosis, portal hypertension, and/or coagulopathy.[29] Histologically confirmed cirrhosis has been described in children as young as four years of age, (range 4 to 21 years), with death due to liver failure occurring as early as seven years of age and 50% of deaths occurring in patients under 21 years.[14] Hepatobilliary malignancies have also been reported in young LALD patients.

Dyslipidaemia in childhood and adult LALD has also been associated with a risk of accelerated atherosclerosis. Adverse cardiovascular outcomes such as stroke and myocardial infarction have been reported in patients with LALD, however, the cardiovascular risk profile of these patients remains poorly understood. The CS reports study data showing baseline dyslipidaemia (mean LDL-cholesterol 207.9 ± 65.9 mg/dL) in 40% of participants, despite lipid lowering medication, [30] and the Bernstein review reported that 87% of 135 LALD patients had cardiovascular manifestations.[14]

In addition to severe failure to thrive in infants, LALD can have an effect on growth in older children. The CS reports study data showing that 12% of 50 patients under 18 years of age were at less than the fifth centile on population growth charts. [30] Similarly, a published review estimated failure to thrive, vomiting, diarrhoea, and gastrointestinal symptoms in approximately 30% of children with LALD.[31]

Other, less common clinical presentations and complications of childhood and adult LALD include pulmonary hypertension, severe splenomegaly and splenic infarcts leading to splenectomies in children, mesenteric lymphadenopathy, anaemia, and thrombocytopenia.[14, 21]

2.2.6 Diagnosis

LALD can be diagnosed on the basis of deficient enzyme activity, using either a dried blood spot (DBS)[32] or isolated leukocytes.[33] LAL activity can be measured, from a DBS, using the fluorimetric substrate 4-methylumbelliferyl palmitate. Because the assay is considered developmental and validation is performed within individual laboratories, it has been recommended that the results of LAL activity testing should be interpreted with respect to the normal reference ranges of the individual laboratory performing the test.[16] The CS states that, for the majority of laboratories using a DBS testing method, the effective diagnostic cut-off is "non-detectable".[1]

A diagnosis of LALD can also be established using genetic testing (complete sequencing of the coding regions of LIPA). The CS states that genetic testing is not considered necessary to establish a diagnosis, but can be useful in pre-natal and carrier testing.[1]

Liver biopsy specimens cannot be used to make a diagnosis of LALD.[21] Liver biopsy is considered to be the most reliable method of evaluating liver abnormalities, such as the development of fibrosis and cirrhosis, however, it is an invasive procedure with associated risks and costs.[34] The CS states that blood tests should be used for initial assessment prior to biopsy.[34, 35] The CS also notes that hepatic magnetic resonance imaging (MRI) is being developed as an assessment technique for patients with LALD. MRI is not considered to be diagnostic, but may be a useful technique for monitoring progression (in preference to multiple repeated biopsies.[36]

2.2.7 Prognosis

As previously noted, LALD in infants is characterised by early and severe symptom onset with a median age of death 3.7 months[16] and almost 100% mortality within six months.

There are limited data on the life expectancy of LALD patients who present in childhood and adulthood, however, the Bernstein review of 135 LALD patients reported that 50% of deaths due to liver failure occurred before the age of 21 years and less than 10% of patients were older than 40 years of age.[14] In addition, a recent observational study of patients with LALD reported that the proportion of patients over 40 years of age identified was substantially lower (18.7%) than would be expected for the normal population (46.7%).[15]

2.2.8 Impact on patients' health-related quality of life (HRQoL)

There are no published data on HRQoL in people with LALD. The CS reports the findings of an on-line survey of patients and their families in the USA and Europe. The survey was conducted by Alexion and distributed through the UK Society for Mucopolysaccharide Diseases (MPS), AE LALD (Spanish LAL Deficiency support group) and a US based LAL Deficiency patient organisation, SOLACE (Support Organization for LAL Deficiency - Advocacy, Care and Expertise) which has some European based members. The CS states that the survey was designed in collaboration with clinicians and was approved by patient associations working with people affected by LALD.[1] In addition, HRQoL data from the

LAL-CL02 (ARISE) trial were reported,[37] and HRQoL data relating to the effects of chronic liver were presented for diseases considered to be comparable.[1] The limitations of this approach were acknowledged.

Eleven participants participated in the survey (median age 11 years, range 3 to 49 years). Eight (73%) of participants were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa.[1] The mean age at diagnosis was 5.6 years for children and 33.5 years for adults; for infantile-onset LALD HRQoL is likely to be a secondary consideration to improving survival. The most commonly reported symptom was abdominal pain (91%) of LALD patients; other symptoms mentioned by more than half of the survey sample were fatigue, diarrhoea, nausea, loss of appetite, itchy skin and having a swollen abdomen.[1] Five of the six school age children who participated in the survey were reported as being "able to follow full-time education"; four of these five children were being treated with sebelipase alpha, but it was not clear whether treatment had any effect on their schooling.[1] The mean EQ-5D scores, before treatment with sebelipase alpha, were 0.76 for children (N=8) and 0.34 for adults (N=2); the CS reported small increases in score after treatment (0.84 for children (N=6) and 0.76 for adults (N=1)).[1]

Quality of life data were collected in the sebelipase alfa study LAL-CL02 (ARISE), which included both children and adults (minimum age five years).[30] Study inclusion criteria meant that the HRQoL of participants, at baseline was similar to that expected for an unaffected population.[30] The study included people with substantial pathological liver damage at baseline, but this was not sufficiently severe to result in significant HRQoL detriment relative to the general population. The CS states that significant HRQoL detriment would be expected with progression to more severe liver disease such as decompensated cirrhosis/liver failure, liver cancer and liver transplantation.[1]

2.3 Current service provision

The CS states that Alexion is not aware of any published NICE, NHS England, other national or expert guidelines for the diagnosis, treatment or management of LALD. It is further stated that clinical guideline from the children's LSD centres in England is currently in draft form and will be submitted to NICE for review.[1] There is currently no standard treatment or typical care pathway for people with LALD. Prior to the development of sebelipase alfa, there were no safe and effective, pharmacological options with regulatory approval for the treatment of LALD.[1] Management options are focussed on supportive care and controlling or treating liver complications and include lipid-lowering therapies, vitamin E supplementation, haemaopoietic stem cell transplantation and liver transplantation.[1] Section 8 of the CS, pages 66 to 73 provides a detailed description of various management options.

2.4 Description of the technology under assessment

2.4.1 Sebelipase alfa

Sebelipase alfa is an enzyme replacement therapy (ERT), which is administered by intravenous infusion. It is a recombinant form of the human LAL enzyme and was developed to treat LALD by replacing the deficient enzyme. Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently taken up by lysosomes,

where it catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Sebelipase alfa is the first pharmacological treatment to undergo regulatory approval specifically for the treatment of LALD.

2.5 Current usage in the NHS

In the UK there is one patient being treated with sebelipase alfa under a compassionate use protocol and 11 patients currently being treated within a clinical trial.[1]

3. CRITIQUE OF THE COMPANY'S INTERPRETATION OF THE DECISION PROBLEM

3.1 Introduction

The remit of this appraisal, as defined in the final agreed NICE scope, is to evaluate the benefits and costs of sebelipase alfa within its marketing authorisation for treating lysosomal acid lipase deficiency for national commissioning by NHS England. The final NICE scope outlines the agreed population, intervention, comparators and outcomes for the appraisal. The NICE scope also sets out wider considerations relating to the impact of the technology beyond direct health benefits and on the delivery of the specialised service, the nature of the condition, costs to the NHS and PSS and value for money.

On 25 June 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Kanuma (sebelipase alfa), intended for the treatment of lysosomal acid lipase (LAL) deficiency. The full indication is: "for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency." It is proposed that Kanuma be prescribed by physicians experienced with the treatment of lysosomal acid lipase (LAL) deficiency, other metabolic disorders or chronic liver disease.

3.2 Adherence to the decision problem

Table 3.1 presents a summary of the decision problem as set out in the NICE scope and the company's adherence to this (based on information presented on pages 25-29 of the CS).

Table 3.1: Adherence of the CS to the agreed decision problem

	Final scope issued by NICE	**Deviations of submission from the scope**
Population	People with lysosomal acid lipase deficiency	The population is in line with scope
Intervention	Sebelipase alfa	The intervention is in line with scope
Comparator(s)	Established clinical practice without sebelipase alfa	The comparator is in line with scope The submitted cost-consequence model compares SA to BSC, in line with the scope. BSC included liver transplant, but other treatment options were not included (see 5.3.2).
Outcomes	The outcome measures to be considered include: • mortality • cholesterol level (total, LDL and HDL) • triglycerides level • transaminase level • liver synthetic function • liver disease progression • liver transplant • liver fat content • cardiovascular events • adverse effects of treatment • health-related quality of life (for patients and carers).	The following outcome measures are not reported: • liver synthetic function, • liver disease progression, • liver transplant, and • cardiovascular events.
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	No variation from final scoping document.
Impact of the new technology	• Clinical effectiveness of the technology • Overall magnitude of health benefits to patients and, when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	No variation from final scoping document.

Cost to the NHS and PSS, and Value for Money	• Budget impact in the NHS and PSS, including patient access agreements (if applicable) • Robustness of costing and budget impact information • Technical efficiency (the incremental benefit of the new technology compared to current treatment) • Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)	The company states that the CS shows no variation from the final scoping document. However, costs falling within PSS have not been included or discussed in the CS.
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • Staffing and infrastructure requirements, including training and planning for expertise.	No variation from final scoping document.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows the following subgroups will be considered • infants with very rapidly progressing lysosomal acid lipase deficiency • people who have had a liver transplant	No subgroup analyses have been undertaken. The company added: "Currently, all patients with LAL deficiency are being considered. Subgroup analysis will not be undertaken." And "No data are available on patients with a liver transplant and therefore this subgroup analysis is not possible."

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The population included in the submission relates to people with lysosomal acid lipase (LAL) deficiency. This is in line with the population in the scope

The studies included in the submission focus on the following populations and studies:

- Paediatric (≤ 2 years) patients with LAL Deficiency: LAL-CL03 (single arm sebelipase alfa study) and LAL-1-NH01 (historical control group)
- Paediatric/adult (≥ 4 years) patients with LAL Deficiency: LAL-CL02 (ARISE, 20 weeks placebo controlled RCT)
- Adults (≥ 18 years) with LAL Deficiency: LAL-CL01 (4 weeks single arm sebelipase alfa study) and LAL-CL04 (156 weeks extension of CL01)

3.3.2 Interventions

The intervention included within the CS relates to sebelipase alfa in line with its licensed indication.

In the CS (page 12 and 31) the recommended dosage regimens of sebelipase alfa are described as: The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL Deficiency is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response. The recommended dose in children and adults who do not present with rapidly progressive LAL Deficiency prior to six months of age is 1 mg/kg administered as an intravenous infusion once every other week. The intervention is expected to be a lifetime therapy.

3.3.3 Comparators

The comparator is described in the CS as Best Supportive Care (BSC). This is in line with the NICE scope which defines the comparator as "established clinical practice without sebelipase alfa".

Data for the comparator were taken from a randomised controlled trial (LAL-CL-02 (ARISE)) for patients aged four years and older with LAL deficiency (N=66, 36 sebelipase alfa and 30 placebo) and from a natural history study including 35 paediatric patients (≤ 2 years) with LAL deficiency (study LAL-1-NH01).

3.3.4 Outcomes

As specified in the Table with the Statement of the decision problem (CS, Table A1.1, page 25), the studies do not provide data on the following outcomes:

- liver synthetic function
- liver disease progression
- liver transplant
- cardiovascular events

This is particularly problematic because liver failure is one of the main manifestations of

LAL Deficiency. As specified in the company submission: "Serious liver complications often develop at an early stage of disease and progress at a faster rate than in most other liver diseases" (CS, page 11). In addition, the CS describes the mechanism of action of sebelipase alfa as follows:

> "Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL). Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Replacement of LAL enzyme activity leads to reductions in liver fat content and transaminases, and enables metabolism of cholesteryl esters and triglycerides in the lysosome, leading to reductions in low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (HDL-c), triglycerides, and increases in HDL-c. Improvement in growth occurs as a result of substrate reduction in the intestine (Kanuma SPC, 2015)." (CS, page 12)

Therefore, only the following outcomes have been reported in the CS:

- mortality
- cholesterol level (total, LDL and HDL)
- triglycerides level
- transaminase level
- liver fat content
- adverse effects of treatment
- health-related quality of life (for patients and carers)

Regarding health-related quality of life, only very small populations were included in the assessment of each instrument, making it impossible to draw strong inferences from the data. In addition, patients in the RCT (LAL-CL02), [redacted]

3.3.5 Cost to the NHS and PSS, and value for money

The CS includes a cost-consequence model in which the primary health outcome is valued in terms of incremental QALYs gained. In general the scope was followed when assessing the costs of sebelipase alfa to the NHS and the value for money it provides.

4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[38] The submission was checked against the interim highly specialised technologies specification for manufacturer/sponsor submission of evidence.[39] The ERG has presented only the major limitations of each search strategy in the main report. Further minor criticisms of each search strategy can be found in Appendix 1.

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on the efficacy and safety of sebelipase alfa. The strategy searched for terms in the intervention facet (sebelipase alfa) only, and did not limit to the LAL Deficiency population.

A good range of resources were searched including: Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, NHS Economic Evaluation Database, MEDLINE and MEDLINE Complete.

The company confirmed in their clarification response[11] that grey literature and conference proceedings were identified through database searches (including PubMed in addition to the databases listed above), reference checking and hand-searching journals publishing conference proceedings. The ClinicalTrials.gov website was also searched. The search terms that were used for grey literature and conference proceedings searches were provided by the company.

No language or date limits were applied. There are minor issues relating to the reporting of the strategy (see Appendix 1), however the database name, database date span, host and date searched were provided for all searches. The searches used indexing terms and free text combined with Boolean logic (AND, OR) and were sufficiently broad to capture all relevant publications on sebelipase alfa. The ERG feels that additional terms such as Kanuma, or the CAS Registry number could have been added to the search, but it is unlikely that relevant records have been missed by not including these terms.

4.1.2 Inclusion criteria

The eligibility criteria for the review are described in Table 4.1 (CS, Table C9.1, page 75 (published studies) and Table C9.2, page 77 (unpublished studies)). The inclusion criteria are broad and aim to include all relevant studies relating to sebelipase alfa.

Table 4.1: Eligibility criteria

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

ERG comment:

As can be seen from the table, the search was not aimed at comparator studies. As far as the ERG can see, no searches were done to identify relevant natural history studies. Therefore, the only natural history studies included in the submission are those performed by the company (LAL-1-NH01 and LAL-2-NH01). The ERG is not aware of other relevant natural history studies.

4.1.3 Critique of data extraction

Methods for the systematic review process have not been reported. Therefore, there is no information regarding the number of reviewers involved in the study selection process and the data extraction process. It is common practice in systematic reviews that every step in the review is performed by at least two reviewers to minimise bias and to prevent mistakes. In this case there is no guarantee that the data extraction process was correct.

4.1.4 Quality assessment

There is no information regarding the number of reviewers involved in the quality assessment process.

The randomised controlled trial (study LAL-CL02) was assessed using criteria from CRD guidance (2009).[40] The other two intervention studies (LAL-CL03, and LAL-CL01/04) were assessed using and adapted checklist from the Critical Appraisal Skills Programme (CASP): 'Making sense of evidence, 12 questions to help you make sense of a cohort study'. No references were provided for this instrument. The quality of the natural history study (LAL-1-NH01) was not assessed.

4.1.5 Evidence synthesis

As stated in the CS, no meta-analyses or indirect comparisons were presented (CS, page 134):

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

ERG comment:

The ERG agrees with this approach.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The company submission includes four sebelipase alfa studies and one historical control study (See Table 4.2). All studies were performed by Alexion.

Two ongoing unpublished studies, LAL-CL06 and LAL-CL08 were reported in the CS. In addition, Alexion states that "no relevant published studies were excluded" (CS, Section 9.3.2, page 80). However, a second historical control study (LAL-2-NH01) was performed by Alexion which is not included in the submission. This study is mentioned below.

Table 4.2: Studies included in the CS

Study Name (Status)	Study Design	Study Objective(s)	Population	Intervention/ Comparator	Treatment Duration	Data source
LAL-CL03 (Primary analysis complete; Follow-up ongoing)	Phase 2/3, single-arm, open-label	Efficacy, Safety, and PK	Paediatric (≤ 2 years) patients with LAL Deficiency, n=9	Sebelipase alfa: Dose escalation from 0.35 to 1 mg/kg once weekly IV; Up to 3 or 5 mg/kg once weekly IV	Up to 208 weeks	CSR LAL-CL03[41]
LAL-1-NH01 (Historical control group for LAL-CL03, Complete)	Observational, non-interventional	Chart review of children with LAL Deficiency	Paediatric (≤ 2 years), n=35	N/A	N/A	Jones, 2015a[16]
LAL-CL02, ARISE (Double-blind period complete; Open-label period ongoing)	Phase 3, randomised, double-blind, placebo-controlled; followed by open-label extension	Efficacy, Safety, and PK	Paediatric / adult (≥ 4 years) patients with LAL Deficiency, n=66 (36 sebelipase alfa / 30 placebo)	Sebelipase alfa 1 mg/kg every other week IV, Placebo	20 weeks double-blind followed by open-label up to 130 weeks	CSR LAL-CL02; Burton 2015a[30, 42]
LAL-CL01 (Complete)	Phase 1/2, single-arm, open-label, dose escalation	Safety, PK, and PD	Adults (≥ 18 years) with LAL Deficiency, n=9 (3/cohort)	3 cohorts: 0.35, 1, and 3 mg/kg once weekly IV	4 weeks	Balwani, 2013a; CSR LAL-CL01[37, 43]
LAL-CL04 (Enrolment; complete; Follow-up ongoing)	Phase 2, single-arm, open-label extension for patients who completed LAL-CL01	Efficacy and Safety	Adults with LAL Deficiency (≥ 18 years), n=8	Sebelipase alfa: 0.35, 1, or 3 mg/kg, once weekly IV for 4 weeks; 1 or 3 mg/kg once every other week IV	Up to 156 weeks	Balwani, 2013a; CSR LAL-CL04[43, 44]

Source: CS, Table C9.3, page 79

4.2.2 Details of relevant studies not included in the submission

As reported above, two ongoing unpublished studies, LAL-CL06 and LAL-CL08 with expected completion dates of June 2017 and December 2018 respectively, were reported in the CS. The efficacy results from these studies are not included in this submission due to lack of availability, however where possible, available safety data has been included in the submission.

Alexion states that "no relevant published studies were excluded" (CS, Section 9.3.2, page 80). However, a second historical control study (LAL-2-NH01) was performed by Alexion which is not included in the submission. According to Alexion: "This study focused on centres with living patients and, as all patients were alive at the time of data collection, this study provided very little insight into end-stage disease and mortality associated with LAL Deficiency". It is unclear how many of these patients were comparable to any of the patients included in the sebelipase alfa studies.

These three studies are described in Table 4.3

Table 4.3: Studies not included in the CS

Study Name (Status)	Study Design	Study Objective(s)	Population	Sebelipase alfa - Dose	Treatment Duration	Data source
LAL-CL06 (Enrolment complete; Follow-up ongoing)	Phase 2, single-arm, open-label	Efficacy, Safety, and PK	Paediatric / adult (> 8 months) (N=31)	1 mg/kg qow IV	Up to 96 weeks	NR Completion date June 2017
LAL-CL08 (Ongoing)	Phase 2, single-arm, open-label	Efficacy, Safety, and PK	Paediatric (< 8 months) (N=Up to 10 planned)	1 mg/kg qw IV; Up to 3 or 5 mg/kg qw IV	Up to 156 weeks	NR Completion date December 2018
LAL-2-NH01 (Historical control group, Complete)	Observational, non-interventional	Chart review of children with LAL Deficiency	Patients with LAL Deficiency, either alive or deceased, who were ≥ 5 years of age at the time of consent and had a documented diagnosis of LAL Deficiency, n=48 (prospective data for 24)	N/A	N/A	CSR LAL-2-NH0[28]

Source: CS, Table A4.1, page 34 and Section 6, page 47

4.2.3 Summary and critique of company's analysis of validity assessment

The following concerns regarding the quality of study LAL-CL02 were reported in the CS:

- Groups were similar in terms of baseline demographics, onset of LAL Deficiency-related abnormality, serum transaminases, liver fat content and volume and history of lipid-

lowering medication. However, levels of Non-HDL-c and cholesterol were significantly lower in the sebelipase group. HDL-c and LDL-c were not significantly different.

- The analyses did not include an ITT analysis. The Full Analysis Set (FAS) comprised patients in the Consented Set who, in addition, were randomised and received at least one dose of sebelipase alfa or placebo.
- The study included a 20-week double-blind period, which was followed by an open-label period of up to 130 weeks.

Studies LAL-CL03 and LAL-CL01/04 were well performed single arm cohort studies. However, the evidence derived from these studies has severe limitations. The main problem with these studies is the lack of a comparable control group. In the case of study LAL-CL03, the company has used data from a historical group as a control group. In the case of studies LAL-CL01/04, no control group has been provided.

4.3 Summary and critique of results

An overview of the baseline disease characteristics for the patients enrolled in studies LAL-CL03, LAL-CL02 and LAL-CL01 is provided in Table C9.9 of the CS and Table 4.4 below.

According to the company, the infants enrolled in study LAL-CL03 presented with an immediately life-threatening disease requiring urgent medical intervention and that the baseline characteristics for this group are consistent with those reported among the patients in the natural history study LAL-1-NH01, supporting the comparison of survival data and outcomes between the patients in these two studies.

However, the target population for study LAL-CL03 was patients presenting with LAL Deficiency in infancy with evidence of rapidly progressive disease based on documented growth failure within the first six months of life. In the natural history study LAL-1-NH01 growth failure within the first six months of life was not an in- or exclusion criterion. Therefore, a subpopulation of 21 infants from study LAL-1-NH01 with growth failure within the first six months of life based on objective criteria similar to those used in study LAL-CL03 and, like patients in study LAL-CL03, who had not received prior HSCT or liver transplant, was used for the primary comparison. In addition, a subpopulation of 25 infants from study LAL-1-NH01 was used, [redacted] This comparison group was added because [redacted]

Table 4.4: Baseline demographic and disease characteristics

Characteristics	LAL-CL03	LAL-1-NH01	LAL-1-NH01	LAL-1-NH01	LAL-CL02			LAL-CL01
	All (N = 9)	All (n=35)	All (n=21)*	All (n=25)**	All (n=66)	Sebelipase alfa (n=36)	Placebo (n=30)	All (N = 9)
Males, n (%)	5 (56)	19 (54.3)	10 (47.6)	[redacted]	33 (50)	18 (50)	15 (50)	6 (67)
White, n (%)	[redacted]	17 (48.6)	[redacted]	[redacted]	55 (83)	27 (75)	28 (93)	9 (100)
Not Hispanic or Latino, n (%)	[redacted]	26 (74.3)	[redacted]	[redacted]	56 (85)	30 (83)	26 (87)	9 (100)
Age at Onset of LAL Deficiency-related abnormality (years) Mean ± SD (Median)	[redacted]	0.12 ± 0.11 (0.08)	[redacted]	[redacted]	6.5 ± 7.12 (4.0)	7.5 ± 8.36 (5.0)	5.4 ± 5.16 (4.0)	13.1 ± 11.19 (9.8)
Age at Randomisation/First Dose (years) Mean ± SD (Median)	[redacted]	N/A	N/A	N/A	16.1 ± 10.93 (13.0)	16.8 ± 11.52 (13.5)	15.2 ± 10.24 (13.0)	32.2 ± 10.54 (29.9)
Age < 12 years, n (%)	9 (100)	35 (100)	21 (100)	25 (100)	24 (36)	14 (39)	10 (33)	0
Mutation								
Homozygous Common	0	1 (8.3[c])	0 (0)	[redacted]	21 (32)	11 (31)	10 (33)	1 (11)
Heterozygous Common	0	2 (16.7[c])	1 (16.7[c])		35 (53)	17 (47)	18 (60)	8 (89)
Other[b]	6 (100[c])	4 (33.3[c])	0 (0)	[redacted]	10 (15)	8 (22)	2 (7)	0
Baseline transaminases (U/L) Mean ±SD								
ALT	[redacted]	NR	NR	NR	102.4±43.71	105.1±45.31	99.0±42.23	76±29
AST		NR	NR	NR	82.8±34.15	86.6±33.49	78.2±34.93	56±12
Baseline serum lipids (mg/dL) Mean ±SD								
LDLc	[redacted]	NR	NR	NR	207.9±65.85	189.9±57.16	229.5±69.95	144±71
Non-HDL-c	[redacted]	NR	NR	NR	240.2±71.06	220.5±61.48	263.8±75.48	NR
TG	[redacted]	NR	NR	NR	162.6±60.42	174.4±65.90	174.4±65.90	152±79
HDL-c	[redacted]	NR	NR	NR	32.8±7.22	32.4±7.09	33.4±7.46	35±10
Liver fat content (%) at baseline, Mean ±SD	NR	NR	NR	NR	8.50±3.50	8.75±3.95	8.16±2.80	NR
Baseline LLM use, n (%)	NA	NA	NA	NA	26 (39)	15 (42)	11 (37)	7 (78)

Source: CS, Table C9.9, page 93 and Response to Clarification Letter, Question A2

LAL = liposomal acid lipase; SD = standard deviation, NA = not applicable, NR = not reported, U/L = Units per litre

[a] [redacted]; [b] 'Other' mutation: at least one of the alleles has a defined mutation, nether allele has the common mutation; [c] [redacted]) 21 patients from study LAL-1-NH01 (with 'failure to thrive within 1st 6 months based on objective criteria similar to those used in LAL-CL03'); **) 25 patients from study LAL-1-NH01 ('all patients who have not received haematopoietic stem cell transplantation or liver transplant, irrespective of whether these patients met objective criteria for early failure to thrive').

The baseline disease characteristics in children and adults in study LAL-CL02 indicate that LAL Deficiency is a multisystem disease in this population with serious complications, including ongoing liver injury, advanced liver fibrosis and cirrhosis occurring at an early age, and marked disturbances of lipid metabolism.

All studies included patients from the UK. Study LAL-CL03 (N=9) included [redacted] paediatric patients. The natural history study LAL-1-NH01 (N=36) included [redacted]. Study LAL-CL02 (N=66) included [redacted] Study LAL-CL01 (N=9) included [redacted]. A full list of countries in each trial is presented in the Response to the Clarification Letter (Question A5).[11]

4.3.1 Efficacy in paediatric (≤ 2 years) patients with LAL Deficiency

LAL-CL03 was a multicentre, open-label, single-arm study of sebelipase alfa in nine patients with LAL deficiency with growth failure or other evidence of rapidly progressive disease prior to six months of age. Patients also had rapidly progressive liver disease and severe hepatosplenomegaly. The age range at study entry was 1-6 months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first two weeks and then 1 mg/kg once weekly. Based on clinical response, dose escalation to 3 mg/kg once weekly occurred as early as one month and up to 20 months after starting treatment at 1 mg/kg. A further dose escalation to 5 mg/kg once weekly was allowed.

4.3.1.1 Survival

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients in LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics (a subgroup of 21 patients from LAL-1-NH01). In LAL-CL03, 6 of 9 sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, one additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival, 95% CI: 0% to 16%).[10]

[redacted]

ERG comment:

The broader historical control group from study LAL-1-NH01 that included [redacted], seems to be the most comparable control group for the nine patients from study LAL-CL03. However, there is still considerable concern about the comparability of any of the patients in study LAL-1-NH01. Patients in study LAL-CL03 were all born in 2010 or later, while patients enrolled in the historical control study LAL-1-NH01

received a clinical diagnosis of "Wolman disease" between 1985 and 2012.[16] From patients listings provided by the company as part of the Response to Clarification Letter, [redacted]. Of course, it needs to be noted that there are very few data other than weight gain by which the patients in each of these studies can be compared. Nevertheless, on the basis of failure to thrive, the prognosis for patients in study LAL-CL03 appears similar to the prognosis for patients in study LAL-1-NH01 without sebelipase alfa.

Figure 4.1: Monthly weight gain by date of first chart review

[redacted]

4.3.1.2 Liver pathology

Transaminase levels: [redacted]

Liver fat content and liver volume: Liver fat content was not assessed in infants in study LAL-CL03 but liver volume was assessed by ultrasound and/or MRI. [redacted]

Liver histopathology: No liver biopsies were obtained in infants enrolled in study LAL-CL03.

4.3.1.3 Dyslipidaemia

LDL-c levels were shown to [redacted]

A summary of results in paediatric (≤ 2 years) patients with LAL Deficiency is presented in Table 4.5. As can be seen from the results presented above and in the table below, no comparable data were presented for the control group on any of the outcomes other than survival.

Table 4.5: Summary of results for paediatric (≤ 2 years) patients with LAL Deficiency

	Sebelipase Alfa (LAL-CL03, N=9)	Control patients* (LAL-1-NH01, N=21)	Control patients** (LAL-1-NH01, N=25)
Survival beyond 12 months	6 out of 9 (67%, 95% CI: 30% to 93%)	0 out of 21 (0%, 95% CI: 0% to 16%)	[redacted]
Median reduction in ALT levels at 4 weeks	[redacted]	NR	NR
Liver Fat Content	NR	NR	NR
Liver volume	[redacted]	NR	NR
Liver Histopathology	NR	NR	NR

*) 21 patients from study LAL-1-NH01 (with 'failure to thrive within 1st 6 months based on objective criteria similar to those used in LAL-CL03');
**) 25 patients from study LAL-1-NH01 ('all patients who have not received haematopoietic stem cell transplantation or liver transplant, irrespective of whether these patients met objective criteria for early failure to thrive').

4.3.2 Efficacy in Paediatric / adult (≥ 4 years) patients with LAL Deficiency

LAL-CL02 was a multicentre, double-blind, placebo-controlled study in 66 children and adults with LAL deficiency. Patients were randomised to receive sebelipase alfa at a dose of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. The age range at randomisation was 4-58 years old (71% were < 18 years old). For study entry, patients were required to have ALT levels of ≥1.5 X upper limit of normal (ULN). The majority of patients (58%) had LDL-cholesterol > 190 mg/dl at study entry, and 24% of patients with LDL-cholesterol > 190 mg/dl were on lipid lowering medicinal

products. Of the 32 patients who had a liver biopsy at study entry, 100% had fibrosis and 31% had cirrhosis. The age range of patients with biopsy evidence of cirrhosis was 4-21 years old.[10]

The following endpoints were assessed: normalisation of ALT, decrease in LDL-cholesterol, decrease in non-HDL-cholesterol, normalisation of AST, decrease in triglycerides, increase in HDL-cholesterol, decrease in liver fat content assessed by multi-echo gradient echo magnetic resonance imaging (MEGE-MRI), and improvement in hepatic steatosis measured by morphometry.

Transaminase levels: A statistically significant improvement in multiple lipid parameters was observed in the sebelipase alfa-treated group as compared to the placebo group at the completion of the 20-week double-blind period of the study, as shown in Table 4.6. The absolute reduction in mean ALT level was -57.9 U/l [redacted] in the sebelipase alfa-treated group and -6.7 U/l (-6%) in the placebo group.

Open-label period
Sixty-five of 66 patients entered the open-label period (up to 130 weeks) at a sebelipase alfa dose of 1 mg/kg once every other week. In patients who had received sebelipase alfa during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels. [redacted]

Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period. Consistent with what was observed in sebelipase alfa-treated patients during the double-blind period, initiation of treatment with sebelipase alfa during the open-label period produced rapid improvements in ALT levels and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Liver endpoints were provided in the company's response to the clarification letter[11] and have been added to Table 4.6. As explained by the company, meaningful interpretation of the outcomes related to liver disease progression at baseline and subsequent follow-up biopsies is challenging because of the short follow-up, small sample size and sampling variability in liver biopsies.

Table 4.6: Summary of primary and secondary efficacy endpoints (Study LAL-CL02)

Endpoint, Statistic	Population	Seb. alfa (N = 36)	Placebo (N = 30)	Difference (p-value)[a]
PRIMARY ENDPOINT:				
Normalisation of ALT, % (n/N)[c]	All, N = 66	31% (11/36)	7% (2/30)	24% (0.0271)
SECONDARY ENDPOINTS:				
Relative reduction in LDL-c, Mean (SD)[d]	All, N = 66	-28% (22.3)	-6% (13.0)	-22% (<0.0001)
Relative reduction in Non-HDL-c , Mean (SD)[d]	All, N = 66	-28% (18.6)	-7% (10.9)	-21% (<0.0001)
Normalisation of AST, % (n/N)[e]	Abnormal at Baseline, N = 65	42% (15/36)	3% (1/29)	39% (0.0003)
Relative reduction in triglyceride, Mean (SD)[d]	All, N = 66	-25% (29.4)	-11% (28.8)	-14% (0.0375)
Relative increase in HDL-c, Mean (SD)[d]	All, N = 66	20% (16.8)	-0.3% (12.3)	20% (<0.0001)
LIVER ENDPOINTS:				
Number of patients with confirmed cirrhosis at baseline / week 20: - No CC - CC	[redacted]	[redacted]	[redacted]	
Number of patients with Ishak score progression at week 20 compared to baseline (%): - Same - Improved - Worsened	[redacted]	[redacted]	[redacted]	

Source: CS, Table C9.11, page 107 and EMA EPAR[10], Table 3
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CC = confirmed cirrhosis; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; MRI = magnetic resonance imaging; SD = standard deviation; ULN = upper limit of normal
[a] p-value for treatment differences (Fisher's exact test for normalisation and liver histology endpoints and Wilcoxon rank sum test for all other endpoints).
[c] Proportion of patients who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34 or 43 U/L depending on age and gender). If the final assessment of ALT was < 10 weeks after the first dose, the patient was considered not to have ALT normalisation.
[d] Presented as mean percentage change from Baseline.
[e] Proportion of patients who achieved normalisation defined as a value below the ULN from the central laboratory (defined as 34-59 U/L depending on age and gender).

Liver fat content and liver volume: The percent reduction in hepatic fat content from Baseline to the end of the double-blind treatment period as assessed by MEGE-MRI was significantly greater for sebelipase alfa treated patients (32%) compared with those who received placebo (4%) ($p < 0.0001$) (Table 4.7). The percent reduction from Baseline in liver volume based on MRI also was greater in the sebelipase alfa group (10%) compared with placebo (3%) ($p = 0.0068$).

Table 4.7: Summary of secondary efficacy endpoints (Study LAL-CL02)

Endpoint, Statistic	Population	Seb. alfa (N = 36)	Placebo (N = 30)	Difference (p-value)[a]
SECONDARY ENDPOINTS:				
Relative reduction in liver fat content, Mean (SD)[d]	MRI Eligible[f] (N = 57)	-32% (26.8)	-4% (15.6)	-28% (<0.0001)
Improvement in liver histopathology, % (n/N)[g]	Consent to Biopsy[h] (N = 26)	63% (10/16)	40% (4/10)	23% (0.4216)
Relative reduction in liver volume, Mean (SD)	MRI Eligible[f] (N = 60)	-10% (10.5)	-3% (10.1)	-8% (0.0068)

Source: CS, Table C9.11, page 107 and EMA EPAR[10], Table 3
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; MRI = magnetic resonance imaging; SD = standard deviation; ULN = upper limit of normal
[a] p-value for treatment differences (Fisher's exact test for normalisation and liver histology endpoints and Wilcoxon rank sum test for all other endpoints).
[d] Presented as mean percentage change from Baseline.
[f] Abdominal MRI was required for all patients except 1) those with internal or otherwise non-removable metal medical items and 2) children for whom sedation was required but medically contraindicated. Multi-echo gradient echo assessments of liver fat content were not required in children who could not hold their breath for 15-30 seconds.
[g] The primary disease-specific histopathological assessment was steatosis as measured by morphometry. Proportion of patients with improvement of ≥ 5% in steatosis score over Baseline is presented.
[h] For patients ≥ 18 years of age, biopsies were required unless medically contraindicated. Biopsies were optional for patients < 18 years of age

Liver histopathology: Paired liver biopsies at baseline and week 20 were available in a subset of patients (n=26). Of patients with paired liver biopsies, 63% (10/16) of sebelipase alfa-treated patients had improvement in hepatic steatosis (at least ≥ 5% reduction) as measured by morphometry compared to 40% (4/10) of placebo patients. This difference was not statistically significant (Table 4.7).

4.3.3 Efficacy in adults (≥ 18 years) with LAL Deficiency

LAL-CL01 was a multicentre, open-label, dose-escalation study of sebelipase alfa in nine adult patients with LAL deficiency. The study was primarily designed to investigate the safety and tolerability of sebelipase alfa. No active or placebo control was included. The mean age at study entry was 32.2 years (SD: 10.54). Patients were allocated to one of three dose cohorts (three patients per cohort at 0.35, 1.0 and 3.0 mg/kg); all nine patients completed the study receiving four infusions of sebelipase alfa once weekly. Eight patients from LAL-CL01 entered the extension (up to 156 weeks) study LAL-CL04 between nine and 28 weeks after their last dose of sebelipase alfa in study LAL-CL01.

4.3.3.1 Liver pathology

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

Initiation of treatment with sebelipase alfa in study LAL-CL01 produced a rapid decline in ALT and AST (CS, Figure C9.6, page 110). When patients went off treatment at the end of study LAL-CL01 (interval between dosing of nine to 28 weeks), both ALT and AST

increased. Normalisation of transaminase levels continued during long-term treatment (through Week 104) in the extension study LAL-CL04.

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

Liver histopathology: In study LAL-CL04, pathology reports of post-treatment liver biopsies as well as historical pre-treatment biopsies were available from two patients. In these cases, pathology reports suggested that histopathological improvements were observed following extended treatment with sebelipase alfa in steatosis and fibrosis, although biopsies were not evaluated in a central laboratory.

4.3.3.2 Dyslipidaemia

In adults in study LAL-CL01, more substantial increases were noted for cholesterol and triglycerides during the initial four week treatment period (CS, Figure C9.9, page 116). This was observed following the initial four weekly infusions in study LAL-CL04 as patients who entered the extension study had been off treatment with sebelipase alfa ranging from nine to 28 weeks. These increases were higher in studies LAL-CL01/LAL-CL04 than those observed in study LAL-CL02; this difference may be due either to the more frequent dosing interval or more frequent assessments conducted in the earlier studies. By Week 104, all seven patients in study LAL-CL04 with data available at the time of the data cut-off showed decreases from their original study LAL-CL01 Baseline values in LDL-c and most had increases in HDL-c and decreases in triglycerides.

4.3.4 Health related quality of life

Patients enrolled in LAL-CL02 reported HRQoL at baseline that suggested [redacted]

Chronic Liver Disease Questionnaire (CLDQ): The CLDQ is a disease-specific instrument designed to assess health-related HRQoL in patients with chronic liver disease.[45] In LAL-CL02, the CLDQ was self -administered to all patients who were ≥17 years of age on the date of informed consent. The CLDQ has 29 items with a range of scores from one (worst possible function) to seven (best possible function); higher values indicate better HRQoL.

[redacted]

[redacted]

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue): The 13-item FACIT-Fatigue scale was developed to measure levels of fatigue in people living with a chronic disease. In this study, the FACIT-Fatigue scale version four was self-administered by all patients who were ≥17 years of age at date of informed consent. The FACIT-Fatigue total score ranges from 0 to 52. A score of <30 indicates severe fatigue. A higher value indicates a better HRQoL. The FACIT-Fatigue total score could only be calculated if more than 50% of the items were answered (a minimum of 7 of 13 items).[46]

[redacted]

Pediatric Quality of Life Inventory (PedsQL): The PedsQL is composed of generic core scales and disease-specific modules. The 23 item PedsQL 4.0 Generic Core Scales was designed to measure the core dimensions of health, as delineated by the World Health Organisation (WHO), as well as role (school) functioning in healthy children and those with acute or chronic health conditions. The PedsQL Generic Core Scales includes four multidimensional scales of physical functioning (eight items), emotional functioning (five items), social functioning (five items) and school functioning (five items). In addition to the total scale score (all 23 items), two summary scores, the Physical Health Summary (eight items) and Psychosocial Health Summary (15 items), were also reported. In this study, the PedsQL 4.0 Generic Core Scales were self-administered by patients who were five to <18 years of age on the date of informed consent, using one of the three self-report forms (ages 5-7, 8-12, or 13-18), as appropriate to the patient's age.[47] Parent proxy reports were not used in this study. The minimal clinically important difference is 4.4.[48]

[redacted]

As full results for health related quality of life (HRQoL) from LAL-CL02 were not reported in the company submission, the ERG asked the company to complete the table below (Table

4.8). Results show that none of the differences between groups were statistically significant, which was expected given the [redacted] baseline scores suggesting [redacted]

Table 4.8: Health related quality of life outcomes from LAL-CL02

	Sebelipase Alfa						Placebo						Difference	
	Baseline			Follow-up (20 wks)			Baseline			Follow-up (20 wks)				
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	Mean	p-value
CLDQ														
AB														
AC														
EM														
FA														
SY														
WO														
FACIT Fatigue														
PedsQL														
PH														
PSY														
PHY														
ES														
SF														
SCH														

CLDQ Subscales: AB=Abdominal Activity, AC=Activity, EM=Emotional Function, FA=Fatigue, SY=Systemic Symptoms, WO=Worry
PedsQL Subscales: PH=Physical Health, PSY=Psychosocial Health, PHY=Physical Score, ES=Emotional Score, SF=Social Functioning, SCH=School Functioning
Difference: Difference between the mean change of sebelipase alfa – Placebo; p-value: Wilcoxon rank sum test for treatment differences.

4.3.5 Safety and tolerability

According to the EMA EPAR[10] the most serious adverse reactions, experienced by 3% of patients taking sebelipase alfa in clinical studies, were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

In addition, EMA provided data describing adverse reactions reported in infants who received sebelipase alfa in clinical studies at doses up to 3 mg/kg weekly (Table 4.9) and adverse reactions reported in children and adults who received sebelipase alfa in clinical studies at a dose of 1 mg/kg once every other week (Table 4.10). Adverse reactions are listed by System Organ Class and frequency. Frequencies are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4.9: Adverse reactions reported in infants[c] receiving sebelipase alfa

MedDRA System organ class	Frequency[a]	MedDRA preferred term
Immune system disorders	Very common	Eyelid oedema
Psychiatric disorders	Very common	Agitation[b], irritability[b]
Nervous system disorders	Very common	Hypotonia
Cardiac disorders	Very common	Tachycardia[b]
Vascular disorders	Very common	Hypertension, pallor[b]
Respiratory, thoracic and mediastinal disorders	Very common	Respiratory distress, wheezing, cough, rhinitis, nasal congestion, sneezing
Gastrointestinal disorders	Very common	Diarrhoea, gastro-oesophageal reflux disease, retching, vomiting[b]
Skin and subcutaneous tissue disorders	Very common	Urticaria[b], rash[b], eczema[b], pruritis, rash maculo-papular
General disorders and administration site conditions	Very common	Chills, hyperthermia, pyrexia[b], oedema
Investigations	Very common	Body temperature increased, oxygen saturation decreased, blood pressure increased, heart rate increased, respiratory rate increased

Source: EMA EPAR[10]
a Very common = Reported in ≥ 1 patient receiving sebelipase alfa
b Reported in ≥ 2 patients receiving sebelipase alfa
c Age at first dose: 1 to 6 months

Table 4.10: Adverse reactions reported in children and adults[d] receiving sebelipase alfa

MedDRA System organ class	Frequency[a]	MedDRA preferred term
Infections and infestations	Common	Urinary tract infection
Immune system disorders	Common	Anaphylactic reaction, eyelid oedema
Metabolism and nutrition disorders	Common	Transient hypercholesterolaemia, transient hypertriglyceridaemia
Psychiatric disorders	Common	Anxiety[c], insomnia
Nervous system disorders	Common	Dizziness
Cardiac disorders	Common	Tachycardia
Vascular disorders	Common	Hyperaemia[e], hypotension
Respiratory, thoracic and mediastinal disorders	Common	Laryngeal oedema[e], dyspnoea[b,c,e]
Gastrointestinal disorders	Common	Diarrhoea[b,e], abdominal pain[b,e], abdominal distension, nausea[b,e]
Skin and subcutaneous tissue disorders	Common	Urticaria, rash[c,e] (including rash papular and rash pruritic), pruritus, eczema[e]
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Common	Chills, chest discomfort[c,e], oedema, fatigue, infusion site induration, pyrexia
Investigations	Common	Body temperature increased[b,c]
Injury, poisoning and procedural complications	Common	Infusion related reaction[c]

Source: EMA EPAR[10]

a Common = Reported in ≥ 1 patient receiving sebelipase alfa

b Reported at the same frequency in patients receiving sebelipase alfa or placebo or more frequently in patients receiving placebo during the double-blind period of LAL-CL02

c Reported as part of an adverse reaction in a single patient receiving sebelipase alfa in LAL-CL02

d Age at first dose: 4 to 58 years

e Reported in ≥ 2 patients receiving sebelipase alfa

Adverse events as reported in the CS are as follows:

Common adverse events in infants: [redacted] enrolled in study LAL-CL03 reported at least one treatment emergent adverse event (TEAE). Table 4.11 presents the most commonly reported TEAEs during study LAL-CL03, i.e., those events reported in three or more patients. This cut-off point was chosen based on the small sample size for this study (N=9).

[redacted]

Table 4.11: Summary of treatment-emergent adverse events, regardless of causality, occurring in three or more patients (Study LAL-CL03, safety population)

MedDRA System Organ Class Preferred Term	Patients (N=9) n (%)
[redacted]	[redacted]
[redacted]	
Vomiting	6 (67)
Diarrhoea	6 (67)
Skin and subcutaneous tissue disorders	
[redacted]	[redacted]
Urticaria	3 (33)
Infections and infestations	
Rhinitis	5 (56)
Catheter site or Device related infection[a]	3 (33)
Nasopharyngitis	3 (33)
[redacted]	[redacted]
Blood and lymphatic system disorders	
Anaemia	4 (44)
Respiratory, thoracic and mediastinal disorders	
Cough	3 (33)

Source: CS, Table C9.12, page 126

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

Common adverse events in children and adults: In study LAL-CL02, 86% (31 of 36) of patients in the sebelipase alfa group and 93% (28 of 30) of patients in the placebo group reported at least one TEAE during the double-blind period. The most common (≥10% incidence) TEAEs reported during the double-blind period in the sebelipase alfa group with corresponding incidence in the placebo group were headache (28% and 20%, respectively), pyrexia/body temperature increased (25% and 23%, respectively), upper respiratory infection (17% and 20%, respectively), diarrhoea (17% in each group), oropharyngeal pain (17% and 3%, respectively), epistaxis (11% and 20%, respectively), and nasopharyngitis (11% and 10%, respectively) (Table 4.12).

In study LAL-CL02, treatment-related AEs were reported in five patients (14%) in the sebelipase alfa group and six patients (20%) in the placebo group during the double-blind

period. All treatment-related TEAEs (by preferred term) in the sebelipase alfa group were reported in only one patient.

Table 4.12: Summary of treatment-emergent adverse events, regardless of causality, occurring in three or more sebelipase alfa-treated patients, by treatment group (Study LAL-CL02, FAS, double-blind treatment period)

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

Source: CS, Table C9.13, page 127

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

Deaths and serious adverse events: Overall, three deaths were reported in the sebelipase alfa clinical programme as of the data cut-off across the four primary studies evaluating safety; all patients who died were enrolled in study LAL-CL03. All fatal events were assessed as unrelated to sebelipase alfa treatment by the investigators. All deaths occurred after receiving four or fewer doses of sebelipase alfa with a median age at death of 2.9 years.

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

Serious AEs were reported in 12 (14.3%) of the 84 patients in the pooled safety set. SAEs were more frequent among infants in study LAL-CL03 with the most rapidly progressive form of LAL Deficiency (eight of nine patients, 89%) and were relatively infrequent among children and adults (4 of 75 patients, 5%). The most commonly reported types of SAEs were

infections (5 of 84 patients, 6%). One patient in study LAL-CL02 reported a serious infection (gastroenteritis). The only other SAE reported in more than one patient in the pooled safety set was pyrexia, reported in two patients in study LAL-CL03.

The majority of SAEs were assessed by the Investigator as unrelated to study treatment; two of 84 patients in the pooled safety set reported treatment-related SAEs, which were also considered potential hypersensitivity reactions, including one patient each in Studies LAL-CL02 and LAL-CL03; in addition, two patients in study LAL-CL08 had treatment-related SAEs which were also considered potential hypersensitivity reactions.

4.4 Summary of evidence presented in other submissions

No other scientific evidence was submitted by other consultees. This ERG report does not include a detailed discussion of non-scientific opinion submitted by other consultees or expert testimony provided by other consultees to the appraisal process; however, some of this information has been used to inform the discussion sections of this report. The following submissions were made to NICE:

- Birmingham Children's Hospital
- The Society for Mucopolysaccharide and Related Diseases (MPS Society)
- British Inherited Metabolic Disease Group and University College London Hospitals
- Royal College of Pathologists and Cambridge University Hospitals
- Salford Royal Hospital NHS Foundation Trust
- Consultant in Paediatric Metabolic Medicine, CMFT – Willink Unit
- NHS England

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work on clinical effectiveness undertaken by the ERG has been included in Section 4.3 of this report. No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The ERG is confident that all relevant studies (published and unpublished) of sebelipase alfa were included in the CS, including data from ongoing extension studies. Regarding historical control patients, two studies were available, but only results from one of these (LAL-1-NH01) were fully included in the submission. However, the clinical study report for the other historical control study (LAL-2-NH01) was part of the additional papers provided by the company. As described in Section 4.1.2, no searches were done to identify relevant LALD studies without the intervention. Therefore, there could be other, possibly better, natural history studies that were not included in the submission.

Several outcomes reported in the NICE final scope have not been assessed in the included studies, i.e. liver synthetic function, liver disease progression, liver transplant, and cardiovascular events. Instead, surrogate outcomes were used in the trials. These surrogate outcomes suggest a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. However, there is no evidence to address key clinical endpoints, such as

progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death. There is also no evidence to address long-term effectiveness of sebelipase alfa. Although, there is considerable follow-up in some of the sebelipase alfa studies, with nine patients having received sebelipase alfa treatment for up to 208 weeks and eight patients receiving up to 156 weeks of treatment, this is only a fraction of the expected lifetime treatment with sebelipase alfa. Therefore, the long-term safety and efficacy profile of sebelipase alfa remains uncertain.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

Evidence is presented for three populations:

- Paediatric (≤ 2 years) patients: a single arm study (N=9) with a historical control group (N=35, although only 25 comparable controls in terms of inclusion criteria). Only survival was reported for the control group; however, results seem biased in favour of sebelipase alfa due to differences in date of first diagnosis between experimental and control patients.
- Paediatric/adult (≥ 4 years) patients: a randomised placebo-controlled trial (N=66, 36SA/30PLA), which shows that "sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in children and adults with lysosomal acid lipase deficiency".[42] However, no comparative evidence was presented showing any improvements in clinical outcomes, including liver function, and quality of life.
- Adult (≥ 18 years) patients: a single arm study (N=9) without any control group.

Overall, there is no reliable comparative evidence showing any improvements in clinical outcomes, including survival, liver function, and quality of life; in addition, the long-term safety and efficacy profile of sebelipase alfa is uncertain.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The main uncertainty regarding the effectiveness evidence is the comparability of baseline characteristics from treated patients and historical control patients, the use of surrogate outcomes and the lack of long-term follow-up.

[redacted], while all nine patients included in LAL-CL03 were diagnosed after 2010. Given the likely improvements in supportive care over time, results from comparisons between treated patients (LAL-CL03) and historical control patients (LAL-1-NH01) may be biased in favour of sebelipase alfa.

Surrogate outcomes showed a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. These outcomes, on well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition. However, there is no evidence to address long-term and key clinical endpoints (progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death).

One of the most important outcomes is slowing the progression of the liver disease and hence delaying or avoiding liver transplant. The duration of trials providing data presented in the submission was not long enough to look at this outcome.

There is no mention in the CS of possible stopping rules for sebelipase alfa. In fact the company assumes treatment will be for the full lifetime of the patient (CS, Section 2.3, page 31). However, given the many differences between patients it cannot be assumed that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

This chapter is aimed to provide an assessment of whether or not sebelipase alfa for LAL Deficiency represents value for money for the NHS in England. The main source of evidence used to inform this assessment is the CS[1] to NICE, which includes a cost-consequence model and description of the methods and results of an economic analysis using the submitted model. This chapter first looks at a review of existing economic analyses for sebelipase alfa. This is followed by a detailed exposition and critique of the submitted model and accompanying economic analysis. Due to the concerns of the ERG with respect to the credibility of the submitted model, Chapter 6 includes exploratory analyses undertaken using an alternative model developed by the ERG. This analysis is in line with the company's choices regarding the use of evidence sources, assumptions and general model structure as much as possible. However inconsistencies and restrictive assumptions within the company's model are adjusted with the intention of providing a more robust basis for informing decision-making.

5.2 Review of existing economic analyses

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on quality of life, cost effectiveness and resource data for patients with LAL Deficiency or provide utilities, resource use or cost data for the economic model. The strategy searched for terms in the population facet (LAL Deficiency, including Wolman disease and cholesterol ester storage disease phenotypes), and did not limit to intervention (sebelipase alfa). The population terms were combined with study design filters for cost effectiveness, resource use and quality of life in a single search each for the Ovid and EBSCO hosts.

A good range of resources were searched including: Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, NHS Economic Evaluation Database, MEDLINE, MEDLINE Complete and EconLit.

The company confirmed in their clarification response[11] that conference proceedings were identified through the database searches and hand-searching conference proceedings.

No language or date limits were applied. The searches were clearly reported and reproducible, and the database name, database date span, host and date searched were provided for all searches. The searches were clearly structured, and used indexing terms and free text combined with Boolean logic (AND, OR).

ERG comment:

The ERG notes that one limitation of the search is that all Ovid databases were searched in one single strategy, and that only indexing terms for the Embase database (EMTREE) appear to have been used for the study design filters. The omission of Medline indexing terms (MeSH) could have resulted in potentially relevant records being omitted from the search results. The ERG also has concerns regarding the sensitivity of the search terms for resource use and HRQoL, and expansion of these elements of the search could have made them more

sensitive, for example with the use of additional indexing terms, and truncation to retrieve spelling variants/pluralisation. Given the small number of records retrieved by the LAL Deficiency facet, an alternative approach would have been to not apply study design filters. Further details are provided in Appendix 1.

The company focused the search strategy on LAL Deficiency only, while it aimed to identify all economic studies that could be used to inform the design of the economic model or provide utilities, resource use or cost data for the economic model. For this purpose the ERG feels a broader definition of the population would have been useful, in particular including non-alcoholic steatohepatitis (NASH), which was mentioned by the company as the appropriate disease analogue for modelling LAL Deficiency. Moreover, the company used an adapted version of the cost-effectiveness analyses by Mahady et al[49] which considered NASH patients (see also Section 5.3.2). Therefore, the ERG performed an additional search strategy to identify any economic studies, health state utility data, resource use data and cost data for NASH patients. The electronic databases MEDLINE and Embase (Ovid host) were searched, and after deduplication a total of 320 records were found and screened by the ERG. Further details are provided in Appendix 1.

In addition to the cost-effectiveness study by Mahady et al[2, 49] used by the company, this search query identified two additional potentially relevant cost-effectiveness studies. The study by Scaglione et al[50] was a conference proceeding only and did not contain sufficient detail to be used as a starting point to build a new model. The study by Zhang et al[51, 52] assessed the cost-effectiveness of screening strategies for NAFLD and could have been used as an alternative starting point to develop a model by the company (removing the screening part of the model).

The additional search did not identify any relevant health state utility data, resource use data nor cost data for LAL Deficiency patients that could have been used in the cost-consequence analysis.

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

The company's submission to NICE presents a model-based cost-consequence analysis for sebelipase alfa versus BSC for the treatment of patients with LAL Deficiency. The analysis is performed using NHS perspective. Potential costs which may fall under PSS are not reported. Costs and consequences are estimated for a population of 11 years-old over a lifetime horizon by extrapolation of health outcomes and costs of the hypothetical model cohort up to age 101, at which 99.9% of the hypothetical population has died. The primary model outcomes are the estimated incremental QALYs and incremental costs obtained by comparing the use sebelipase alfa with BSC. The company's model also estimates survival, which is used to estimate the QALYs for both arms. Adverse events were not included in the cost-consequence analysis. Health outcomes and costs are both discounted at a rate of 1.5%.

Patients receiving sebelipase alfa will remain on sebelipase alfa treatment for their entire lives, since in the sebelipase alfa group it is not possible in the model to progress to a worse health state and possibly receive other treatment. In the BSC group, the only treatment option

is a liver transplant, which is offered to patients that have progressed to "HCC". Hence, within the BSC group, any drug costs for BSC were not incorporated into the model, however other components of BSC, such as hospitalisations, were incorporated as background healthcare resource use costs, and estimated separately for infants.

ERG comment:

A few variations exist from the final scope issued by NICE in the submission. For instance, cardiovascular events and adverse events of sebelipase alfa treatment were in the final NICE scope, but were not included in the cost-consequence analysis. These issues are further discussed in Section 5.3.2. Other issues and adherence of the CS to the reference case principles can be seen in Table 5.1 below.

Table 5.1: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE	The scope of the economic analysis is generally in line with the scope developed by NICE. Adverse events and cardiovascular events, however, have not been incorporated (see 5.3.2).
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	The submitted cost-consequence model compares sebelipase alfa to BSC, in line with the scope. BSC included liver transplant, but other treatment options were not included (see 5.3.2).
Perspective on costs	NHS and PSS	The company states that the CS shows no variation from the final scoping document. However, costs falling within PSS have not been reported in the CS.
Perspective on outcomes	All health effects on individuals	Patient health benefits are included.
Type of economic evaluation	Cost-effectiveness analysis*	Incremental costs and benefits are assessed in the form of a QALY-based cost-consequence analysis.
Synthesis of evidence on outcomes	Based on a systematic review	Unclear whether appropriate sources were used (see 5.2 & 5.3.3).
Measure of health effects	QALYs	Health outcomes are valued in terms of QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Unclear whether appropriate sources were used (see 5.2 & 5.3.3.6).
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	Costs and outcomes were discounted at 1.5%.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to QALY gains.

**Not stated within the current HST methods guide*

5.3.2 Model structure

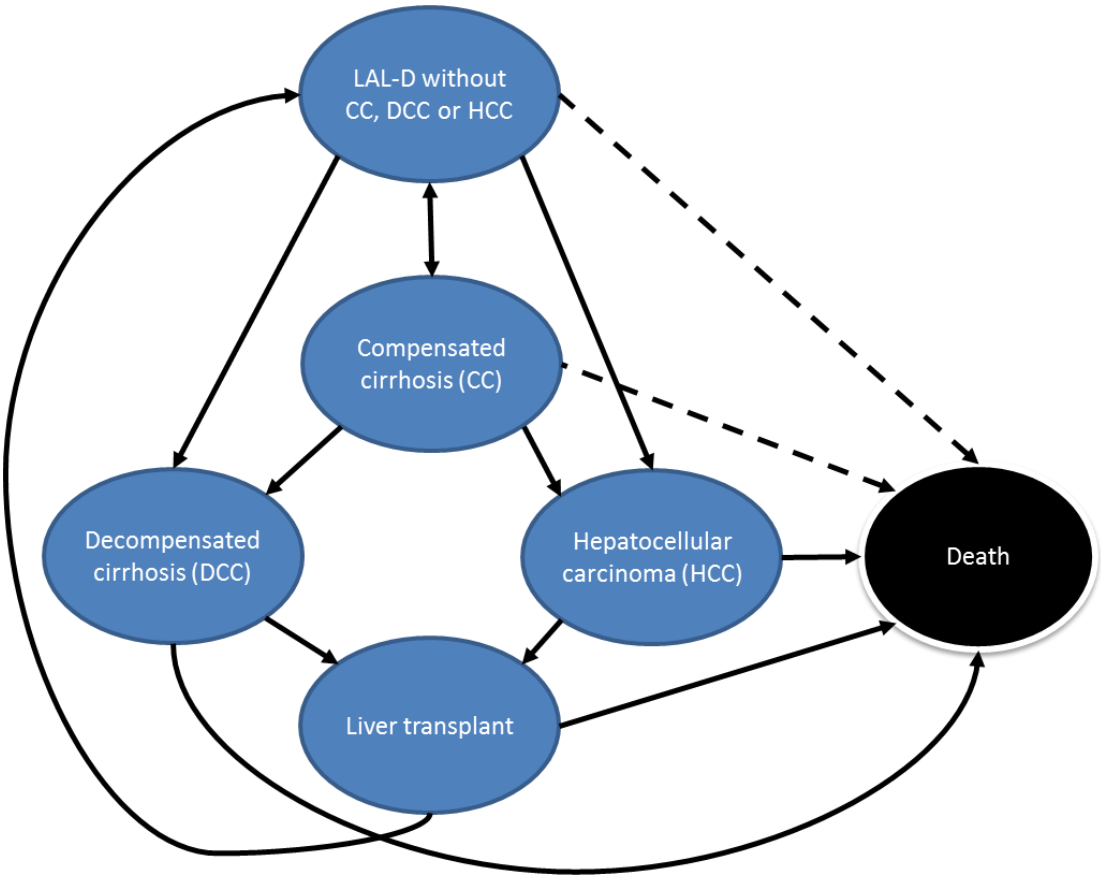
A decision-analytic Markov model was developed in Excel to perform the cost-consequence analyses of sebelipase alfa compared to BSC in LAL Deficiency patients by adapting a model for non-alcoholic fatty liver disease (NAFLD) published by Mahady et al (2012).[2] The CS stated that "NAFLD/NASH (non-alcoholic stepatohepatitis) is the closest disease analogue to LAL-D", which was justified based on clinical opinion of one expert (CS Table D12.1). The model aims to simulate the disease progression of LAL deficiency in both patient groups through liver disease progression, which is the primary manifestation of disease in LAL deficiency patients. Cardiovascular, gastrointestinal and other manifestations that commonly occur in patients with LAL deficiency are not included. Progression of liver disease over time, for patients receiving sebelipase alfa, is calculated based on the LAL-CL02 trial data,[4] whereas for BSC progression is derived from literature.[2] The impact of the disease is translated to costs, survival, and HRQoL via the submitted cost-consequence model.

The model consists of four health states representing different stages of liver disease progression; compensated cirrhosis ("CC"), decompensated cirrhosis ("DCC"), hepatocellular carcinoma ("HCC"), and "LALD without CC, DCC, or HCC". Furthermore, it includes a liver transplant state and a death state. These stages of liver disease are based on the proxy model by Mahady et al,[2] which is consistent with the stages of other liver disease progression models in the literature.[3, 5, 53-55]

Liver transplantation is included as a tunnel state, representing the patients in the "DCC" and "HCC" state that receive a liver transplant and corresponding health utility decrements and additional costs. After liver transplantation these patients automatically transition back to the "LALD without CC, DCC or HCC" health state, with the justification that the underlying disease is not cured and progression can again occur. "Death" is represented by one absorbing state while patients can transfer to this state through background mortality in each health state. Moreover, excess mortality is added for the "DCC", "HCC" and "Liver transplant" states. In the infant scenario, only two health states were used "Alive" and "Death".

Figure 5.1 provides the graphical presentation of the model as reported in the CS (CS Fig D12.1), where the dashed arrows are only possible for infants (age <1 year) and reflect potential for death within first year of diagnosis in patients with infant-onset disease.

Figure 5.1: Model structure as provided by the company



Apart from background mortality, transitions between the health states are not age-dependent. Age-gender specific background death risks are estimated from UK life tables.[56] Liver transplant mortality rates, as well as rates for "DCC" and "HCC" mortality, are obtained from the proxy model by Mahady and other literature.[2, 5] For the sebelipase alfa group, transition probabilities between the liver disease states are estimated from the LAL-CL02 data,[4] whereas for the BSC group they are mostly obtained from the proxy model.[2] Derivation of the "Liver transplant", "DCC", and "HCC" mortality risks and transitions between the "Alive" health states will be further explained in Section 5.3.3.

The model has a lifetime time horizon and adopted NHS perspective. A cycle length of one year was used. The model employs a half-cycle correction. A discount rate of 1.5% per year for health effects and costs was used. In the base case, a starting age of 11 and an initial liver disease distribution of (84%; 16%; 0%; 0%) for ("LALD without CC, DCC, or HCC"; "CC"; "DCC"; "HCC) was used based on the LAL-CL02 data.[4]

In the infant scenario, the starting age is 0 and all infants start in an "Alive" state, based on the LAL-1-NH01 study[6] and the LAL-CL03 study[7].

ERG comment:
Given the differences in assumptions between the comparators (e.g. some transitions are assumed to be absent for sebelipase alfa), the model structure differs largely between the sebelipase alfa and BSC group, as well as between the base case and the infants scenario. This is not clear from Figure 5.1, which is also missing the transition between the "DCC" and

"HCC" state. Therefore, the model structures for the sebelipase alfa and BSC group in the base scenario, as well as the infants scenario, are displayed in Figure 5.2 and Figure 5.3, respectively. Arrows to the "Death" state represent excess mortality. For infants in the sebelipase alfa group, the dashed arrow represents the transition for those surviving the first year to the "LALD without CC, DCC, or HCC" state, in which they then remain according to the base case scenario.

Figure 5.2: Model structure as provided by the ERG for the base case scenario

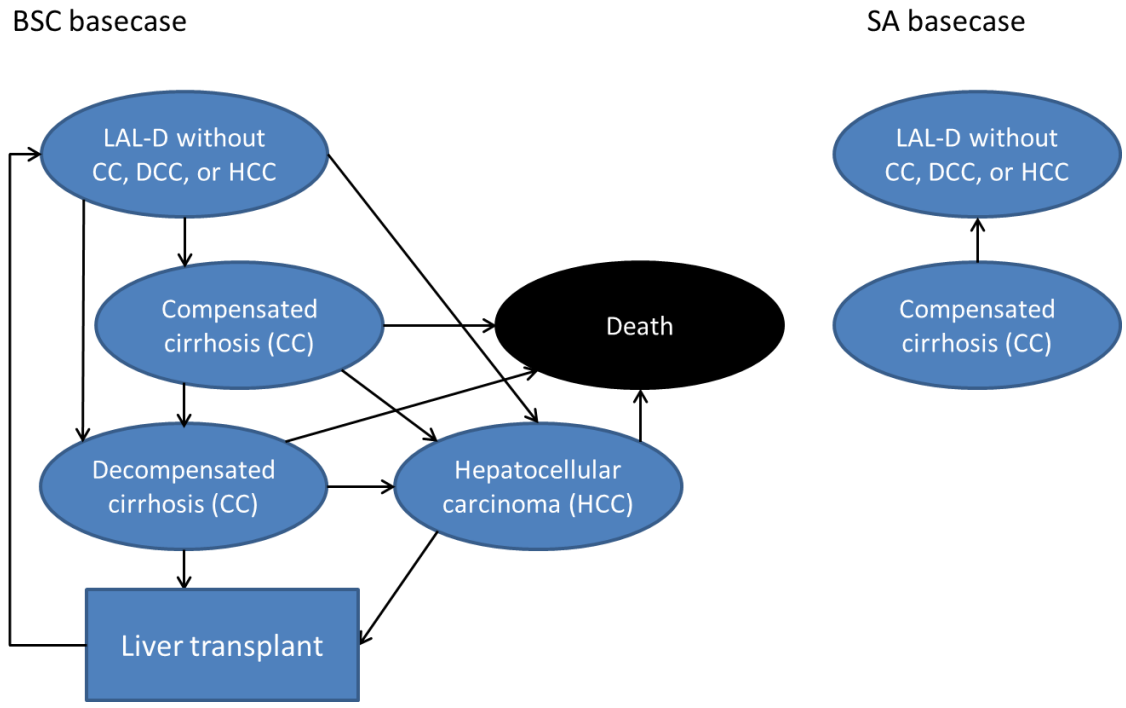
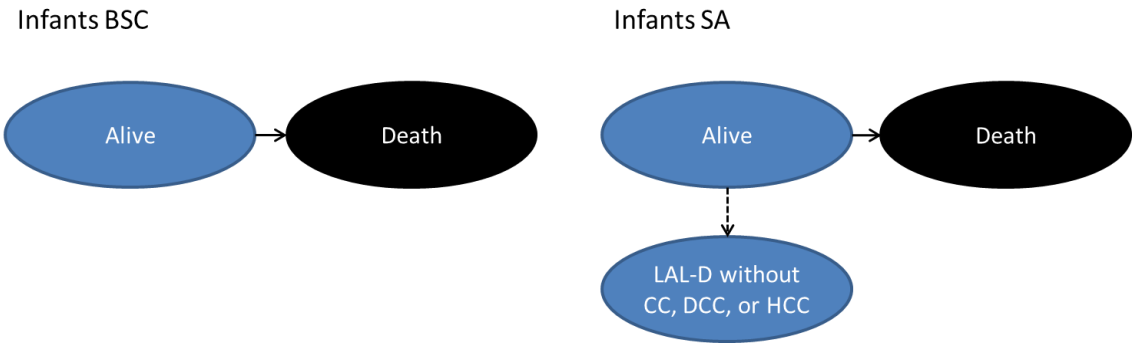


Figure 5.3: Model structure as provided by the ERG for the infant scenario



The model structure for BSC was mainly based on the economic model by Mahady et al.[2] It was assumed based on Mahady et al[2] that for the BSC group it was not possible to transit from "CC" to "LALD without CC, DCC or HCC", whereas this was possible for sebelipase alfa group, based on the LAL-CL02 trial.[4] For the sebelipase alfa group it was assumed that it was not possible to transit to the "DCC", "HCC" and "Liver transplant" health states. As can be seen in Figure 5.3, and alternative model structure was used for the first year in the infant scenario (afterwards the same model structure as for the base case, Figure 5.2, is used). During the first year in the infant scenario, only two health states were used "Alive" and

"Death".[6, 7] An overview of probabilities corresponding to the transitions between the health states is provided in Table 5.2.

Various issues concerning the model structure were identified by the ERG. The main issues are first summarised in Box 5.1 and elaborated afterwards.

Box 5.1: Main issues identified within the model structure in company's economic analysis

1. Appropriateness of use and adaptations of Mahady model as a proxy for LAL Deficiency
   - 1.1.1. Lack of any treatment related adverse events
   - 1.1.2. Effect on other organ systems not modelled
   - 1.1.3. Post-liver transplant state excluded
   - 1.1.4. Exclusion of treatment options for HCC
2. Appropriateness of discount factor

1. Appropriateness of use and adaptations of Mahady model as a proxy for LAL Deficiency

As there is very little evidence available on LAL Deficiency, the company chose to use evidence from other liver disease models to model the long-term progression of LAL Deficiency. It was unclear why the model (structure, cycle time, transition probabilities etc.) by Mahady et al, which was developed for a population with a much older starting age of 50 years, was selected from the available literature (see Section 5.2).[2] When the ERG requested more information on this choice the company explained that "clinical experts identified NAFLD as the most appropriate analogue to LAL deficiency so Mahady et al was used". As no formal expert elicitation has been performed and this was based on the opinion of only one expert, it remains unclear why NAFLD would be the best proxy disease.

The company also explained that "Mahady et al, which was used in our model, was the only NAFLD model identified in a literature review published in 2015 sponsored by NICE[2]". However, this literature review was not a review of NAFLD models, but aimed to identify "papers comparing the diagnostic accuracy of different non-invasive tests in the diagnosis and monitoring of liver fibrosis and cirrhosis with liver biopsy". Hence, if NAFLD would be the best proxy for LAL deficiency then this review may not have found the best available model as this was not the intention of their search strategy. Following the additional search and screening by the ERG (see Section 5.2) the study by Zhang et al,[51, 52] assessing the cost-effectiveness of screening strategies for NAFLD, could have been used as an alternative starting point to develop a model by the company (removing the screening part of the model). However, because of the differences in disease progression and population, compared to LAL deficiency, it might have been better to develop a de novo model that allows better capturing of the characteristics of the LAL deficiency population and LAL deficiency disease progression.

1.1 Lack of any treatment related adverse events

Treatment related adverse events, such as allergic reactions (including anaphylaxis), which were identified as important risks of sebelipase alfa by the EMA,[57] were not incorporated in

the cost-consequence analysis. In the clinical studies 21 of 106 patients (20%) experienced signs and symptoms either consistent with or that may be related to an allergic reaction (nine out of 14 infants (64%) and 12 out of 92 children and adults (13%)). The CS reports that "A total of 16 (19%) of the 84 subjects who received sebelipase alfa during Studies LAL-CL02, LAL-CL03 and LAL-CL01/LAL-CL04, including 5 (56%) of 9 infants and 11 (15%) of 75 children and adults, were reported to have experienced signs and symptoms either consistent with or potentially related to a hypersensitivity reaction". The majority of these events were mild to moderate in severity. The most serious adverse reactions experienced by 3% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. No subject permanently discontinued sebelipase alfa treatment due to a hypersensitivity reaction. Treatment with sebelipase alfa (or placebo) did not negatively impact the HRQoL of patients in the LAL-CL02 study and therefore the company did not include them in the cost-consequence analysis.

The ERG team understands the challenges of incorporating adverse events into the model with limited evidence. However, not incorporating adverse events into the model adds an additional level of uncertainty and results in QALY outcomes and costs that may be too optimistic. Hence the ERG requested to perform scenario analyses incorporating utility decrements and costs for these allergic reactions. Assuming that 3% of sebelipase alfa patients get an anaphylaxis reaction, the company performed a sensitivity analysis including event costs for anaphylaxis, but no health utility decrement. Further details and results of this analysis are reported in Section 5.4.2.

1.2 Effect on other organ systems not modelled

LAL Deficiency affects multiple organ systems and its manifestations can extend to for instance cardiovascular effects and gastrointestinal problems. While it is estimated that 87% of patients with LAL Deficiency experience manifestations in more than one organ,[14] these are excluded from the model owing to lack of data. In the CS it is stated that this is a serious shortcoming of the model and that "by excluding these other severe disease manifestations associated with LAL Deficiency, it is likely that this model underestimates the value of sebelipase alfa in the treatment of LAL Deficiency. This statement is however regarded as speculative and should be supported with data. The exclusion of other organ systems might potentially also overestimate the value of sebelipase alfa. For instance, not including cardiovascular effects may underestimate health state costs and overestimate utilities of health states.

1.3 Post-liver transplant state excluded

Instead of including a post-liver transplant state the CS model assumes that following a successful liver transplant, patients return to the "LALD without CC, DCC or HCC" state. Hence it was assumed that a previous liver transplant would not affect HRQoL or costs as the CS model assumed no utility decrement nor cost increase after liver transplant. The ERG considered this a conservative assumption as only BSC patients will receive a liver transplant in the model.

1.4 Exclusion of treatment options for HCC

In the CS it is stated that "the model is based on the structure in Mahady et al (2012) with a few exceptions".[2] One of these exception is the exclusion of the treatment options for HCC (Resection, Locoregional Therapy, Sorafenib & Palliation) as these "are a function of treatment decisions and patient access that may not apply to LAL deficiency patients" (stated in Section 12.1.4 of the CS). The ERG requested to justify why this does not apply to LAL Deficiency and hence why these treatment options have been omitted. The company has responded that "There are no data on the efficacy or effectiveness, or any other outcome measure, on using resection, locoregional therapy, or sorafenib in a LAL deficiency patient population" and "exclusion of these states is consistent with other liver disease models including the HCV models that were published and sponsored by NICE, for example Hartwell et al. (2011)." However, it was already concluded that the Mahady model had to be used as a proxy model, because of the limited available data, and that NASH/NAFLD was most similar to LAL Deficiency. It is unclear why, concerning these treatment options, the disease is then more similar to other liver diseases for which these states were also not modelled as well as how these adjustments of the model structure affect the outcomes.

2. Appropriateness of discount factor

The NICE Technology Appraisal Methods Guide specifies that a rate of 1.5% may be considered by the Appraisal Committee if it is highly likely that the long-term benefits will be achieved.[58] The ERG agrees that as the company states in the response letter 'For LAL deficiency, the cost-consequences model estimates incremental QALYs = 20.48 using a 1.5% discount rate. When discounted at 3.5%, these gains fall by more than half to 9.99, representing the situation described above in the NICE Methods Guide where "cost-effectiveness analyses are very sensitive to the discount rate used".[11] However, it is not specified that this rate should be applied in the base case analysis. Therefore, the ERG will additionally present the ERG base case with a discount rate of 3.5%.

5.3.3 Evidence used to inform the company's model parameters

The main evidence the company used to inform transition probabilities in the model was retrieved from the economic model by Mahady et al[2] considering NASH, the LAL-CL02 trial[4] and a paper by Hartwell et al.[5] In addition, for the infants scenario analysis the LAL-1-NH01 study[6] and LAL-CL03 study[7] were used to inform the transition probabilities for the first year. Health state utilities were retrieved from the economic model by Mahady[2] and based on assumptions for the infant scenario analysis. Costs were based on published papers[3] and for the infant scenario analysis NHS reference costs.

5.3.3.1 Relative treatment effects of sebelipase alfa versus best supportive care

No relative treatment effects were calculated nor explicitly used in the cost-consequences analysis.

5.3.3.2 Transition probabilities for best supportive care

The transition probabilities for BSC were mainly retrieved from the economic model by Mahady et al.[2] Only the transition from the "LALD without CC, DCC or HCC" health state to the "CC" health state was based on the LAL-CL02 trial.[4] Survival analysis was conducted to estimate this transition probability using the time to "CC". Specifically, the subset of

patients with a known baseline Ishak score (N=32) was analysed. For this purpose, the data collected prior to the treatment period in the LAL-CL02 trial were used (presumably retrospectively collected data). The event was defined as the earliest mention of a confirmed case of "CC" (N=12). Date of LAL Deficiency symptom onset was defined based on the earliest medical history of a LAL Deficiency symptom. If the month or day of symptom onset is missing, it was assumed to be January and the first of the month respectively. The resulting probability was 3.2% (standard error: 3.1%). Although this is not explicitly stated by the company, giving that the estimated probably is constant over time, the ERG suspects that an exponential parametric survival model is fitted by the company.

It was assumed based on Mahady et al[2] that it was not possible to transit back to the "LALD without CC, DCC or HCC" health state from the "CC" health state. The transition probability from the "HCC" health state to the "Death" health state was retrieved from a paper by Hartwell et al[5] as this probability could not be retrieved from Mahady et al.[2] An overview of transition probabilities is provided in Table 5.3.

5.3.3.3 Transition probabilities for sebelipase alfa

There were multiple differences in sources and assumptions for the transition probabilities used for sebelipase alfa (compared with those for BSC):

- The probability to transit from the "LALD without CC, DCC or HCC" health state to the "CC" health state was calculated differently (using the FIB-4 score; see below).
- It was assumed that patients could transit back from the "CC" health state to the "LALD without CC, DCC or HCC" health state (probability calculated using the FIB-4 score; see below).
- It was assumed that it was not possible to transit to the "DCC", "HCC" and "Liver transplant" health states (hence transition probabilities from these health states were not applicable for sebelipase alfa).
- No additional mortality (in addition to the background mortality from the general population of England[56]) was assumed for patients in the "CC" health state.

The transition probabilities between the "LALD without CC, DCC or HCC" and "CC" health states for sebelipase alfa were calculated by comparing the baseline and 20-week FIB-4 score using a threshold of 1.45. The FIB-4 score is developed as a non-invasive scoring system to predict liver fibrosis in patients with HIV/hepatitis C virus co-infection and is particularly used in Hepatitis C and NASH. The FIB-4 score can be calculated by using age, aspartate aminotransferase (AST), platelet count and alanine transaminase (ALT).[59] Depending on whether patients had a baseline FIB-4 score (calculated based on the LAL-CL02 trial[4]) above or below the threshold of 1.45 it is assumed whether they had "CC" (n=4) or not (n=25) at baseline. Similarly, if patients had a 20-week FIB-4 score above or below the threshold of 1.45 it is assumed whether they had "CC" (n=3) or not (n=26) at 20-weeks. Based on this a transition probability of 0% (=0/25) was calculated for transiting from the "LALD without CC, DCC or HCC" health state to the "CC" health state. Additionally, a transition probability of 25% was calculated (=1/4) is calculated for transiting from the "CC" health state to the "LALD without CC, DCC or HCC" health state. This is illustrated in Table 5.2.

Table 5.2: Transition probabilities between the "LALD without CC, DCC or HCC" and "CC" health states for sebelipase alfa (based on Table D12.6 from the CS)

		Week 20	
		No CC; FIB-4 ≤ 1.45 (n=26)	CC; FIB-4 > 1.45 (n=3)
Baseline	No CC; FIB-4 ≤ 1.45 (n=25)	100%	0%
	CC; FIB-4 > 1.45 (n=4)	25%	75%

An overview of transition probabilities is provided in Table 5.3.

5.3.3.4 Additional transition probabilities for the infant scenario analysis

In addition to the transition probabilities described above, alternative transition probabilities were used for the first year in the infant scenario (afterwards the abovementioned probabilities were used). During the first year in the infant scenario, only two health states were used "Alive" and "Death". During this first year, survival for BSC was 0% (based on the LAL-1-NH01 study,[6] considering the subpopulation of 21 infants with growth failure within the first six months of life) while this was 67% for sebelipase alfa (based on the LAL-CL03 study[7]). Afterwards, equal transition probabilities were used as in the base case.

5.3.3.5 Overview of transition probabilities

An overview of transition probabilities is provided in Table 5.3.

Table 5.3: Overview of annual transition probabilities (retrieved from the submitted model)[a]

Transition		BSC			Sebelipase alfa			Distribution[c]
From	To	Estimate	Standard error	Source	Estimate	Standard error	Source	
LALD without CC, DCC or HCC	CC	0.032	0.022	LAL-CL02[4]	0.000	Not applicable	LAL-CL02[4]; based on FIB-4	Beta
LALD without CC, DCC or HCC	DCC	0.010	0.020	Mahady[2]	0.000	Not applicable	Assumption	Beta
LALD without CC, DCC or HCC	HCC	0.003	0.003	Mahady[2]	0.000	Not applicable	Assumption	Beta
CC	LALD without CC, DCC or HCC	0.000	Not applicable	Assumption / Mahady[2]	0.250	0.125	LAL-CL02[4]; based on FIB-4	Beta
CC	DCC	0.063	0.032	Mahady[2]	0.000	Not applicable	Assumption	Beta
CC	HCC	0.032	0.012	Mahady[2]	0.000	Not applicable	Assumption	Beta
CC	Death[b]	0.042	0.005	Mahady[2]	0.000	Not applicable	Assumption	Beta
DCC	HCC	0.030	0.011	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
DCC	Liver transplant	0.050	0.050	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
DCC	Death[b]	0.160	0.058	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
HCC	Liver transplant	0.200	0.050	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
HCC	Death[b]	0.430	0.030	Hartwell[5]	Not applicable	Not applicable	Assumption	Beta
Liver transplant	Death[b]	0.120	0.053	Mahady[2]	Not applicable	Not applicable	Assumption	Beta
Infant scenario								
Alive	Death[b]	1.000	Not applicable	LAL-1-NH01[6]	0.330	0.156	LAL-CL03[7]	Beta

[a]The transition probability of staying in the "LALD without CC, DCC or HCC", "CC", "DCC" and "HCC" health states is calculated by 1 minus the sum of the probabilities to transit to another health state. Moreover, the transition from "Liver transplant" to "LALD without CC, DCC or HCC" was calculated by 1 minus the probability of dying.
[b]This is excess mortality (in addition to the background mortality from the general population of England[56]).
[c]The distribution only applies if a standard error is provided (otherwise this parameter is fixed in the probabilistic sensitivity analysis or not applicable)

In addition to the probabilities reported in Table 5.3, age-dependent background mortality from the general population of England is incorporated for both BSC and sebelipase alfa.[56]

ERG comment:
The main critiques on the transition probabilities used in the economic are described in Box 5.2:

Box 5.2: Main critiques on transition probabilities

1. Lack of transparent reporting of input parameters
2. Unclear whether the transition probabilities used are the most appropriate transition probabilities
3. Uncertainty due to using FIB-4 scores
4. Inconsistency in assumptions regarding input parameters
5. Incorrect usage of 20-week data
6. Survival for infant scenario

1. Lack of transparent reporting of input parameters

Despite requested (clarification question B3[11]), the company did not provide details on the primary sources for the transition probabilities retrieved from Mahady et al.[2] The requested information included details how the transition probabilities (and its confidence intervals) are calculated and a description of the accompanying assumptions. Therefore, the ERG did check a random sample of the transition probabilities reported by Mahady et al[2] and the primary source reported by Mahady et al.[2] Based on this assessment, it was unclear how multiple transition probabilities reported by Mahady et al[2] and hence also the company[1] were calculated from their primary sources (e.g. probability of developing hepatoma from Bhala et al[60]). Additionally, it was unclear how transition probabilities were calculated if multiple sources are reported by Mahady et al[2], as was the case for most transition probabilities. Moreover, the company applied an artificial correction as not all transition probabilities by Mahady et al[2] summed up to 100% (see CS[1] and clarification question B3[11]) instead of determining the correct transition probabilities from the original sources (this might well be induced by a typographical or rounding error in Mahady et al[2]). It was also unclear how the survival analyses, to estimate the time to "CC", were exactly applied by the company (e.g. which parametric distribution is exactly used, which covariates were used and what the coefficients were). This extremely hampers the ERG´s assessment of the validity of the economic model and hence the outcomes of the cost-consequence analysis reported in the CS[1] should be interpreted with extreme caution.

2. Unclear whether the transition probabilities used are the most appropriate transition probabilities

The transition probabilities were mainly retrieved from the economic model by Mahady et al.[2] The company identified this economic model from a systematic review focusing on the use of the non-invasive liver tests (NILT) in a NAFLD population. Given the restriction to NILT, it is unclear whether there are more appropriate economic models available that were not identified in this systematic search (e.g. the economic model by Zhang et al[51, 52] identified in the additional searches performed by the ERG). Moreover, it might have been more

appropriate if the company would have aimed to identify clinical studies considering NAFLD to inform transition probabilities instead of limiting itself to cost-effectiveness studies identified in a systematic review which is not entirely suitable for this assessment (see Section 5.2). Also, the observation that a certain transition probability is used by Mahady et al,[2] does not justify the usage for the present model neither does it indicate that it is the most appropriate transition probability even if it would be the only NAFLD economic model available. Therefore, even when NAFLD would be considered the most appropriate analogue for LAL deficiency, it is unclear whether the transition probabilities used are the most appropriate transition probabilities. The impact of this potential selection bias is however unclear.

3. Uncertainty due to using FIB-4 scores

Despite the fact that the FIB-4 score was not developed using data from NAFLD patients, it is considered better than other non-invasive tests in diagnosing advanced fibrosis in NAFLD.[61] The sensitivity and specificity of the FIB-4 score for assessing liver fibrosis are 66.7% and 71.2% when applying the commonly used threshold of 1.45 (using liver histology as reference standard).[59] Although the 1.45 threshold is commonly used, it can only reliably be used to determine the absence of cirrhosis. FIB-4 scores between 1.45 and 3.25 are considered inconclusive.[62] However, in the current assessment the patients with a FIB-4 score above 1.45 are assumed to have cirrhosis while for the majority of these patients this should be considered inconclusive (see Table 5.4). To illustrate this: a recent UK study showed that only five out of 40 NAFLD patients (12.5%) with a FIB-4 score between 1.30 and 3.25 had a confirmed cirrhosis on biopsy.[63] Therefore, the usage of the FIB-4 score, although considered reasonable, induces uncertainty which is neglected by the company, nor is it completely explored in the sensitivity analyses (e.g. the 3.25 threshold is not used for BSC in any of the analyses). The ERG is unable to explore the impact of this uncertainty given the low number of patients with a FIB-4 score larger of equal than 3.25.

Table 5.4: Compensated cirrhosis based on the FIB-4 scores (based on Table D12.6 of the CS and the response to clarification question B5

	Sebelipase alfa		**BSC**	
	Baseline N (%)	**20 week** N (%)	**Baseline** N (%)	**20 week** N (%)
Absence of CC (FIB-4 ≤ 1.45)	25 (86%)	26 (90%)	25 (86%)	26 (90%)
Inconclusive (FIB-4 > 1.45 and < 3.25)	3 (10%)	3 (10%)	4 (14%)	3 (10%)
Presence of CC (FIB-4 ≥ 3.25)	1 (3%)	0 (0%)	0 (0%)	0 (0%)

4. Inconsistency in assumptions regarding input parameters

As illustrated in Table 5.3, for sebelipase alfa the LAL-CL02[4] data are exclusively used to inform the transition probabilities whereas for BSC also transition probabilities retrieved from Mahady et al[2] and Hartwell et al[5] were used. Moreover, to estimate transition probabilities for sebelipase alfa, the FIB-4 score is used while this is not used for BSC. No appropriate justification was found for these inconsistencies. Based on the comparable FIB-4 categorisations (Table 5.4), the ERG does not see any reason to use different sources or

assumptions for both comparators. This also holds true for the probabilities to transit to "DCC" and "HCC". These were assumed to be 0% for sebelipase alfa whereas these were assumed >0% for BSC. No plausible justification was found for this inconsistency. The 0% "DCC" probability is justified by the company by stating that this was not observed in the LAL-CL02[4] trial. This is however equally true for BSC (clarification question A8[11]). Moreover, it can be questioned whether it is plausible to assume 0% probabilities of "CC", "DCC" and "HCC" for sebelipase alfa based on a follow-up period of 20 weeks. Therefore, the ERG would prefer to assume:

1. Equal probability of transiting from "LALD without CC, DCC or HCC" to "CC" for both comparators, using the annual probability of 3.2% obtained through the survival analysis.
2. Probability of transiting from "CC" to "LALD without CC, DCC or HCC" based on FIB-4 scores for both comparators.
3. All other transition probabilities based on Mahady et al[2] (equal for both comparators).

5. Incorrect usage of 20-week data

The transition probabilities derived from the LAL-CL02[4] trial using the FIB-4 scores reflect a 20-week period, these 20-week probabilities were included in the model as annual probabilities without adjustment. These probabilities were adjusted to reflect an annual period in the ERG preferred base case.

6. Survival for infant scenario

For the infant scenario analysis, the company did use data from the LAL-CL03 study[7] for the first year only. Despite requested (clarification question B2[11]), the company did not provide a scenario analysis using data from the LAL-CL03 study[7] to inform (mortality) transition probabilities after the first year. According to Table A4.1 of the CS,[1] follow-up from the LAL-CL03 study is substantially longer than 1 year, i.e. up to 260 weeks (five year). In the infant scenario analysis provided by the company (in their initial submission), there is a substantial decrease in the annual probability of excess mortality for sebelipase alfa from 33% (first year) based on the LAL-CL03 study[7] to 0.0%-2.5% thereafter based on Mahady et al[2] (Table 5.3). It is unclear whether this steep decrease is plausible and hence adds to the uncertainty considering the interpretation of the outcomes for the infant scenario.

In addition to the estimation of long-term survival in the infant scenario, it is unclear to what extent patients included in the in LAL-1-NH01 study[6] and the LAL-CL03 study[7] are comparable. Hence, it is unclear to what extend the survival gain presented in the infant scenario is due to sebelipase alfa or due to differences between patients.

Conclusion

The results of the cost-consequences analysis presented by the company should be interpreted with extreme caution given the abovementioned issues. To salvage these issues the ERG proposed several adjustments for the ERG preferred base case (see Table 5.5). In particular, the ERG did not find any plausible justifications to use different sources and assumptions for the probabilities to develop "CC", "DCC" and "HCC" nor for the probability to transit back "LALD without CC, DCC or HCC" (from "CC"). Hence, this was adjusted in the ERG base case.

Table 5.5: Overview of annual transition probabilities (ERG base case)[a]

Transition		BSC			Sebelipase alfa			Distribution[c]
From	To	Estimate	Standard error	Source	Estimate	Standard error	Source	
LALD without CC, DCC or HCC	CC	0.032	0.031	LAL-CL02[4]	0.032	0.031	LAL-CL02[4]	Beta
LALD without CC, DCC or HCC	DCC	0.010	0.020	Mahady[2]	0.010	0.020	Mahady[2]	Beta
LALD without CC, DCC or HCC	HCC	0.003	0.003	Mahady[2]	0.003	0.003	Mahady[2]	Beta
CC	LALD without CC, DCC or HCC	0.528	0.282	LAL-CL02[4]; based on FIB-4	0.528	0.282	LAL-CL02[4]; based on FIB-4	Beta
CC	DCC	0.063	0.032	Mahady[2]	0.063	0.032	Mahady[2]	Beta
CC	HCC	0.032	0.012	Mahady[2]	0.032	0.012	Mahady[2]	Beta
CC	Death[b]	0.042	0.005	Mahady[2]	0.042	0.005	Mahady[2]	Beta
DCC	HCC	0.030	0.011	Mahady[2]	0.030	0.011	Mahady[2]	Beta
DCC	Liver transplant	0.050	0.050	Mahady[2]	0.050	0.050	Mahady[2]	Beta
DCC	Death[b]	0.160	0.058	Mahady[2]	0.160	0.058	Mahady[2]	Beta
HCC	Liver transplant	0.200	0.050	Mahady[2]	0.200	0.050	Mahady[2]	Beta
HCC	Death[b]	0.430	0.030	Hartwell[5]	0.430	0.030	Hartwell[5]	Beta
Liver transplant	Death[b]	0.120	0.053	Mahady[2]	0.120	0.053	Mahady[2]	Beta
Infant scenario								
Alive	Death[b]	1.000	Not applicable	LAL-1-NH01[6]	0.330	0.156	LAL-CL03[7]	Beta

[a]The transition probability of staying in the "LALD without CC, DCC or HCC", "CC", "DCC" and "HCC" health states is calculated by 1 minus the sum of the probabilities to transit to another health state. Moreover, the transition from "Liver transplant" to "LALD without CC, DCC or HCC" was calculated by 1 minus the probability of dying.
[b]This is excess mortality (in addition to the background mortality from the general population of England[56]).
[c]The distribution only applies if a standard error is provided (otherwise this parameter is fixed in the probabilistic sensitivity analysis or not applicable)

5.3.3.6 Health-related quality of life

The company did not identify health state utilities in their systematic literature review (see Section 5.2). Instead the company referred to a recent systematic review by Crossan et al.[64] In this systematic review, three studies that contained information on HRQoL for NAFLD/NASH patients were identified,[65] two of which had estimated HRQoL values for these patients.[65] For the economic model, the health state utilities were retrieved from Mahady et al[2] and not from David et al (2009)[66] and Donnan et al (2009).[65] The company argued that: "In light of the methods used and data reported by David et al. (2009) and Donnan et al. (2009), utilities reported by Mahady et al (2012) were deemed the most appropriate to use in the cost-consequence analysis." However, no specific methods used to calculate the health state utility scores retrieved from Mahady et al[2] were provided by the company. The utility scores retrieved from Mahady et al[2] ranged between 0.60 and 0.92 (Table 5.6).

No health state utility data were found for infants. Hence for the infants scenario analysis, utilities of 0.25 and 0.50 were assumed for infants that die within the first year of life and infants that survive beyond the first year respectively. No further justification for these utility scores was provided. For infants dying during the first year it is assumed based on LAL-1-NH01[6] that infants die after 3.45 months.

Table 5.6: Overview of health state utilities

Health state	Estimate	Standard error	Source	Distribution[c]
LALD without CC, DCC or HCC	0.92	0.08	Mahady[2]	Beta
CC	0.82[a]	0.06	Mahady[2]	Beta
DCC	0.60[b]	0.09	Mahady[2]	Beta
HCC	0.73[c]	0.08	Mahady[2]	Beta
Liver transplant	0.69	0.06	Mahady[2]	Beta
Infant scenario				
Alive	0.50	0.19	Assumption	Beta
Dying	0.07[d]	0.04	Assumption	Beta

[a]The utility for the "CC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "LALD without CC, DCC or HCC" health state in all simulations.
[b]The utility for the "DCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[c]The utility for the "HCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[d]The utility for the "dying" infants is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility for the infants "alive" in all simulations. For this health state a QALY of 0.07 is calculated ((3.45 / 12) × 0.25) which is subsequently incorporated as utility in the model for infants dying during the first year.

ERG comment:

The company mentioned that the systematic literature review by Crossan et al[64] considered HRQoL in NAFLD. This is incorrect as this review by Crossan et al[64] considered treatment effectiveness and also identified three studies that contained information on HRQoL in

patients with NAFLD. Given this systematic review did not focus on identifying HRQoL studies, potentially relevant HRQoL studies might have been missed by the company.

Based on the review by Crossan et al[64] the company selected Mahady et al[2] as source for health state utilities. Similarly as for the transition probabilities, there was a lack of transparent reporting (despite the requested clarifications[11]). It was unclear why the utilities from Mahady et al[2] were considered most appropriate. Additionally, it was unclear how the health state utilities were calculated if multiple sources are reported by Mahady et al,[2] as was the case for all but one health state utility. To salvage this issue, the ERG used the health state utilities as reported by Crossan et al.[64] These health state utilities were measured using the EQ-5D for hepatitis C patients and in part measured in the UK.[54, 67] Here it is assumed that the utilities for the different health states would be similar for different liver diseases irrespective of the initial cause. Please note that this latter assumption is also applicable to the health state utilities reported by Mahady et al[2] as these were primarily retrieved from hepatitis C populations.

The health state utility used in the economic model by the company did exceed the UK general population utility scores,[8] e.g. in the economic model approximately 90% of the patients are still expected to be alive at age 65 with a utility of 0.92 whereas the UK general population utility for persons aged 65 is expected to be 0.784. Despite requested (clarification question B6[11]), the company did not provide a plausible justification for the seemingly implausible high health state utility nor any scenario analyses using alternative health state utilities (e.g. age dependent utilities). Therefore, the ERG implemented a minimum function in the model to ensure the health state utilities in the model would not exceed those of the general population with the same age.[8]

The health state utilities used for infants in the infant scenario were assumed by the company without any evidence neither were these infant utilities specifically considered by clinical experts (as mentioned by the company in response to clarification question B7[11]). Given the lack of evidence to sustain the infant utilities and particularly the difference between the utilities, the ERG adopted a more conservative approach using a utility of 0.5 for all health states during the first year for the infant scenario. This would result into a QALY of 0.144 for infants dying during the first year (= (3.45 / 12) × 0.50) instead of 0.072. In addition, given that the QALY is calculated for infants dying in the first year and subsequently incorporated as a utility, the half-cycle correction should not be applied. The half-cycle correction applied by the company for the first year leads to an underestimation of the total QALYs. This is corrected by the ERG.

Table 5.7 provides an overview of the health state utilities used in the ERG base case.

Table 5.7: Overview of health state utilities used in the ERG base case

Health state	Estimate	Standard error	Source	Distribution[c]
LALD without CC, DCC or HCC	0.66	0.02	Crossan[64]	Beta
CC	0.55[a]	0.03	Crossan[64]	Beta
DCC	0.49[b]	0.06	Crossan[64]	Beta
HCC	0.49[c]	0.06	Crossan[64]	Beta
Liver transplant	0.51	0.05	Crossan[64]	Beta
Infant scenario				
Alive	0.50	0.19	Assumption	Beta
Dying	0.14[d]	0.07	Assumption	Beta

[a]The utility for the "CC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "LALD without CC, DCC or HCC" health state in all simulations.
[b]The utility for the "DCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[c]The utility for the "HCC" health state is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility of the "CC" health state in all simulations.
[d]The utility for the "dying" infants is adjusted in the probabilistic sensitivity analyses to be smaller or equal to the health state utility for the infants "Alive" in all simulations. For this health state a QALY of 0.14 is calculated ((3.45 / 12) × 0.50) which is subsequently incorporated as utility in the model for infants dying during the first year.

5.3.3.7 Resources use and costs included in the model

Resources use and costs included in the cost-consequences analysis include technology costs and non-drug direct medical costs. The former consists of drug and administration costs while the latter entails health state costs.

Technology costs

The annual costs of the technology consist of drug costs and administration costs. Drug costs are determined by two dosing schemes and by patients' weight. The first dosing scheme concerns infant patients, who are diagnosed within their first year of life and the second concerns children/adult patients, who are diagnosed after their first year of life. The infant patients dosing scheme consists of a weekly 3 mg/kg dose of sebelipase alfa. As there was no evidence of dose reduction after one year of treatment in the infant patient population,[7] the company assumes that infant patients receive a weekly 3 mg/kg dose of sebelipase alfa for the remainder of their life. Children/adult patients are administrated a 1 mg/kg dose of sebelipase alfa every other week.

Patients' weight is estimated based on their age. The UK growth charts from the Royal College for Paediatrics and Child Health[68] and a 50/50 ratio of male and female patients[4] is used to determine the mean weight for each age. After their 18th birthday, patients are not assumed to gain weight anymore; consequently, the average patient weight remains 68.25 kg until the maximum age of the model (101 years).

The list price that is used for sebelipase alfa is £6,286 for 20 mg vials. After a period of 10 years in the model, the price of sebelipase alfa is reduced by 30%. The company assumes this discount because of patent expiration and hence the introduction of biosimilar competition.[69] The company includes wastage by taking into account entire vial prices whether or not it was

fully emptied during administration. It is assumed that 5 mg vials at a list price of £1,572 are available from the second year of the model onwards. This reduces waste and therefore the net drug costs of sebelipase alfa treatment. The list price of a single infusion in an outpatient setting is £68.66.[70] The number of administrations is dependent on the patients' dosing scheme.

ERG comment:
In the company's cost-consequences analysis, infant patients receive a weekly 3 mg/kg dose of sebelipase alfa during their entire life. This results in markedly higher drug costs in later life for infants patients than for patients with a later start of treatment. Furthermore, patients are assumed to stop to gain weight after their 18th birthday. The ERG questions the validity of this assumption. If patients would still gain weight after their 18th birthday, sebelipase alfa costs are underestimated in the company's base case cost-consequences analysis. After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market. Therefore, the ERG asked the company to perform all analyses without 30% discount on sebelipase alfa after a period of 10 years. The ERG did not incorporate this 30% discount in its base case cost-consequences analysis. Furthermore, drug costs is influenced by the introduction of 5 mg vials of sebelipase alfa after the first cycle. This reduces waste and costs associated with sebelipase alfa. The ERG did not incorporate the 5 mg vials of sebelipase alfa in its base case cost-consequences analysis because these are not yet available.

Non-drug direct medical costs

Health state costs are retrieved from the literature on hepatitis C patients because LAL deficiency-specific costs were not available in the literature.[1] The two main sources are Backx et al[71] and Shepherd et al.[3] Backx et al is a retrospective chart review of 193 HCV patients who had received at least two months of pegylated interferon and ribavirin therapy. The aim of that study was to quantify resource use and costs depending on whether patients had achieved a sustained virological response (SVR) to therapy or not. The mean age of patients was 40.5 years in the SVR group and 48.0 years in the non-SVR group.[71] Shepherd et al is an economic evaluation which assesses the cost-effectiveness of interferon alfa and ribavirin for the treatment of mild chronic HCV.[3] In this economic evaluation, health state costs are retrieved from an observational study conducted by Wright et al[54] which is a retrospective database review of 358 UK patients with HCV. Wright et al[54] identify resources use and costs for different liver disease stages: "moderate disease", "CC", "DCC" and "HCC". Resources use and costs for each of these health state are based on 183, 115, 40 and 20 observations respectively. The mean age of the population was 42.1 years.[54]

Both Backx et al[71] and Shepherd et al[3] contain health state costs for the "LALD without CC, DCC or HCC", "CC" and "DCC" health states. However, Backx et al[71] was used for the "LALD without CC, DCC or HCC" and "CC" health state costs and Shepherd et al [3] for the "DCC" health state costs in the cost-consequences analysis.[1] Shepherd et al[3] further provided health state costs for the "HCC" and "Liver Transplant" health states. Costs of these studies

are inflated to 2014 values based on the Office for National Statistics Consumer Price Indices for Health.[72]

In the infant scenario of the cost-consequences analysis, infants incur specific costs in their first year of life because of long-term hospitalisation. The costs associated with resource use of infant patients in their first year of life is based on NHS reference costs[70] and assumptions. The company assumes that the annual costs of infant patients who die in their first year of life is equal to 3.45 months of hospitalisation because the mean survival of this group is 3.45 months.[6] Infant patients treated with sebelipase alfa are assumed to stay three months at the hospital in their first year of life. The cost of a hospitalisation day is £1,001.[70] An overview of health state costs is given in Table 5.8 (CS, Table D12.13 [1]).

No adverse events and miscellaneous costs are included in the cost-consequences analysis. A half-cycle correction is applied to all health care costs in the first and last cycles of the base case and sensitivity analyses performed by the company.

Table 5.8: Health state costs, variation in health state costs, population used to obtain health state costs and source of these costs, as used in the cost-consequence analysis (based on CS, table D12.13)

Health state	Mean cost (£)	Variation*	Population characteristics from which the estimate is retrieved*	Source
Base case scenario				
LALD without CC, DCC or HCC	620	439 - 877	54 HCV patients, mean age = 48.0 years	[71]
CC	962	590 – 1,570	27 HCV patients, mean age = 48.0 years	[71]
DCC	12,523	10,018 - 15,028	40 observations of HCV patients, mean age = 51.6 years	[3] from [73]
HCC	11,159	8,927 - 13,391	20 observations of HCV patients, mean each not specified for this subgroup, general mean age of sample = 42.1 years	[3] from [73]
Liver Transplant	50,515	40,412 - 60,618	Not able to retrieve, no access to original article67 HCV patients eligible for liver transplant	[3] from [74]
Infant scenario				
1st year cost for dying infants	103,604	82,883- 124,324	-	
1st year cost for surviving infants	90,090	As mentioned in cost-consequences model attached to the CS[1]: "varies proportionally vs. base cost for infants dying"	-	

* Added by the ERG

ERG comment:

Health state costs used in the cost-consequences analysis are predominantly based on two studies in adult hepatitis C patients (Backx et al[71]; Shepherd et al[3]). It is unclear to the ERG how these studies were identified, and hence whether these sources of evidence are the most appropriate ones. The ERG asked the company to justify why cost estimates from these studies were considered most applicable to the LAL Deficiency patient population because these studies included older patients (affected by HCV) than modelled in the cost-consequences analysis. The company replied as follows: "We included costs for an HCV patient population because they are available in a UK setting; costs for LAL deficiency or NAFLD patients in the UK are not available".[11] No details were provided on why Backx et al[71] and Shepherd et al[3] were appropriate sources for the cost-consequences analysis.

Furthermore, the ERG asked why Backx et al[71] was used for the "LALD without CC, DCC or HCC" and "CC" health states and Shepherd et al[3] for the "DCC" health state since both studies provide health state costs for these three health states. The company considers the cost estimate of Back et al[71] for "DCC" unreliable because it is based on 12 patients only. Therefore, Shepherd et al[3]'s cost estimate was used for the "DCC" health state. However, the "DCC" cost estimate of Shepherd et al[3] is based on Wright et al[54] who used the data of 40 patient observations to determine "DCC" costs.

The ERG is aware that LAL Deficiency-specific costs might not be available in the literature. However, the company was not transparent in the methodology used to retrieve studies providing health state costs and why these studies might be the most appropriate sources for the current economic evaluation. The ERG would also like to note that the recent review and economic evaluation from Crossan et al[64] used health state costs provided by Longworth et al[67] for the following health states: "DCC", "HCC" and "Liver Transplant" (for a hepatitis C population). It is uncertain which health state costs are the most appropriate for the current cost-consequences analysis. Therefore, the ERG performed a sensitivity analysis using the health state costs retrieved from Crossan et al.[64]

Furthermore, the company was not transparent about the variation in costs used in the cost-consequences analysis (CS, table D12.13[1]). After clarification, it was clear that these costs were varied by +/-20% around the mean. However, the company did not provide the rationale behind these +/-20% variations.

The ERG noted an inconsistency between health state costs provided in table D12.11 and table D12.13 of the CS which both summarise health state costs used in the cost-consequences model.[1] The ERG asked the company to clarify why the tables did not provide the same health state costs. The company noticed that costs of Table D12.13 of the CS,[1] Table 5.8 of the current report, were correct. The company also sent an updated version of the CS on 14 November 2015, however, this inconsistency was not corrected. Table 5.8 provides an overview of health state costs, with variation and the population from which they were retrieved.

A scenario analysis includes infant patients only. In this sensitivity analysis, a half-cycle correction is applied to drug costs and non-drug medical costs (hospitalisation costs only). However, drug use and the duration of hospitalisation were already based on actual survival.

Applying a half-cycle correction in this situation leads to an underestimation of the costs incurred by infants in this scenario analysis. Therefore, the ERG deleted the half-cycle correction from analyses for the infant population in the ERG base case.

There are no treatment adverse event costs included in the cost-consequences analysis. This might underestimate resource use and costs associated with sebelipase alfa treatment. For completeness of the model, the ERG asked the company to perform an analysis containing utility decrements and health care costs for anaphylaxis reactions, the major adverse events caused by sebelipase alfa administration. In its response to the clarification letter,[11] the company included health care costs associated with the HRG codes WA16W (Shock and Anaphylaxis with CC) and WA16Y (Shock and Anaphylaxis without CC), both of which cost £207, to model treatment adverse event costs. Results of this analysis are shown in Section 5.4.2.

The cost-consequences analysis does not include any concomitant medication costs. This makes the costs of BSC lower than can be expected. This assumption is conservative.

5.3.4 Model evaluation

The results of the health economic analysis are presented in terms of the (incremental) QALYs and costs for sebelipase alfa versus BSC. The model included a probabilistic sensitivity analysis (500 probabilistic samples), which incorporated both sampling uncertainty (i.e. second order uncertainty) and variability (i.e. first order uncertainty) simultaneously. In addition to the probabilistic sensitivity analysis, a number of simple one-way and multi-way sensitivity/scenario analyses were also performed by the company. The following parameters were varied using the 95% confidence intervals in the one-way sensitivity analyses (see Table D12.4 of the CS[1] for more details):

Transition probabilities BSC

- "LALD without CC, DCC, or HCC" to "CC"
- "LALD without CC, DCC, or HCC" to "DCC"
- "LALD without CC, DCC, or HCC" to "HCC"
- "CC" to "LALD without CC, DCC, or HCC"
- "CC" to "DCC"
- "CC" to "HCC"
- "CC" to "death"
- "DCC" to "HCC"
- "DCC" to "Liver transplant"
- "DCC" to "death"
- "HCC" to "Liver transplant"
- "HCC" to "death"
- "Liver transplant" to "death"

Transition probabilities sebelipase alfa

- "LALD without CC, DCC, or HCC" to "CC"
- "CC" to "LALD without CC, DCC, or HCC"

Utilities

- "LALD without CC, DCC or HCC" utility
- "CC" utility

- "DCC" utility
- "HCC" utility
- "Liver transplant" (first year) utility
- First year utility for surviving infants
- First year utility for dying patients

Costs

- "LALD without CC, DCC or HCC"
- "CC"
- "DCC"
- "HCC"
- "Liver Transplant"
- First year cost for dying infants

Other parameters

- Discount rate

Multi-way sensitivity analyses (Table D12.16 of the CS[1]) were performed wherein the method of calculating the transition probabilities between the "LAL Deficiency without CC, DCC or HCC" and "CC" health states (described above) was adjusted by using different thresholds for the FIB-4 score and using other liver scoring algorithms (i.e. the Forns Index and the Aspartate aminotransferase to Platelet Ratio Index (APRI)). In addition, scenario analyses (Table D12.15 of the CS[1]) were performed by the company for the infant population (modelled age: 0 year; based on the LAL-L03[7] and LAL-1-NH01[6] studies) and the children/adult population (modelled age: 17 year; based on the LAL-CL02 trial[4]). For the infant population, also different transition probabilities, health state utilities and costs were used for the first year (see Table 5.3 and Table 5.6).

ERG comment:

The standard errors of the input parameters were used in the sensitivity analyses. The ERG noted that multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges (e.g. the transition from "CC" to "LALD without CC, DCC, or HCC" for sebelipase alfa, health state utility for infants and health state costs for the "DCC", "HCC" and "Liver transplant" states). Moreover, the standard errors for the transition probabilities were underestimated by 2% as these were calculated by dividing the 95% confidence interval by four (instead of 3.92). Also, some standard errors are (re)calculated incorrectly based on the range. For instance, the annual transition probability of 0.032 to transit to the "CC" health state for BSC is calculated based on a survival analysis. This survival analysis also provided a standard error of 0.031, however based on the range the standard error was incorrectly recalculated (a standard error of 0.022 is used in the probabilistic sensitivity analysis). Hence, this was adjusted in the ERG base case (Table 5.5). Finally, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect[75] and therefore variability was not incorporated in the probabilistic sensitivity analysis performed by the ERG (i.e. age and hence also weight were assumed to be fixed). Moreover, the number of simulations was relatively low and hence increased to 1,000 in the ERG base case.

5.4 Headline results reported within the company's submission

This section summarises the results of the cost consequence analysis as presented in the CS. Figure 5.2 presents the base case Markov traces for sebelipase alfa while Figure 5.3 presents the base case Markov traces for BSC. Patients treated with sebelipase alfa are expected to spend the majority of their time alive in the "LALD without CC, DCC, or HCC state", whereas the BSC patients spend the majority of their time in the death state.

Figure 5.4: Base case: sebelipase alfa Markov trace

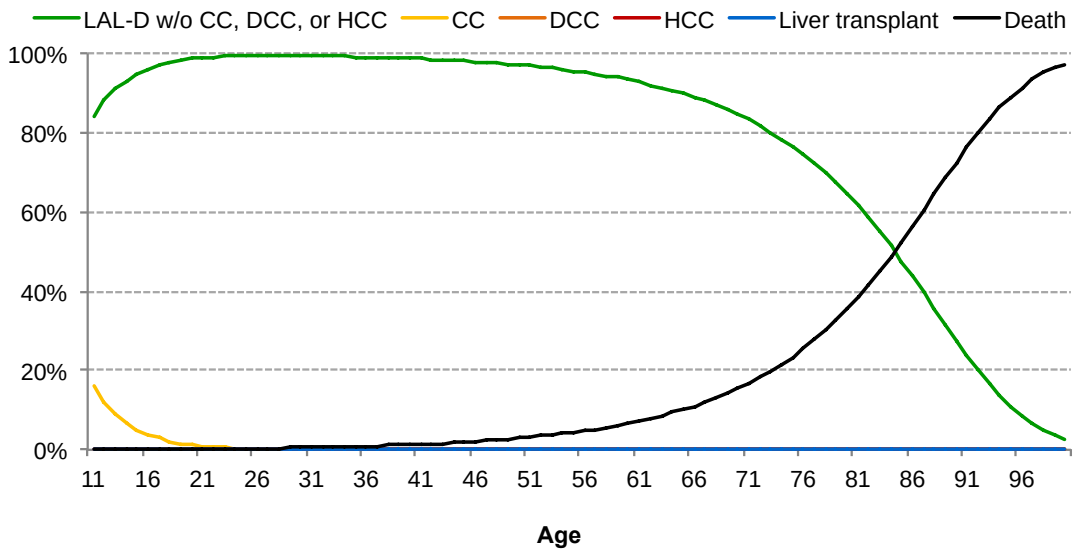
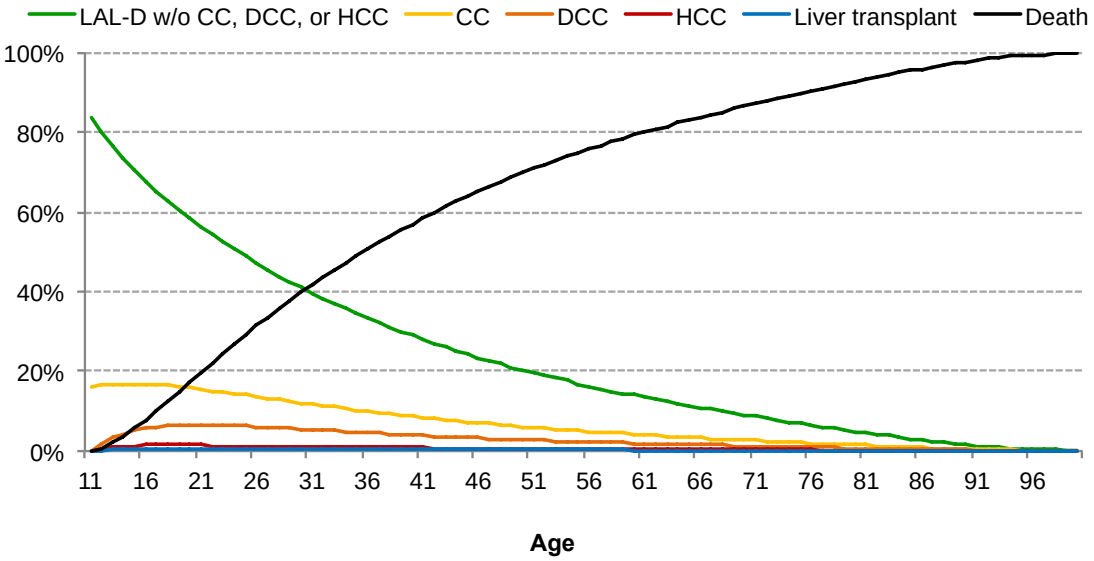


Figure 5.5: Base case: BSC Markov trace



5.4.1 Headline total QALYs and total costs for sebelipase alfa versus standard care

The estimates of incremental QALYs and costs for sebelipase alfa versus BSC are presented in Table 5.9. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient

compared to BSC and the incremental costs would be [redacted] per patient compared the BSC.

Table 5.9: Summary results of the company's model

	Costs (Disc.)	Mean (PSA)	95% CI (PSA)	QALYs (Disc.)	Mean (PSA)	95% CI (PSA)
BSC	£46,748	£45,093	(£29,721; £75,624)	19.24	20.6	(10.9; 31.8)
sebelipase alfa	£[redacted]	[redacted]	[redacted]	39.73	39.8	(31.5; 44.6)
Incremental	£[redacted]			20.48		

Table 5.10 and Table 5.11 below present a breakdown of discounted QALYs and costs for sebelipase alfa and BSC. The company's model suggests that under the sebelipase alfa treatment patients survive longer; they stay longer in the "LALD without CC, DCC, or HCC" state, stay shorter in the "CC" state and spend no time in the "DCC", "HCC", or "Liver transplant" state. Although much shorter, because of shorter survival, patients receiving BSC also spend most of their time in the "CC" state, and much shorter in the "CC", "DCC", "HCC", and "Liver transplant" state. This difference between the distributions of years spent in each disease state with and without sebelipase alfa treatment results in more than 20 incremental discounted QALYs.

On the other hand, health state costs (in terms of background resource use) barely make a difference between sebelipase alfa and BSC. The difference between sebelipase alfa and BSC is almost fully associated with sebelipase alfa drug costs, summing up to approximately [redacted]

Table 5.10: QALY gain by health state for the base case analysis

Health state	QALY BSC	QALY sebelipase alfa	Increment	% Increment
LALD without CC, DCC, or HCC	14.37	39.29	24.92	173%
CC	3.49	0.44	-3.05	-87%
DCC	1.01	0.00	-1.01	-100%
HCC	0.27	0.00	-0.27	-100%
Liver transplant	0.11	0.00	-0.11	-100%
Death	0.00	0.00	0.00	
Total	**19.24**	**39.73**	**20.48**	106%

Table 5.11: Costs associated with sebelipase alfa and BSC per health state for the base case analysis

Health state	Costs BSC	Costs sebelipase alfa	Increment	% Increment
LALD without CC, DCC, or HCC	£9,685	£26,480	£16,796	[redacted]
CC	£4,095	£512	-£3,582	[redacted]
DCC	£21,066	£0	-£21,066	[redacted]
HCC	£4,090	£0	-£4,090	[redacted]
Liver transplant	£7,813	£0	-£7,813	[redacted]
Drug Costs	£0	£[redacted]	£[redacted]	
Total	**£46,748**	**£[redacted]**	**£[redacted]**	[redacted]

5.4.2 Sensitivity analyses presented within the company's submission

Five sensitivity analyses were conducted to test structural assumptions, specifically with regard to the transition probabilities between the "LALD without CC, DCC or HCC" and "CC" states, the effect of sebelipase alfa on a cohort of only patients with infant-onset LAL Deficiency, and the effect of sebelipase alfa on a cohort of only patients with infant- or adult-onset LAL deficiency.

Furthermore, deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were undertaken. PSA was conducted using 500 model runs. For details on the distributions and parameters used for the PSA we refer to Table D12.11 of the CS. Results of the PSA are given in Table 5.9. Mean results of PSA are comparable to the deterministic point estimates of the base case analysis.

5.4.2.1 One-way sensitivity analyses presented within the company's submission

For DSA, the following variables were varied using the 95% confidence intervals: health state utilities (including first year utilities for surviving infants and dying patients), health states costs (first year cost for dying infants), BSC transition probabilities, natural history transition probabilities for BSC and sebelipase alfa, sebelipase alfa transition probabilities, and discount rates. The results of the DSA are presented in Figures 5.6 – 5.8.

Figure 5.6: Tornado diagram of incremental QALYs

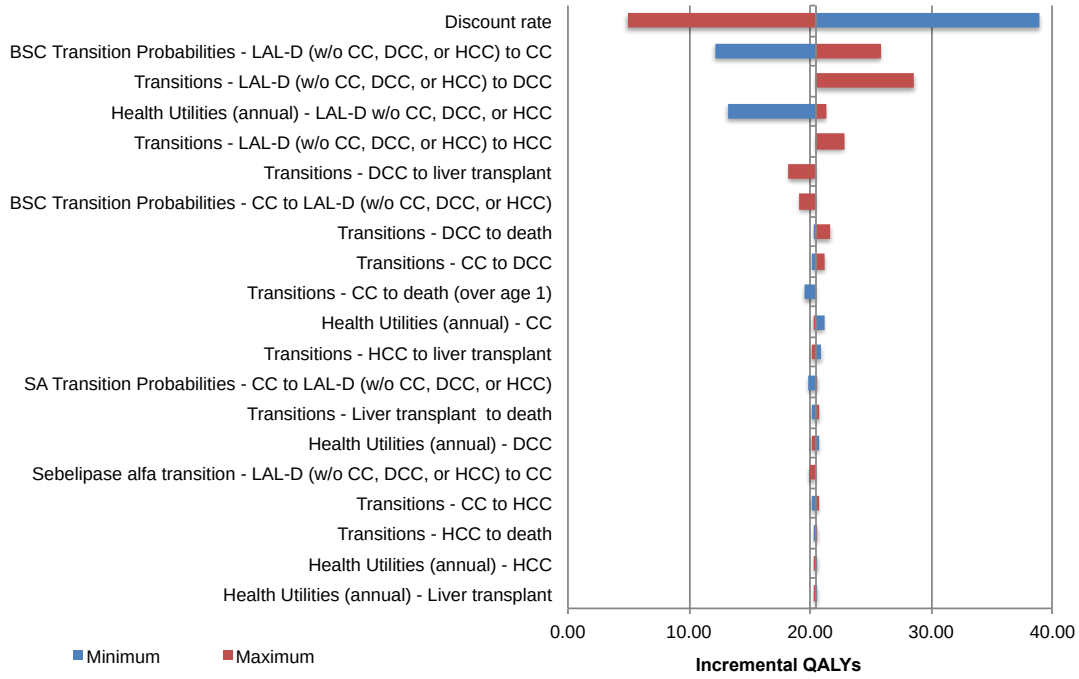


Figure 5.7: Tornado diagram of incremental life years (undiscounted)

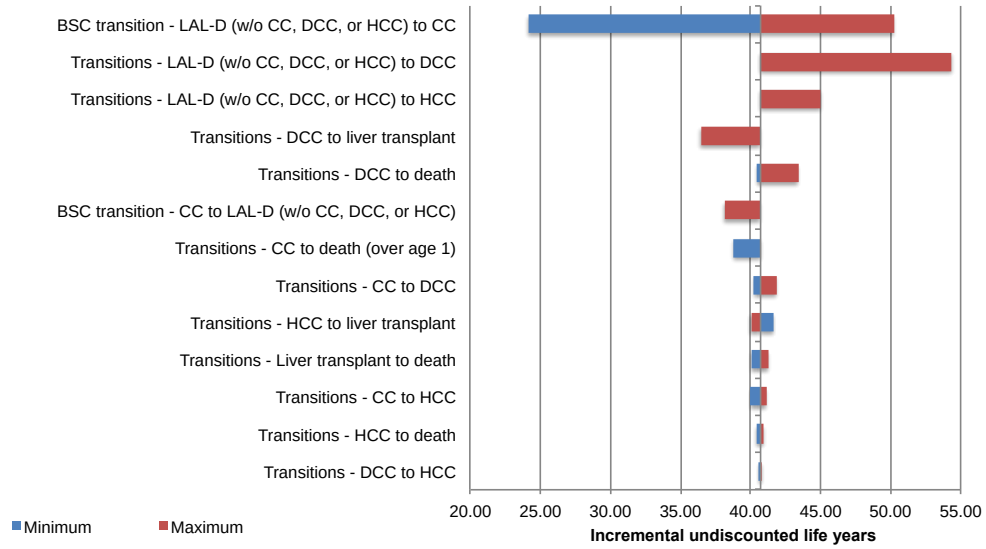


Figure 5.8: [redacted]

[redacted]

Among these one-way DSA results, it seems that the discount rate has the biggest impact on total incremental costs (apart from the cost of sebelipase alfa) as well as on the incremental QALYs. Besides the discount rate, transition probabilities to and from the LAL Deficiency without CC, DCC and HCC state has the highest impact on incremental life years (undiscounted) and incremental QALYs.

5.4.2.1 Multi-way sensitivity analyses presented within the company's submission

On top of the one-way DSAs, additional scenario analyses were performed. The population was varied by changing the baseline age, corresponding health state distribution, and transition probabilities. In Table 5.12 the incremental QALYs and costs of sebelipase alfa compared to BSC for the base case (age 11), the infant population (age 0; LAL-L03 and LAL-1-NH01) and the LAL-CL02 cohort (age 17) are presented.

Table 5.12: Multi-way scenario-based sensitivity analysis of patient scenarios

Scenario	N	Average Age	Modelled Age	Percentage at Baseline					
				LALD without CC, DCC or HCC	CC	DCC	HCC	Incr. Costs	Incr. QALYs
Base case	96	11.46	11	84%	16%	0%	0%	[redacted]	20.5
Infants (LAL-L03 and LAL-1-NH01)	30	0.08	0	100%	0%	0%	0%	[redacted]	28.6
LAL-CL02 cohort	66	16.63	17	69%	31%	0%	0%	[redacted]	20.4

In the multi-way scenario-based sensitivity analyses of the transition probabilities, several scenarios are compared for the transition probability between the "LALD without CC, DCC or HCC" and CC states for the BSC and sebelipase alfa group:

BSC:

Base case: Based on Mahady et al, adjusted

1. FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4>1.45)
2. FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)
3. Potentially Significant Fibrosis (Forns>4.2)
4. Potentially Significant Fibrosis (APRI>1.5)

SA:

Base case: FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4>1.45)

1. FIB-4: Mild to Moderate/Advanced Fibrosis (FIB-4>0.6)
2. FIB-4: Non-Cirrhotic to Potentially Cirrhotic (FIB-4≥3.25)
3. Potentially Significant Fibrosis (Forns>4.2)
4. Potentially Significant Fibrosis (APRI>1.5)

The results of these scenario analyses are given in Table 5.13 below. Among all the scenario analyses the costs remain comparable. The incremental QALYs however, largely differ in the BSC scenarios. In BSC scenario 1, where FIB-4 cut-offs of 1.45 are used for both BSC and sebelipase alfa, incremental QALYs are approximately half of that in the base case. In BSC scenario 2, using the FIB-4>0.6 cut-off for BSC and the FIB-4>1.45 cut-off for sebelipase alfa, incremental QALYs are slightly higher, whereas in BSC scenario 4, using the APRI for the BSC group (and FIB-4>1.45 for sebelipase alfa), the incremental QALYs are much lower. Among the different scenarios for the sebelipase alfa group, incremental QALYs remain similar.

Table 5.13: Multi-way scenario-based sensitivity analysis of transition probabilities

	Transition probabilities					
	Remaining in LALD without CC, DCC, or HCC	**LALD without CC, DCC, or HCC to CC**	**CC to LALD without CC, DCC, or HCC**	**Remaining in CC**	**Incr. costs**	**Incr. QALYs**
BSC						
Base case	97%	3.2%	0%	100%	[redacted]	20.5
1	100%	0%	25%	75%	[redacted]	10.2
2	92%	8%	0%	100%	[redacted]	24.9
3	96%	4%	0%	100%	[redacted]	20.6
4	96%	4%	33%	67%	[redacted]	15.2
sebelipase alfa						
Base case	100%	0%	25%	75%	[redacted]	20.5
1	94%	6%	33%	67%	[redacted]	19.9
2	100%	0%	100%	0%	[redacted]	20.5
3	100%	0%	0%	100%	[redacted]	19.8
4	100%	0%	86%	14%	[redacted]	20.5

After a request from the ERG, an additional sensitivity analysis was performed assuming that 3% of sebelipase alfa patients get an anaphylaxis reaction. This analysis assumed that the cost per event is equal to HRG codes WA16W (Shock and Anaphylaxis with CC) and WA16Y (Shock and Anaphylaxis without CC), both of which cost £207. Despite the ERG request, no health utility decrement for anaphylaxis, with the company explaining that this was "owing to the brief, episodic nature of the events, which is consistent with the literature".[76] According to these assumptions, the change in the base case output would be an additional £6.27 in incremental costs per sebelipase alfa treated patient."

ERG comment:

The sensitivity analyses for the transition probabilities between the "LALD without CC, DCC or HCC" and "CC" states contain unsystematic comparisons. Only BSC scenario 1, comparing the use of FIB-4 with equal cut-offs in the BSC and sebelipase alfa group, contains a fair and useful comparison. This scenario results in only half the incremental QALYs of the base case scenario.

5.4.3 Validation

Face validity

The company reported that "an advisory board was conducted in October 2014 with four clinical experts in hepatology or rare disease and two health economists to review sebelipase alfa clinical data and discuss the health economic analysis. Four European markets were represented: UK, Spain, Germany and Italy" (CS Section 12.2.5). The health economic model framework and assumptions with emphasis on identifying the correct disease states, transition probabilities, health utilities and medical resource utilisation parameters were discussed. The

approach taken to modelling the clinical progression of LAL Deficiency patients was deemed appropriate by hepatologists.

Internal validity

The internal validity of the model was checked by the ERG through reproducing the Markov traces.

External validity

In their clarification letter the company explained that the model predicts that in 10 years, 15.6% of BSC-treated patients will have had a successful liver transplant in the base case, which is a slight overestimation when compared with the 6/48 (12.5%) subjects from the LAL-2-NH01 natural history study who required a transplant.[11]

Cross validity

No cross validity check was performed, presumably as no other relevant cost-effectiveness models were identified by the company.

5.5 Discussion of available evidence relating to value for money for the NHS and PSS

This chapter focused on the economic evidence for sebelipase alfa submitted to NICE by the company. The analysis from the company is a QALY-based cost-consequence model comparing sebelipase alfa against BSC. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient compared to BSC and the incremental costs would be [redacted] per patient compared with BSC. In the company's sensitivity analyses this result was most sensitive to discount rate and the transition probabilities to and from the "LAL deficiency without CC, DCC" and "HCC" health state. The infants' scenario analysis resulted in 28.6 QALYs gained and incremental costs of [redacted].

The ERG's critique of the cost-consequence model entails the following main points: the health economic search, model structure and estimates for transition probabilities, costs of sebelipase alfa, health state utility estimates, and the handling of uncertainty. In order to address some of the problems identified within the critical appraisal of the economic analysis, the next chapter outlines the additional analyses conducted by the ERG.

Health economic literature search

The ERG notes that one limitation of the health economic literature search is that all Ovid databases were searched in one single strategy. Moreover, the company focused the search strategy on LAL Deficiency only, while it aimed to identify all health economic studies that could be used to inform the design of the cost-consequence model or provide utilities, resource use or cost data for the model. For this purpose the ERG feels a broader definition of the population as the basis for the literature review would have been useful, in particular including non-alcoholic steatohepatitis (NASH), which was appointed by the company as the disease analogue for modelling LAL Deficiency.

Model structure and estimates for transition probabilities

The model structure used in the cost-consequence analysis differs between the comparators as a result of using different sources for transition probabilities (LAL-CL02[4] data for sebelipase alfa and Mahady et al[2] and Hartwell et al[5] for BSC). For sebelipase alfa it is assumed that,

based on surrogate endpoints in LAL-CL02, patients cannot progress to the "CC", "DCC", "HCC" health states, and, as a result, cannot receive a liver transplant. In absence of comparative evidence on the clinical endpoints underlying these health states, the ERG questions this model structure.

The transition probabilities (for BSC) were mainly retrieved from the economic model by Mahady et al.[2] The company identified this economic model from a systematic review focusing on the use of the non-invasive liver tests (NILT) in a non-acid fatty liver disease (NAFLD) population. Given the restriction to NILT, it is unclear whether there are more appropriate economic models available that were not identified in this systematic search. Specifically the economic model by Zhang et al[51] could have been used as an alternative starting point to develop a model by the company. Moreover, it might have been more appropriate if the company would have aimed to identify clinical studies considering NAFLD to inform transition probabilities instead of limiting itself to cost-effectiveness studies identified in a systematic review.

Costs of sebelipase alfa

After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price, a generic version of the drug would enter the market. Furthermore, drug costs were influenced by the foreseen introduction of 5 mg vials of sebelipase alfa one year after market access. This reduces waste and costs associated with sebelipase alfa. The ERG thinks the 5 mg vials of sebelipase alfa should not be incorporated in the cost-consequences analysis because these are not yet available.

Health state utility estimates

The health state utility used in the cost-consequence analysis exceeded the UK general population utility scores.[8] For instance, approximately 90% of the patients are still expected to be alive at age 65 with a utility of 0.92 in the "LAL Deficiency without CC, DCC, or HCC" health state, whereas the UK general population utility for persons aged 65 is expected to be 0.784. Despite requested, the company did not provide a plausible justification for the seemingly implausible high health state utility nor any scenario analysis using alternative health state utilities (e.g. age dependent utilities). Moreover, it was unclear whether the health state utility scores selected by the company were the most appropriate ones for the UK context.

Handling of uncertainty

In the probabilistic sensitivity analysis, multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges. In addition, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect.

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Introduction

In this chapter the additional analyses performed by the ERG are presented. As described in Chapter 5, the following five issues were adjusted in the ERG base case (all probabilistic analyses):

1. A minimum function was implemented in the economic model to ensure the health state utilities would not exceed those of the general population (with the same age); see Section 5.3.3.6.
2. The utilities reported by Crossan et al[64] were incorporated in the economic model; see Section 5.3.3.6.
3. The transition probabilities were adjusted according to the ERG preferred assumptions; see Section 5.3.3.5.
4. The price reduction of sebelipase alfa by 30% after 10 years is removed; see Section 5.3.3.7.
5. The use of 5 mg vials for sebelipase alfa was excluded (these are currently not available); see Section 5.3.3.7.

The ERG base case will also be presented using an alternative discount rate of 3.5%.

In addition to the adjustments above, the following adjustments were made to the infant scenario (both probabilistic analyses):

6. The application of the half-cycle correction was corrected; see Sections 5.3.3.6 and 5.3.3.7.
7. Alternative utilities were assumed; see Section 5.3.3.6.

These adjusted infant scenarios were also presented using an alternative discount rate of 3.5%.

Finally, the following explorative analyses were performed (all deterministic; conditional on the adjustments made in the ERG base case):

Base case

8. Exploring the benefit of sebelipase alfa if for sebelipase alfa 1) the transition probability from "LALD without CC, DCC, or HCC" to "CC" would be reduced by 50% and; 2) the transition probability from "CC" to "LALD without CC, DCC, or HCC" would be increased by 50%
9. Using the health state costs reported by Crossan et al[64]; see Section 5.3.3.7.

Infant scenario

10. Assuming a four year time horizon (consistent with follow-up in LAL-CL03) and assuming for sebelipase alfa that after the first year one out of six surviving patients dies at 15 months and the remaining patients survive for the remainder of the time horizon; see Section 4.3.1.1. Survival during the first year is consistent with survival in the company's analysis. Moreover, after the first year, the health state costs and utility for the "LALD without CC, DCC, or HCC" health state was applied.

11. Assuming a four year time horizon (consistent with follow-up in LAL-CL03) and assuming for sebelipase alfa equal survival as in the previous scenario analysis. For BSC it is assumed that 21 out of 25 would survive on average 3.45 months, of the remaining patients three would survive one year and the remaining patient would survive for the remainder of the time horizon; see Section 4.3.1.1. After the first year, the health state costs and utility for the "LALD without CC, DCC, or HCC" health state was applied.

6.2 Re-analysis of the company's economic analysis following the correction of technical programming errors

No technical programming errors were identified in the company's base case after reproducing the Markov trace and examining the visual basic code.

6.3 Development of the exploratory ERG model

The ERG analyses as numbered in Section 6.1 will be discussed below.

Analysis 1

The cells CP22:CU123 (worksheets "BSC calcs" and "SA calcs") were adjusted to incorporate a minimum function in the economic model. This minimum function ensured that the health state utility would not exceed the age-dependent utility of the general population. The age-dependent utility of the general population was calculated using the linear function from Ward et al[8] consisting of an intercept of 1.060 (SE: 0.029) and a coefficient for age of 0.004 (SE: 0.001). These parameters were incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 2

The cells CR7:CR11 (worksheets "BSC calcs" and "SA calcs") were adjusted to incorporate the health state utilities reported in Table 5.7. These parameters were incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 3

The cells K23:P28 and K63:P68 (worksheets "Transition probabilities") were adjusted to incorporate the transition probabilities reported in Table 5.5. These parameters were incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 4

Cell CH7 of the "SA calcs" worksheet was set to '200' to remove the price reduction of sebelipase alfa by 30% after 10 years.

Analysis 5

Cell BY7 of the "SA calcs" worksheet was set to '20' to exclude the use of 5 mg vials for sebelipase alfa.

Analysis 6

For infants dying during the first year, the half cycle-correction was removed in cells BK22:BO22 and CV22 (worksheets "BSC calcs" and "SA calcs").

Analysis 7

The cell CR14 (worksheets "BSC calcs" and "SA calcs") was adjusted to incorporate the health state utility of 0.144 (SE: 0.073) reported in Table 5.7. This parameter was incorporated as stochastic parameters in the probabilistic sensitivity analysis.

Analysis 8

Cells L63 and K64 (worksheet "Transition probabilities"), which were already adjusted in the ERG base, are now multiplied by 0.5 and 1.5 respectively to explore an alternative for the benefit of sebelipase alfa.

Analysis 9

In this analyses, the health sate costs for "LALD without CC, DCC or HCC", "CC", "DCC", "HCC" and "Liver transplant" were assumed to be £959, £1,521, £38,871, £38,871 and £69,174 respectively.[64] These values were incorporated in cells BL11:BL15 (worksheets "BSC calcs" and "SA calcs").

Analysis 10 and 11

These analyses were performed using a simple survival model to explore the impact of the adjustments described above. Hence, no adjustments were made to the economic model of the company to perform these analyses.

6.4 Cost-consequence results produced using the ERG model

The following sections provide the scenarios analyses (Section 6.4.1) and explorative analyses (Section 6.4.2) performed by the ERG.

6.4.1 Headline cost-consequence results produced using the ERG model

Table 6.1 provides an overview of the scenario analyses described in Section 6.1 (development of these explorative analyses is described in Section 6.3). Moreover, the infant scenario analyses are conditional on the adjustments made for the ERG base case. The company base case showed incremental QALYs and costs of 19.2 and [redacted] respectively. For the infant scenario these estimates were 28.6 QALYs and [redacted].

Table 6.1: Scenario analyses performed by the ERG

Scenario 1: minimum function for health state utility (see description of scenario 1; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£45,118 (£29,930 - £73,645)	20.24 (11.28 - 29.64)
SA	[redacted]	37.15 (30.44 - 41.76)
Increment	[redacted]	16.91 (8.00 - 26.56)
Scenario 2: alternative health state utilities incorporated (see description of scenario 2; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£44,666 (£29,744 - £75,279)	15.1 (8.49 - 22.35)
SA	[redacted]	28.49 (25.23 - 30.89)
Increment	[redacted]	13.39 (5.89 - 20.62)
Scenario 3: alternative transition probabilities incorporated (see description of scenario 3; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£42,116 (£25,659 - £74,778)	27.52 (13.68 - 38.12)

SA	[redacted]	27.52 (13.68 - 38.12)
Increment	[redacted]	0.00 (0.00 – 0.00)
Scenario 4: price reduction of sebelipase alfa by 30% is removed (see description of scenario 4; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£44,875 (£29,437 - £74,198)	20.87 (11.23 - 31.47)
SA	[redacted]	39.75 (30.89 - 44.77)
Increment	[redacted]	18.87 (8.73 - 29.74)
Scenario 5: 5 mg vials for sebelipase alfa were excluded (see description of scenario 5; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£44,925 (£29,996 - £73,343)	20.88 (11.52 - 31.44)
SA	[redacted]	39.72 (30.71 - 44.64)
Increment	[redacted]	18.84 (8.33 - 29.44)
ERG base case (combination of scenario 1-5)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£41,685 (£25,857 - £76,648)	19.79 (10.19 - 26.92)
SA	[redacted]	19.79 (10.19 - 26.92)
Increment	[redacted]	0.00 (0.00 - 0.00)
ERG base case (combination of scenario 1-5) using a 3.5% discount rate		
	Costs (95%CI)	QALYs (95%CI)
BSC	£27,629 (£16,166 - £52,297)	12.92 (7.80 - 16.23)
SA	[redacted]	12.92 (7.80 - 16.23)
Increment	[redacted]	0.00 (0.00 - 0.00)
Scenario 6 (infants): half-cycle correction removed for infants dying during the first year (see description of scenario 6; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£52,212 (£43,111 - £62,193)	0.07 (0.02 - 0.15)
SA	[redacted]	14.36 (5.6 - 23.42)
Increment	[redacted]	14.29 (5.5 - 23.34)
Scenario 6 (infants): half-cycle correction removed for infants dying during the first year using a 3.5% discount rate (see description of scenario 6; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£52,595 (£42,711 - £64,149)	0.07 (0.02 – 0.15)
SA	[redacted]	9.17 (4.17 – 14.14)
Increment	[redacted]	9.1 (4.09 – 14.07)
Scenario 7 (infants): alternative utilities were assumed for infants (see description of scenario 7; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£52,466 (£42,391 - £62,459)	0.07 (0.02 - 0.16)
SA	[redacted]	14.34 (5.29 - 24.14)
Increment	[redacted]	14.27 (5.22 - 24.03)
Scenario 7 (infants): alternative utilities were assumed for infants using a 3.5% discount rate (see description of scenario 7; Section 6.1)		
	Costs (95%CI)	QALYs (95%CI)
BSC	£51,876 (£42,390 - £63,478)	0.07 (0.02 – 0.16)
SA	[redacted]	9.13 (4.14 – 14.14)
Increment	[redacted]	9.06 (4.11 – 14.07)

6.4.2 Exploratory analyses produced by the ERG model

Table 6.2 provides an overview of the explorative analyses described in Section 6.1 (development of these explorative analyses is described in Section 6.3). Please note that these explorative analyses are deterministic and performed conditional on the adjustments made in the ERG base case.

Table 6.2: Results of explorative analyses (conditional on ERG base case)

Explorative scenario 1: Adjustment of transition probabilities for sebelipase alfa (see description of scenario 8; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£44,744	[redacted]	[redacted]
QALYs	19.38	20.91	1.53
Explorative scenario 2: using health state costs from Crossan et al (see description of scenario 9; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£101,399	[redacted]	[redacted]
QALYs	19.38	19.38	0.00
Explorative scenario 3 (infants): using different survival assumptions for sebelipase alfa (see description of scenario 10; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£103,604	[redacted]	[redacted]
QALYs	0.14	1.59	1.44
Explorative scenario 4 (infants): using different survival assumptions for sebelipase alfa and BSC (see description of scenario 10; Section 6.1)			
	BSC	**SA**	**Incremental**
Total Costs	£103,135	[redacted]	[redacted]
QALYs	0.28	1.59	1.31

6.5 Discussion

In this chapter the additional analyses performed by the ERG have been presented. The ERG preferred base case resulted in a substantial decrease of the incremental QALYs; from 19.2 QALYs in the company base case to 0.0 QALYs in the ERG base case, indicating no additional health benefit for sebelipase alfa. This decrease was mainly due to the use of alternative transition probabilities removing inconsistent assumptions that were incorporated by the company. In addition, the use of alternative utilities had a substantial impact on the incremental QALYs. The incremental costs estimated by the company ([redacted]) were substantially lower than the incremental costs estimated in the ERG base case ([redacted]). This could mainly be explained by removing the 30% cost reduction after 10 years. Moreover, there was also a substantial uncertainty regarding the incremental costs (95% confidence interval showed a range of approximately [redacted]; Table 6.1). The incremental costs and the uncertainty surrounding this estimate were smaller when applying a discount rate of 3.5%.

The infant scenario presented by the company showed incremental costs and QALYs of [redacted] and 28.6, respectively. In the infant scenarios performed by the ERG using the 1.5% discount rate, the incremental costs were relatively similar while the incremental QALYs were approximately halved (Table 6.1). The incremental costs and QALYs were smaller when applying a discount rate of 3.5%. Moreover, similar to the base case, the

uncertainty surrounding the incremental costs was considerable (95% confidence interval showed a range of approximately [redacted]; Table 6.1).

7. COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

The same search as used for the review of existing economic analyses section of the submission was used for costs to the NHS and PSS, therefore any limitations discussed in Section 5.2 also apply here.

7.1.1 Model approach

In the CS, a budget impact model estimates the total costs to the NHS of adopting sebelipase alfa in the UK for a period of five years. The budget impact model starts in 2016 and is related to the cost-consequences model since the latter provides inputs for the budget impact model. Two hypothetical scenarios are presented: one where a proportion of patients would receive sebelipase alfa with the remainder receiving BSC, and a second scenario in which all patients would receive BSC. The net budget impact is the difference in total costs to the NHS between these two hypothetical scenarios over the period of five years. The budget impact model includes two groups of patients. The first group contains patients diagnosed with LAL Deficiency in their first year of life (Age 0-1 presentation group) and the second group includes patients with presentation of symptoms after one year of age (Age 1+ presentation group).

ERG comment:

The ERG agrees with the model approach chosen by the company.

7.1.2 Prevalence and incidence

For both presentation groups, population size data were retrieved from the latest estimates of the Office of National Statistics.[77] Population size estimates for 2016 were obtained by increasing population size data according to a yearly average population growth of 0.63% for both groups.[78] This resulted in baseline population sizes of 689,454 and 54,200,854 for the Age 0-1 presentation and Age 1+ presentation group respectively. To determine the number of LAL Deficiency patients in the UK, the company applies prevalence and incidence rates on these population size estimates. Prevalence and incidence rates are defined for each presentation group and are based on calculations and assumptions described in the following paragraphs.

The company assumes that all patients in the Age 0-1 presentation group die within a year[6] before the start of the budget impact model because sebelipase alfa is unavailable for treatment. Therefore, no prevalent patients belong to this presentation group in the company's budget impact model. The incidence rate for the Age 0-1 presentation group is 1.52 per million which resulted in approximately one incident patient per year. This incidence rate was determined as follows (CS, Section 13.1[1]):

"[…]this (incidence) estimate is based on the frequency analysis from Scott et al. (2013) combined with null-allele assessment from Reiner et al. (2014), which enable an assessment of incidence of presentation of symptoms at birth."

The presented prevalence rate of 4.38 per million LAL Deficiency patients for the Age 1+ presentation group (corresponding with 237 prevalent patients in the first year of the budget

impact model) is the result of an adjustment of the prevalence rate estimate reported by Scott et al.[9] The steps taken in the adjustment are described in the CS as follows (CS, Section 13.1[1]):

"Starting with a prevalence-rate estimate from Scott et al. (2013), adjusted for the ethnicity mix of England, one would estimate 10.1 cases per million. However, this approach analyses a subset of LALD causal mutations (those related only to the exon 8 splice junction mutation E8SJM) and has a broad estimate range given the small number of E8SJM carriers found in the study. We take three steps to refine and improve this estimate further:

- **Step 1: Strengthen E8SJM Data**: Include a larger number of E8SJM carriers in the analysis from Stitziel et al. (2013) and the Exome Aggregation Consortium (ExAC) Broad database (ExAC, 2015) which tightens the range and reduces the estimate to 2.8-4.9 cases per million.
- **Step 2: Add Causal Mutations**: Consider all causal mutation combinations with or without E8SJM, which contribute to LAL Deficiency. Combining mutations from Reiner et al. (2014), Alexion's clinical studies, and analysis of the ExAC database, this increases the estimate to 6.7-12.5 cases per million.
- **Step 3: Incorporate Mortality**: Scott et al.'s original analysis did not consider the reduced life-span of patients with LAL Deficiency. Incorporating mortality as it is reported in Burton et al. (2015c), and also observed in Alexion's clinical studies, leads to an estimate of 1.5-7.3 cases per million."

Furthermore, the company assumes between five and eight incident patients each year in the Age 1+ presentation group. This number of incident patient is based on above-described prevalence rate and the age distribution at symptom presentation from Bernstein et al.[14]

Beside incidence and prevalence rates, mortality rates are applied in the Age 0-1 presentation group. These mortality rates are treatment-dependent and apply only to the first year of the budget impact model. Patients receiving sebelipase alfa have an annual mortality rate of 33%[7] while patients treated with BSC have a 100% annual mortality rate[6] in the first year of the model. After the first year of the budget impact model, patients in the Age 0-1 presentation group have the same mortality rate as patients in the Age 1+ presentation group.

In the absence of evidence to support a difference in mortality between patients receiving BSC or sebelipase alfa in the Age 1+ presentation group, the company assumes a mortality rate of 0% for all patients in the Age 1+ presentation group, regardless of their treatment. This assumption is considered conservative by the company (CS, Section 13.1[1]).

ERG comment:
The calculations performed to determine the incidence rates of both presentation groups and to determine the prevalence rate of the Age 1+ presentation group were unclear to the ERG since no description of the calculations was provided in the CS.[1] The ERG therefore asked the company to clarify the methodology used to adjust the prevalence rate of Scott et al.[9] The answer was the following:

"These adjustments were made by Alexion's bioinformatics department using a model, which incorporates allelic frequencies from the EXAC database and accounts for novel mutations through in-silico and statistical methods. The 4.38 per million estimate represents Alexion's most accurate estimation of the prevalence of LAL Deficiency in the Age 1+ presentation group".[11]

Because of this lack of transparency, the ERG was not able to assess the quality and the validity of the adjustments made by the company on Scott et al's prevalence rate.[9] The ERG performed sensitivity analyses in order to explore how prevalence and incidence rates influence the results of the budget impact analysis. Results of these analyses are provided in Table 7.9 in Section 7.1.6 of the current report.

The company assumes an annual mortality rate of 100% for patients in the Age 0-1 presentation group treated with BSC. However, this assumption was not respected in the budget impact model in both scenarios. The ERG corrected this and the results are provided in Table 7.8, Section 7.1.5 of the current report. This corrected model is used in further sensitivity analyses performed by the ERG.

7.1.3 Uptake of sebelipase alfa

In the company's budget impact model, the uptake of sebelipase alfa is determined by diagnosis and treatment rates. Furthermore, the model assumes that several patients will not continue sebelipase alfa treatment or will not comply with prescribed dosing. Diagnosis, treatment, treatment continuation and compliance rates are based on the company's experience in ultra-rare disease and discussions with clinical experts.[1] These rates are provided in Tables 7.1 to Table 7.4 (CS, table D13.10, D13.11, D13.13 and D13.14[1]).

Table 7.1: Diagnosis rate of LAL Deficiency (CS, table D13.10)

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

Table 7.2: Treatment rate of LAL Deficiency (CS, table D13.11)

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

Table 7.3: Treatment continuation rate amongst treated patients, by years from start of treatment (CS, table D13.13)

	Years from patient's start of treatment				
	1st	2nd	3rd	4th	5th
Age 0-1 presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7.4: Compliance rate of LAL Deficiency (CS, table D13.14)

	Year 1	Year 2	Year 3	Year 4	Year 5
Age 0-1 presentation	100%	100%	100%	100%	100%
Age 1+ presentation	85%	85%	85%	85%	85%

Applying diagnosis, treatment and treatment continuation rates results in [redacted] of the total group of LAL Deficiency patients ([redacted]) treated with sebelipase alfa in the first year of the budget impact model. The proportion of treated patients increases to a maximum of [redacted] in the fifth year of the model. An overview of the number and proportion of sebelipase alfa treated patients is provided in Table 7.5 for each presentation group separately and in total.

Table 7.5: Comparison of the number of sebelipase alfa treated patients versus total number of patients after applying diagnosis, treatment and treatment continuation rates to the LAL Deficiency patient population (CS, budget impact model)

	Year 1	Year 2	Year 3	Year 4	Year 5
Children and adult patients					
Total UK LAL D patient in the Age 1+ presentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of treated patients (%) after applying diagnosis, treatment and treatment continuation rates on the Age 1+ presentation group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infant patients					
Total UK LAL D patient in the Age 0-1 presentation group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of treated patients (%) after applying diagnosis, treatment and treatment continuation rates on the Age 0-1 presentation group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All patients					
Total number of UK LAL D patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of treated patients (%) after applying diagnosis, treatment and treat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG comment:

The diagnosis, treatment, treatment continuation and compliance rates applied to the LAL Deficiency patient population to determine the amount of patients treated with sebelipase alfa. These rates are based on the company's experience with ultra-rare disease (CS, Section 13.2; CS, budget impact model[1]). The ERG asked the company to clarify how this experience was used to determine these rates. The company provided several estimates concerning eculizumab treatment rates in paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), two other ultra-rare diseases. In the case of PNH, the company claims that "*around* [redacted] *of the patients are on eculizumab treatment"*; while the uptake of eculizumab in the aHUS population [redacted] than expected.[11] The ERG acknowledges that in absence of other evidence, these rates might be a suitable basis to determine the uptake for sebelipase alfa because similarities exist (eculizumab is an expensive drug which is administrated intravenously and with an adverse event profile comparable to the adverse event profile of sebelipase alfa). Uncertainty remains however, because aHUS and PNS are different diseases, and experience with eculizumab is based on small patient numbers. Furthermore, the company did not specify how exactly the eculizumab uptake-related rates were used to inform sebelipase alfa's uptake. As a result, the ERG was unable to assess the validity of the rates used by the company. The ERG notes that the estimated proportion of patients treated with sebelipase alfa in the fifth year ([redacted]) is half the proportion of patients with aHUS on eculizumab (around [redacted]). This seems inconsistent with the statement of the company that experience with eculizumab can be used to inform the uptake of sebelipase alfa. The ERG performed sensitivity analyses on diagnosis and treatment rates. Results of these sensitivity analyses are provided in Table 7.10 in Section 7.1.6 of this report.

In its base case analysis, the company assumes that patients might discontinue treatment (in both presentation groups) and might not be compliant with the prescribed dosing schemes (especially in the Age 1+ presentation group). Due to the nature of the disease and the treatment (sebelipase alfa is administrated by intravenous injection), the ERG thinks these assumptions might underestimate the number of patients continuing treatment and complying with prescribed doses. This also decreases the net costs of sebelipase alfa treatment. Furthermore, the company provided little insight in the experience it has with other ultra-rare diseases and did not explain how its experience was used to determine treatment continuation and compliance rates. The company only mentioned in its response to the clarification letter that "compliance rates for patients receiving homecare drug administration are high with [redacted] of patients having compliance rates of [redacted]".[11] The ERG performed sensitivity analyses on these rates in order to assess the impact of these rates on the net budget impact. Results are shown in Table 7.11 in Section 7.1.6 of the current report.

7.1.4 Technology costs

The company uses patients' weight and two dosing schemes to determine sebelipase alfa costs in its budget impact model. Patients' weight is age-dependent. The UK growth charts from the Royal College for Paediatrics and Child Health[68] and a 50/50 ratio of male and female patients[4] is used to determine the mean weight for each age. As in the cost-consequences analysis, patients' weight does not vary after their 18th birthday. Dosing

schemes are dependent on the presentation group of the patients. Patients in the Age 0-1 presentation group receive a weekly 3 mg/kg dose of sebelipase alfa. However, assuming a weekly 3 mg/kg dose in the first year for the Age 0-1 presentation group would have overestimated sebelipase alfa costs because infants escalate sebelipase alfa dose from 1 mg/kg every week to 3 mg/kg every week in their first year of life. Therefore, the company adjusted the administrated doses in the first year of the model for patients in the Age 0-1 presentation group according to the time infant patients need to escalate to the weekly 3 mg/kg dose, based on LAL-CL03.[7] This resulted in a weekly 2.3 mg/kg dose of sebelipase alfa for infant patients in their first year of life. Patients in the Age 1+ presentation group receive 1 mg/kg of sebelipase alfa every other week and are allocated to different age based on Bernstein's et al[14] age distribution of LAL Deficiency patients.

Only 20 mg vials of sebelipase alfa are available for treatment in the first year of the model at a list price of £6,286. In the remaining years of the model, 5 mg vials are also available at a list price of £1,572. The availability of 5 mg vials reduces waste and the net drug cost of sebelipase alfa.

Non-drug direct medical costs for the Age 1+ presentation group are based on the five year average non-drug direct medical costs of a 16.6 year-old patient at baseline (baseline age of ARISE/LAL-CL02[4]) as calculated in the cost-consequences analysis. Non-drug direct medical costs for the Age 0-1 presentation group are based on daily hospital costs and survival rates of infants treated with BSC and sebelipase alfa. Infant patients receiving BSC are assumed to receive care at the hospital until they decease, which equals a period of 3.45 months of hospital care.[7] Infant patients receiving sebelipase alfa are assumed to be treated three months of their first year of life at the hospital. The cost of a hospitalisation day is £1,001.[70] Non-drug direct medical costs used in the company's budget impact model are provided in Table 7.6 (CS, table D13.16[1]).

Table 7.6: Non-drug direct medical costs, by treatment option and age of presentation group (adapted from CS, table D13.16)

	Mean cost	**Source**
Age 0-1 presentation		
BSC	£103,604	Calculation (see Section 12.3.7)
Sebelipase alfa	£94,586	Calculation (see Section 12.3.7)
Age 1+ presentation		
BSC	£1,699	Calculation (see Section 12.3.7)
Sebelipase alfa	£668	Calculation (see Section 12.3.7)

ERG comment:

Sebelipase alfa costs are dependent on patients' weight and dosing scheme. However, two assumptions decrease the net costs associated with sebelipase alfa treatment: assuming that patients' weight does not vary after their 18th birthday and the availability of 5 mg vials of sebelipase alfa. For an extensive discussion of these concerns, the ERG refers to Section 5.3.3.7 of this report. In addition to these two issues, the following points needed clarification: how non-drug medical costs are obtained from the cost-consequence model, the

choice of the age distribution to determine non-drug medical costs, and the choice of the age distribution to populate the budget impact model.

The ERG was unable to reproduce the non-drug direct medical costs and asked for clarification. After explanation, non-drug medical costs could be reproduced by the ERG. However, there was a discrepancy between the calculation performed and the description of the calculation in the CS.[1] The non-drug direct medical costs were calculated based on a 18 year-old population at baseline instead of a 16.6 year-old population, as described in the CS.[1] The ERG corrected this and used these corrected non-drug direct medical costs in its analyses. The recalculated non-drug medical costs are higher for the sebelipase alfa group (£684 instead of £668) and lower for the BSC group (£1,444 instead of £1,699). As a result, non-drug direct medical costs increase for the sebelipase alfa treated patients and decrease for the BSC treated patients. The results of the corrected budget impact model are provided in Table 7.8 of Section 7.1.5 of the current report.

For the Age 1+ presentation group, non-drug direct medical costs are calculated based on the mean age at baseline of the ARISE clinical trial[4] and then applied to the age distribution of Bernstein et al.[14] The ERG thinks this is inconsistent and asked the company to clarify why the age distribution of Bernstein et al[14] was thought to be more representative for the UK patient population and used to populate the first year of the budget impact model while the ARISE age distribution was used to calculate non-drug direct medical costs[4]. The company explained that the Bernstein et al[14] age distribution was used for the prevalence and incidence rates calculation and was therefore used to populate the base case budget impact analysis. No explanation of why Bernstein et al[71] age distribution of patients was more appropriate for the UK setting was provided. The ARISE age distribution was used to calculate non-drug direct medical costs in order to be more in line with the cost-consequences analysis.[11]

Because the ERG thought it was inconsistent to apply non-drug direct medical costs based on ARISE and apply them to the Bernstein et al[14] age distribution, the ERG asked the company to perform an additional analysis where data from Bernstein et al[14] are used to determine both non-drug direct medical costs and to populate the baseline age of the population in the budget impact model. Results are provided in Section 7.1.5 of the current report.

7.1.5 Results

The five year net budget impact of granting market access to sebelipase alfa will be £53,548,573. In the first year of the company's budget impact model, the net budget impact will be £4,292,136 and will rise to £18,515,491 in the fifth year of the model (Table 7.7; CS, table D13.19[1]).

Table 7.7: Net budget impact: company's base case scenario (CS, table D13.19)

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA without market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	**£4,292,136**	**£6,952,175**	**£10,051,079**	**£13,737,692**	**£18,515,491**	**£53,548,573**

The company provides three sensitivity analyses based on its base case analysis. In the first sensitivity analysis, the ARISE[4] baseline age distribution replaces the Bernstein et al[14] age distribution to allocate patients in the different age categories in the first year of the model. The second sensitivity analysis assumes the availability of only 20 mg vials for the five year period and the last sensitivity analysis assumes an annual per-patient cost cap of [redacted]. Results of these sensitivity analyses are provided in table D13.20 to table D13.22 of the CS.[1] These sensitivity analyses highlight the influence of the patients' age distribution on the net budget impact. Patients in ARISE[4] are older than in Bernstein et al[14] which increases the five year net budget impact from £53,548,573 to £82,194,168. Furthermore, the unavailability of 5 mg vials of sebelipase alfa would increase the five year net budget impact by £10,317,741, while the per-patient cost cap of [redacted] would decrease the five year net budget impact by [redacted].

ERG comment:

The company did not implement its budget impact model as described in the CS.[1] First, the assumption that infant patients receiving BSC die within their first year of life was not incorporated in the calculations. Second, the non-drug direct medical costs were not calculated as described in the CS.[1] The ERG has re-calculated non-drug direct medical costs and has set mortality of infant patients treated with BSC to 100%. Furthermore, the ERG did not account for the availability of 5 mg vials of sebelipase alfa after the first year of the model because these are not available yet. This led to a five year net budget impact of £63,689,818 (Table 7.8) which corresponds to approximately a 19% increase in five year net budget impact compared with the company's net budget impact analysis. This increase is caused by the unavailability of 5 mg vials in the ERG corrected model. Sensitivity analyses of the ERG are performed on this corrected budget impact model. The sensitivity analyses presented in the CS were not performed again by the ERG since the results of these analyses will not be dramatically influenced by the corrections made on the budget impact model.

Table 7.8: Net budget impact: base case analysis (ERG correction)

Total costs	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
SA with market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA without market access	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	**£4,296,378**	**£8,423,173**	**£11,909,493**	**£16,436,536**	**£22,624,238**	**£63,689,818**

Because the ERG thinks it is inconsistent to apply non-drug medical costs based on the age distribution of one population (ARISE/LAL-CL02[4]) to another (Bernstein et al[14]), the ERG asked the company to provide an analysis where both non-drug medical costs and the age distribution of the population were based on Bernstein et al.[14] Using Bernstein et al[14] for both non-drug medical costs and age distribution led to a five year net budget impact of £ 53 million,[11] which is equal to the company's base case analysis.

7.1.6 ERG additional analyses

The ERG performed additional analyses to assess the influence of remaining uncertainties around certain model parameters. These analyses concern the prevalence and incidence rates and the uptake of sebelipase alfa over the five year period. All analyses are performed on the ERG corrected version of the budget impact model, presented in Table 7.8 of Section 7.1.5 of the current report.

The ERG performed analyses on incidence and prevalence rates in the Age 1+ presentation group as these were considered uncertain due to the lack of transparency concerning the calculations of these rates in the CS[1] and in the clarification letter.[11] The prevalence rate and incidence rates were varied +/-50%. The results show that a 50% increase of the prevalent population will increase the five year net budget impact by more than 40% (and vice versa for 50% decrease of the prevalence rate). The incidence rate does not dramatically influence the five year budget impact. The five year net budget impacts of these sensitivity analyses are displayed in Table 7.9.

Table 7.9: Five year net budget impact resulting from sensitivity analyses on prevalence and incidence rates (based on ERG corrected model)

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

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

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

The ERG acknowledges that it is highly probable that all diagnosed infant patients will receive sebelipase alfa treatment. However, diagnosis and treatment rates for the adult population are highly uncertain. The ERG therefore performed sensitivity analyses on diagnosis and treatment rates in the Age 1+ presentation group by increasing and decreasing these rates with 10% or 20% in the sebelipase alfa with market access scenario. The ERG only focused on the Age 1+ presentation group and did not modify diagnosis and treatment rates of the Age 0-1 presentation group for the same reasons as above-described (small number of patients and hence small influence of these patients on budget impact). When varying diagnosis and treatment rates, the five year net budget impact ranged from £23,439,245 to £126,845,898 and the number of treated patients in the fifth year of the budget impact model varied from [redacted] to [redacted]. Results of these analyses are provided in Table 7.10.

Table 7.10: Five year net budget impact resulting from sensitivity analyses on diagnosis and treatment rates of the Age 1+ presentation group (based on ERG corrected model)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates - 20%	Treatment rates - 10%	Treatment rates as in base case	Treatment rates +10%	Treatment rates +20%
Diagnosis rates - 20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£23,439,245	£28,853,852	£34,268,458	£39,683,065	£45,097,672
Diagnosis rates - 10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£32,423,548	£40,701,343	£48,979,138	£57,256,933	£65,534,728
Diagnosis rates as in base case [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£41,407,851	£52,548,835	£63,689,818	£74,830,802	£85,971,785
Diagnosis rates +10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£50,392,155	£64,396,326	£78,400,498	£92,404,670	£106,408,842
Diagnosis rates +20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£59,376,458	£76,243,818	£93,111,178	£109,978,538	£126,845,898

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955); [2] Rates were varied to a minimum of 0% and a maximum of 100%; [3] Treatment rates in Year 1 until 5; [4] Diagnosis rates in Year 1 until 5.

The ERG performed sensitivity analyses on treatment continuation and compliance rates because these parameters influence drug costs, and because the ERG was not able to assess the validity of these estimates due to lack of reporting by the company. Furthermore, the ERG considers it probable that LAL Deficiency patients will continue treatment and comply with the dosing schemes due to the nature of the disease and of the treatment (sebelipase alfa is administrated through an intravenous infusion). Sensitivity analyses on treatment continuation and compliance rates were performed by setting both rates on 100% in both presentation groups. The sensitivity analyses were performed on the above described sensitivity analyses where diagnosis and treatment rates were varied by +/-10% or 20%. Results of the different sensitivity analyses where treatment continuation and compliance rates are set on 100% are provided in Table 7.11. All ERG sensitivity analyses concerning diagnosis, treatment, treatment continuation and compliance rates were also performed assuming the availability of 5mg vials of sebelipase alfa one year after its introduction. Results of these analyses are provided in Appendix 2.

Setting treatment continuation and compliance rates on 100% increases the number of treated patients and the five year net budget impact in each sensitivity analysis. The number of treated patients varies between [redacted] and [redacted] and the five year net budget impact varies between £36,137,359 and £206,367,686. The company stated that approximately [redacted] of the PNH patients are on eculizumab treatment.[11] Based on this information, the ERG thinks that the sensitivity analysis where treatment rates are increased by 10%, diagnosis rates increased by 20% and both treatment continuation and compliance rates are set on 100% may be the most plausible because it provides [redacted] of treated patients with sebelipase alfa. This scenario results in a five year net budget impact of £178,527,667 which is more than three times higher than the company's base case five year net budget impact.

Table 7.11: Five year net budget impact resulting from sensitivity analyses on treatment continuation and compliance rates of the Age 1+ presentation group (based on ERG corrected model)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates -20%	Treatment rates -10%	Treatment rates as in base case	Treatment rates +10%	Treatment rates +20%
Diagnosis rates -20%	Number (%) of treated patient in the fifth year					
	5-year net budget impact	£36,137,359	£45,211,920	£54,286,481	£63,361,042	£72,435,603
Diagnosis rates -10%	Number (%) of treated patient in the fifth year					
	5-year net budget impact	£50,854,922	£64,620,848	£78,386,773	£92,152,698	£105,918,624
Diagnosis rates as in base case	Number (%) of treated patient in the fifth year					
	5-year net budget impact	£65,572,486	£84,029,775	£102,487,065	£120,944,355	£139,401,644
Diagnosis rates +10%	Number (%) of treated patient in the fifth year					
	5-year net budget impact	£80,290,050	£103,438,703	£126,587,357	£149,736,011	£172,884,665
Diagnosis rates +20%	Number (%) of treated patient in the fifth year					
	5-year net budget impact	£95,007,613	£122,847,631	£150,687,649	£178,527,667	£206,367,686

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955); [2] Rates were varied to a minimum of 0% and a maximum of 100%; [3] Treatment rates in Year 1 until 5; [4] Diagnosis rates in Year 1 until 5.

In conclusion, the implementation of the company's budget impact model did not totally correspond to its description in the CS.[1] Furthermore, the ERG performed several sensitivity analyses which revealed that the model parameters used by the company to determine the net budget impact of granting market access to sebelipase alfa dramatically influenced the outcomes of the model. Cautions should therefore be taken when interpreting the results of the budget impact model because the validity of the parameters used by the company could not be assessed. The ERG most plausible scenario resulted in a five year net budget impact which is more than three times higher than the five year net budget impact provided by the company.

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the CS

8.1.1 Nature of estimates presented

The CS includes estimates of impacts of sebelipase alfa for LALD in (i) lost productivity in patients due to premature death and morbidity, (ii) lost productivity in carers, (iii) respite care and other welfare payments, (iv) out of pocket costs associated with transportation and dietary requirement, and (v) carer's time. The main source of information was the EU-LAL-D Survey.(Appendix 5 MS[1]) This online survey was conducted by Alexion and distributed through three patient organisations from the UK, Spain and the USA. Eleven participants participated in the survey (median age 11 years, range 3 to 49 years). Eight (73%) of participants were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa. The company states: "Due to the very low sample size of the survey and the fact that not all patients answered all questions, the results must be interpreted with caution." (Section 7.1 MS[1]).

8.1.2 Societal costs

Section 14.1 of the CS describes the impact of LALD on productivity in patients and carers. Affected infants with rapidly progressive disease die before the age of six months after and affected paediatric and adult patients are unlikely to survive beyond 40 years of age as their life is impacted by portal hypertension, chronic liver failure and premature atherosclerosis.[26, 27, 79] No studies were identified that quantify the impact of this premature death and morbidity on lost productivity. Two of the three adult participants in the EU LAL-D Survey indicated their working status and provided useful, as stated in the CS, information (CS Section 7.1):

"One patient worked full time, 37 hours per week. This patient reported missing one hour during the previous week because of problems associated with LAL Deficiency. She also indicated a moderate impact (score 4 of 10, where 0 equals "no effect" on work and 10 equals "completely prevented" work) on her ability to work. The other patient retired early due to LAL Deficiency at the age of 48 years." (CS, Section 14.1).

Seven carers of children with LAL Deficiency and one carer of an adult patient took part in the EU LAL-D Survey. All carers were parents of the LAL Deficiency patient. Their responses are summarised in Table 8.1 (Table E14.1 in the CS). Two (Spanish female) carers were unemployed. This unemployment rate (25%) is similar to the general country and gender specific unemployment rate,[80] but higher than the EU average (9.5%[81]). The proportion of carers working part-time (83%) is higher than the EU average (32.2%[81]) In addition to this quantitative information qualitative information on the experiences of carers regarding their employability is provided. Carers stated they are unable to fully fulfil their employment obligations.

Table 8.1: Changes in hours of work and professions for carers (n=8) (CS, Table E14.1)

Employment status	Hours worked in the past week	Number of hours reduced per week	Had to reduce hours of work?	Had to change work?	Hours / week spent providing care for LAL Deficiency patients
Working part-time	16	Full time to part time	Yes	Yes	70
	24	8	Yes	No	NR
	7	30	Yes	Yes	NR
	20	NR	No	No	3
	20	12	Yes	No	
Working full-time	35	3	Yes	No	24
Unemployed	N/A	N/A	N/A	Yes	5
	N/A	N/A	N/A	No	14
MEAN	**21.2**	**14.6**			**11.5**

N/A-not applicable

8.1.3 Costs borne by patients

In Section 14.3 in the CS[1] it is stated that some LALD patients are required to follow a low fat diet, that may be more costly than a regular diet. Furthermore, it is mentioned that family members who accompany patients to the hospital will have travel expenses and may be required to take time off work. Treatment with sebelipase alfa may be associated with travel expenses to receive treatment as long as administration is not transitioned to home care.

8.1.4 Other carer costs

In Section 14.4 in the CS[1] time costs parents of LALD patients are mentioned:

"Survey carers reported providing an average of 11.5 hours of care for their children with LAL Deficiency. 38% of carers took fewer holidays to support or care for someone with LAL Deficiency, and 63% reported spending less time with other children and family members."

8.1.5 ERG discussion of wider societal (non-health) benefits

A major source of information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is the EU-LAL-D Survey (Appendix 5 CS[1]). The ERG agrees with the company that due to the very low sample size and missing values, the results of this survey must be interpreted with caution. In addition, the survey was performed in various European countries, so does not only reflect the situation in the UK. Moreover, the survey did not use validated instruments to assess impact on, for instance, labour productivity and caregiving burden. This adds to the uncertainty of the information from this survey.

In addition to information from the survey, information from the literature is presented. It is unclear to the ERG how the studies mentioned in the CS have been retrieved. As a result, the ERG is unable to assess whether the information is complete, and provides an unbiased reflection of the evidence available in the literature.

The information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is descriptive in nature. No attempt has been made to value the impact in terms of costs. The ERG thinks that, using literature and assumptions, some quantification of wider societal benefits is possible. Presumably, the impact on productivity loss would be

highest in terms of costs. Therefore, the ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency. In the searches the ERG conducted to retrieve additional information for the CCA, the study by Scalone[12] was identified. This study reports on productivity loss due to chronic hepatic diseases. Productivity loss corresponded to on average 6.8 days/patient-month by patients and caregivers, and 14.4 days/patient-month for transplant patients. This was incorporated in the ERG base case model as 6.8 days/month for the "No CC, DCC, HCC", "CC", "DCC", and "HCC" health states, and 14.4 days for a patient who receives a transplant. The costs per day with lost productivity were based on the average annual gross earnings in the UK in 2015 (£27,607[82]) and 253 workdays per year. The ERG performed the productivity loss calculations in two ways: based on the human capital approach (HCA) and the friction costs method (FCM).[83] The human capital approach assumes that the relevant value of the production loss is equal to the present value of all lost future earnings of a person. That is, income acts as a proxy for the production value of the individual and all production not produced by this person is counted as production loss. An important, implicit underlying assumption of this approach is no involuntary unemployment occurs. In reality, involuntary unemployment is rather common; ill workers are often replaced. In that case, productivity losses due to long term absence would be limited to the 'friction period', or the period it takes to replace the ill worker by a formerly unemployed person and, hence, to restore production to its initial level. Production losses and transaction costs (related to advertising, hiring, training, etc.) occur during the friction period only. Moreover, since a reduction in labour time is often assumed to cause a less than proportional decrease in production, an elasticity factor is often used in empirical studies applying the friction cost approach. Productivity costs using this method are markedly lower than using the HCA, especially in the case of long term absence and premature death. The ERG used a friction period of three months, hence time horizon does not impact these calculations. The lifetime HCA calculation resulted in productivity loss of £268,856, and the FCM resulted in £2,226. The results are presented in Table 8.2.

Table 8.2: Exploratory scenario analysis of productivity loss in patients/carers (discounted at 1.5%)

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

8.2 Staffing and infrastructure requirements associated with the use of the technology

Sebelipase alfa treatment should be supervised by an experienced healthcare professional experienced in the management of patients with LAL Deficiency, other metabolic disorders, or chronic liver diseases.[10] Sebelipase alfa is administered by intravenous infusion. The administration time is approximately two hours. If patient tolerability is established, a one hour infusion may be considered. On the other hand, the infusion period may be extended in the event of dose escalation or infusion related events. During administration, appropriate

medical support must be readily available. The company states that in England, it is expected that initiation of the infusions and stabilisation of the patient will occur at specialist LSD centres followed by transition to local hospital outpatient clinics or homecare arrangements, as is the case for currently available enzyme replacement therapies. It is anticipated that besides this, no additional infrastructure is necessary. The company also notes that the management of infants is more complex than in older children and adults. Managing infants may require prolonged hospital stay and multi-disciplinary treatment approaches which may impact on resource requirements for the expert centres managing these infants.

ERG comment:
The ERG thinks it is reasonable to assume that the specialist LSD centres present in the UK will provide the necessary infrastructure to use sebelipase alfa in LAL deficiency patients. The costs of administration of sebelipase alfa in both infants and children older than one year and adults are incorporated in the CCA and the budget impact model.

9. DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

The CS presents results from four intervention studies and one historical control study. One of the intervention studies was a placebo controlled randomised trial.

Paediatric (≤ 2 years) patients with LAL Deficiency:

Two studies were included for this population: study LAL-CL03 was a single arm dose escalation study of sebelipase alfa (from 0.35 to 1 mg/kg once weekly IV; up to 3 or 5 mg/kg once weekly IV) including nine patients with follow-up up to 208 weeks; and study LAL-1-NH01 was a retrospective historical control study including 35 patients diagnosed between 1985 and 2012.

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients who survived past 12 months of age in LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics. In LAL-CL03, six of nine sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, one additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival, 95% CI: 0% to 16%).

No other comparative data were presented for this population.

Paediatric/adult (≥ 4 years) patients with LAL Deficiency:

Study LAL-CL02 (ARISE) was a 20-week placebo controlled randomised trial including 36 sebelipase alfa-treated patients (1 mg/kg) and 30 placebo patients.

A statistically significant improvement in multiple lipid parameters was observed in the sebelipase alfa-treated group as compared to the placebo group at the completion of the 20-week double-blind period of the study, as shown in Table 4.6. The absolute reduction in mean ALT level was -57.9 U/l [redacted] in the sebelipase alfa-treated group and -6.7 U/l (-6%) in the placebo group.

Sixty-five of 66 patients entered the open-label period (up to 130 weeks) at a sebelipase alfa dose of 1 mg/kg once every other week. In patients who had received sebelipase alfa during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels. [redacted].

Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period. Consistent with what was observed in sebelipase alfa-treated patients during the double-blind period, initiation of treatment with sebelipase alfa during the open-label period produced rapid improvements in ALT levels and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Adults (≥ 18 years) with LAL Deficiency:

Study LAL-CL01 was a four week single arm sebelipase alfa study including nine patients divided over three cohorts: 0.35, 1, and 3 mg/kg once weekly IV. Study LAL-CL04 was a 156-week extension including 8 adult patients who had completed LAL-CL01.

Changes in serum transaminase levels observed in adults in study LAL-CL01 were consistent with those reported in study LAL-CL02 and were maintained over long-treatment during the extension study LAL-CL04. Initiation of treatment with sebelipase alfa in study LAL-CL01 produced a rapid decline in ALT and AST. When patients went off treatment at the end of study LAL-CL01 (interval between dosing of nine to 28 weeks), both ALT and AST increased. Normalisation of transaminase levels continued during long-term treatment (through Week 104) in the extension study LAL-CL04.

Safety and tolerability

According to the EMA EPAR[10] the most serious adverse reactions experienced by 3% of patients taking sebelipase alfa in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

In addition, three deaths were reported in the sebelipase alfa clinical programme as of the data cut-off across the four primary studies evaluating safety; all patients who died were enrolled in study LAL-CL03. All fatal events were assessed as unrelated to sebelipase alfa treatment by the investigators.

Serious AEs were reported in 12 (14.3%) of the 84 subjects in the pooled safety set. SAEs were more frequent among infants in study LAL-CL03 with the most rapidly progressive form of LAL Deficiency (eight of nine subjects, 89%) and were relatively infrequent among children and adults (four of 75 subjects, 5%). The most commonly reported types of SAEs were infections (five of 84 subjects, 6%). One patient in study LAL-CL02 reported a serious infection (gastroenteritis). The only other SAE reported in more than one patient in the pooled safety set was pyrexia, reported in two patients in study LAL-CL03.

9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis

9.2.1 Cost-consequence analysis

The CS[1] includes a systematic search of the literature which aimed to identify all published evidence on quality of life, cost effectiveness and resource data for patients with LAL Deficiency or provide utilities, resource use or cost data for the economic model. The company did not identify any economic studies, health state utility data, resource use data nor cost data for LAL Deficiency patients. Hence, a de novo model-based cost-consequence analysis (CCA) is presented by the company to compare the costs, life years and QALYs of sebelipase alfa and best supportive care (BSC) for the treatment of LAL Deficiency from an NHS perspective. Costs and consequences are estimated for a population of 11 years-old over a lifetime horizon. For patients with infant disease onset, a scenario analysis is presented. The Markov model is an adaptation of a model for non-alcoholic fatty liver disease (NAFLD)

published by Mahady et al.[2] The model consists of four health states representing different stages of liver disease progression; compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and "LAL deficiency without CC, DCC, or HCC". Furthermore, it includes a liver transplant tunnel state and an absorbing death state. Adverse events were not included in the cost-consequence analysis. Patients receiving sebelipase alfa will remain on treatment for their entire lives. In the BSC group, the only treatment option is a liver transplant, which is offered to patients that have progressed to HCC. Health state utilities were retrieved from the economic model by Mahady.[2] Costs were based on literature.[3] The costs of sebelipase alfa depend on dosing scheme (different for infant onset and later onset) and patient weight. The transition probabilities for sebelipase alfa are mostly based on the LAL-CL02[4] data, whereas for BSC also transition probabilities retrieved from Mahady et al[2] and Hartwell et al[5] are used. When discounted at a rate of 1.5%, the company's model estimates that for patients treated with sebelipase alfa the QALY gain would be 20.48 QALYs per patient compared to BSC and the incremental costs would be [redacted] per patient compared the BSC. In the company's sensitivity analyses this result was most sensitive to discount rate and the transition probabilities to and from the "LAL deficiency without CC, DCC" and "HCC" health state. In the infants scenario analysis the LAL-1-NH01 study[6] and LAL-CL03 study[7] were used to inform the transition probabilities for the first year. Health state utilities and costs were mostly based on assumptions. This scenario results in 28.6 QALYs gained and incremental costs of [redacted]

The ERG's critique of the CCA entails the following main points: the health economic search, model structure and estimates for transition probabilities, costs of sebelipase alfa, health state utility estimates, and the handling of uncertainty.

Health economic literature search

The ERG notes that one limitation of the health economic literature search is that all Ovid databases were searched in one single strategy. Moreover, the company focused the search strategy on LAL Deficiency only, while it aimed to identify all health economic studies that could be used to inform the design of the cost-consequence model or provide utilities, resource use or cost data for the model. For this purpose the ERG feels a broader definition of the population as the basis for the literature review would have been useful, in particular including non-alcoholic steatohepatitis (NASH), which was appointed by the company as the disease analogue for modelling LAL Deficiency.

Model structure and estimates for transition probabilities

The model structure used in the cost-consequence analysis differs between the comparators as a result of using different sources for transition probabilities (LAL-CL02[4] data for sebelipase alfa and Mahady et al[2] and Hartwell et al[5] for BSC). For sebelipase alfa it is assumed that, based on surrogate endpoints in LAL-CL02, patients cannot progress to the "CC", "DCC", "HCC" health states, and, as a result, cannot receive a liver transplant. In absence of comparative evidence on the clinical endpoints underlying these health states, the ERG questions this model structure.

The transition probabilities (for BSC) were mainly retrieved from the economic model by Mahady et al.[2] The company identified this economic model from a systematic review

focusing on the use of the non-invasive liver tests (NILT) in a non-acid fatty liver disease (NAFLD) population. Given the restriction to NILT, it is unclear whether there are more appropriate economic models available that were not identified in this systematic search. Specifically the economic model by Zhang et al[51] could have been used as an alternative starting point to develop a model by the company. Moreover, it might have been more appropriate if the company would have aimed to identify clinical studies considering NAFLD to inform transition probabilities instead of limiting itself to cost-effectiveness studies identified in a systematic review.

Costs of sebelipase alfa

After 10 years, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market. Furthermore, drug costs were influenced by the foreseen introduction of 5 mg vials of sebelipase alfa one year after market access. This reduces waste and costs associated with sebelipase alfa. The ERG thinks the 5 mg vials of sebelipase alfa should not be incorporated in the cost-consequences analysis because these are not yet available.

Health state utility estimates

The health state utility used in the cost-consequence analysis exceeded the UK general population utility scores,[8] For instance, approximately 90% of the patients are still expected to be alive at age 65 with a utility of 0.92 in the "LAL Deficiency without CC, DCC, or HCC" health state, whereas the UK general population utility for persons aged 65 is expected to be 0.784. Despite requested, the company did not provide a plausible justification for the seemingly implausible high health state utility nor any scenario analysis using alternative health state utilities (e.g. age dependent utilities). Moreover, it was unclear whether the health state utility scores selected by the company were the most appropriate ones for the UK context.

Handling of uncertainty

In the probabilistic sensitivity analysis, multiple assigned standard errors for input parameters appeared to be calculated based on arbitrary ranges. In addition, first order uncertainty (i.e. variability) and second order uncertainty (sampling uncertainty) were incorporated simultaneously in the probabilistic sensitivity analyses. This is methodologically incorrect.

9.2.2 Cost to the NHS and PSS

The budget impact model in the company's submission estimates the total costs to the NHS of adopting sebelipase alfa in the UK for a period of five years. Two hypothetical scenarios are presented: one where a proportion of patients would receive sebelipase alfa with the remainder receiving BSC, and a second scenario in which all patients would receive BSC. The budget impact model includes two groups of patients. The first group contains patients diagnosed with LAL Deficiency in their first year of life (Age 0-1 presentation group) and the second group includes patients with presentation of symptoms after one year of age (Age 1+ presentation group). Prevalence and incidence are based on various sources of literature and internal modelling by the company. Diagnosis, treatment, treatment continuation and

compliance rates are based on the company's experiences with other treatments for rare diseases. The applied rates result in [redacted] of LAL Deficiency patients treated with sebelipase alfa in the first year, to [redacted] of patients treated in the fifth year. The net five year budget impact amounts to £53,548,573.

The ERG's critique on the budget impact model entails three main points. Firstly, the estimation of incidence and prevalence was not transparently reported. As a result, the ERG was not able to assess the quality and the validity of the adjustments made by the company on Scott et al's prevalence rate.[9] The ERG performed sensitivity analyses in order to explore how prevalence and incidence rates influence the results of the budget impact analysis. Secondly, the estimation of diagnosis, treatment, treatment continuation and compliance rates seem to result in an underestimation of patients receiving sebelipase alfa, when compared to the company's experiences with other treatments for rare diseases. Thirdly, the costs of sebelipase alfa are conditional upon the availability of a 5 mg vial one year after market access. As this vial size is not yet available, the ERG used the 20 mg vial in its calculations.

9.2.3 Non-health benefits

The CS includes estimates of impacts of sebelipase alfa for LAL Deficiency in (i) lost productivity in patients due to premature death and morbidity, (ii) lost productivity in carers, (iii) respite care and other welfare payments, (iv) out of pocket costs associated with transportation and dietary requirement, and (v) carer's time. The main source of information was the EU-LAL-D Survey (Appendix 5 CS[1]). This online survey was conducted by the company and distributed through three patient organisations from the UK, Spain and the USA. Eleven participants participated in the survey (median age 11 years, range 3 to 49 years). Eight participants (73%) were children (survey completed by or with the assistance of parents). The majority of participants, seven (64%), were treated with sebelipase alfa. The ERG agrees with the company that due to the very low sample size and missing values, the results of this survey must be interpreted with caution. In addition, the survey was performed in various European countries, so does not only reflect the situation in the UK. This adds to the uncertainty of the information from this survey.

Based on the survey, the company gives an overview of qualitative accounts of patients and carers on productivity. In addition, quantitative accounts of changes in work hours are provided. The impact of sebelipase alfa on these accounts is unclear. It is mentioned that some LAL Deficiency patients are required to follow a low fat diet, which may be more costly than a regular diet. Furthermore, it is mentioned that family members who accompany patients to the hospital will have travel expenses and may be required to take time off work. Treatment with sebelipase alfa may be also associated with travel expenses to receive treatment as long as administration is not transitioned to home care. In addition to information from the survey, information from the literature is presented. It is unclear to the ERG how the studies mentioned in the CS have been retrieved. As a result, the ERG is unable to assess whether the information is complete, and provides an unbiased reflection of the evidence available in the literature.

The information on the impact of sebelipase alfa on wider societal non-health benefits provided in the CS is descriptive in nature. No attempt has been made to value the impact in

terms of costs. The ERG thinks that, using literature and assumptions, some quantification of wider societal benefits is possible. Presumably, the impact on productivity loss would be highest in terms of costs. Therefore, the ERG performed an exploratory scenario analysis on the productivity losses due to caring for children and adults with LAL Deficiency.

9.3 Strengths and limitations

9.3.1 Strengths of the CS

The ERG believes that the following represent strengths within the CS:

- Despite LAL Deficiency being a rare disease, the company presented an impressive series of studies in treated patients and historical controls, including a randomised placebo-controlled trial in 66 patients.
- The CS contains details of a recent on-line survey of patients and their families from the USA and Europe which provides relevant information concerning the impact of the disease on patients and their families as well as information on resource use.
- Despite the limited evidence available, particularly regarding the long-term consequences of the disease and treatments, the company presented a CCA with a lifetime time horizon along with several sensitivity and scenario analyses

9.3.2 Weaknesses of the CS

The ERG observes the following weaknesses of the CS:

- Data from treated patients and historical controls may be biased in favour of sebelipase alfa, [redacted] while all nine patients included in LAL-CL03 were diagnosed after 2010 and supportive care will most likely have improved over time.
- Results from the randomised controlled trial show effects on surrogate endpoints, but no evidence is presented to address long-term and key clinical endpoints, such as progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death.
- The CCA and the budget impact model lacked transparency, which made it difficult for the ERG to assess whether the results are complete and valid.
- In absence of comparative evidence on long-term and key clinical endpoints, the modelling of the long-term impact of the technology is extremely uncertain.
- The calculation of the incidence and prevalence of LAL deficiency in the UK for the budget impact model lacked transparency. As a result, the ERG was unable to assess the validity of these estimates.

9.4 Uncertainties

The main uncertainties regarding the effectiveness evidence are the comparability of results from treated patients and historical control patients, the use of surrogate outcomes and the lack of long-term follow-up.

[redacted], while all nine patients included in LAL-CL03 were diagnosed after 2010. Given the likely improvements in supportive care over time, results from comparisons between treated

patients (LAL-CL03) and historical control patients (LAL-1-NH01) may be biased in favour of sebelipase alfa.

Surrogate outcomes showed a strong pharmacodynamic effect on lipid levels, hepatic fat content, and liver enzymes. These measures of well-established surrogate markers of progression of liver disease, indicate a fundamental impact on the pathogenesis of the condition. However, there is no evidence to address long-term and key clinical endpoints (progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events and death). One of the most important outcomes is slowing the progression of the liver disease and hence delaying or avoiding liver transplant. The duration of trials providing data presented in the submission was not long enough to look at this outcome.

There is no mention in the CS of possible stopping rules for sebelipase alfa. In fact the company assumes treatment will be for the full lifetime of the patient (CS, Section 2.3, page 31). However, given the many differences between patients it cannot be assumed that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

Although, there is considerable follow-up in some of the sebelipase alfa studies, with nine patients having received sebelipase alfa treatment for up to 208 weeks and eight patients receiving up to 156 weeks of treatment, this is only a fraction of the expected lifetime treatment with sebelipase alfa. Therefore, the long-term safety and efficacy profile of sebelipase alfa remains uncertain.

The availability of a 5 mg vial after one year of market access is considered uncertain. Also, after 10 years of market access, a 30% discount on sebelipase alfa was assumed because of patent expiration. Patent expiration is usually not included in health economic modelling. Moreover, in this case (small target population; need to develop a biosimilar) it is highly uncertain if and when, and at which price a generic version of the drug would enter the market.

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Appendix 1: Further Search Critique and ERG Search Strategies

Further search strategy critique

Table 17.2

The ERG notes that the structure of Table 17.2 makes it unclear which search lines were indexing terms, and which lines were free text searches of all fields (search lines #1-#4). It is assumed that this is a transcription error, however it would be clearer if indexing terms were identified in the conventional Ovid format (e.g. 'sebelipase alfa/').

Additional search terms such as 'Kanuma', or the CAS Registry number could have been added to the strategy, but the ERG believes that it is unlikely that relevant records have been missed by not including these terms.

Table 17.5

The study design filter indexing terms used in search lines #10 and #13 appear to be Embase (EMTREE) indexing terms only. This Ovid search strategy was also used to search MEDLINE, CENTRAL, DARE, NHS EED and the HTA database, all of which use MEDLINE (MeSH) indexing terms. The ERG therefore believes that MeSH terms should have been added to the strategy to increase the sensitivity of the searches. For example, the MeSH term 'exp Cost and Cost Analysis/' would have been a useful addition to the search to retrieve records on this topic from the above databases. MeSH indexing was used in the EBSCO searches (Table 17.6), so this could have also been adopted for the Ovid search. The ERG also notes that the search terms used in #11 for resource use and #14 for HRQoL are limited, and that these search lines could have been extended with additional terms and truncation to improve the sensitivity of the search.

Given the above concerns about the filters used, and the low number of records retrieved by the search for LAL Deficiency before being limited using filters, the ERG believes that a search for the condition alone could have been a less restrictive approach to the search.

ERG Search Strategies

- Search strategies to identify economic studies, health state utility data, resource use data and cost data for NASH patients.

Embase (Ovid). 1974 to 2015 November 20
Date searched: 23.11.15
Records found: 321

1 (non alcoholic steatohepatitis or nonalcoholic steatohepatitis or non alcoholic steato hepatitis or nonalcoholic steato hepatitis).ti,ab,ot,hw. (7246)
2 nash.ti,ab,ot,kw. (8645)
3 1 or 2 (10788)
4 quality adjusted life year/ or quality of life index/ (16916)
5 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (17345)
6 "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (1986)

7 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (27673)
8 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1676)
9 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (5432)
10 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (899)
11 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (370)
12 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (530)
13 "health related quality of life".ti,ab,ot. (36477)
14 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (10875)
15 "assessment of quality of life".ti,ab,ot. (2008)
16 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (9384)
17 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (18958)
18 (hye or hyes).ti,ab,ot. (98)
19 health$ year$ equivalent$.ti,ab,ot. (39)
20 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2369)
21 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (870)
22 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (2642)
23 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (13896)
24 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (6590)
25 15d.ti,ab,ot. (1873)
26 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (359)
27 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (11999)
28 (utilities or disutili$).ti,ab,ot. (7488)
29 or/4-28 (114528)
30 health-economics/ (34952)
31 exp economic-evaluation/ (235383)
32 exp health-care-cost/ (226450)
33 exp pharmacoeconomics/ (177227)
34 or/30-33 (523296)
35 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (708995)
36 (expenditure$ not energy).ti,ab. (27511)
37 (value adj2 money).ti,ab. (1605)
38 budget$.ti,ab. (27508)
39 or/35-38 (735992)
40 34 or 39 (1024851)
41 (metabolic adj cost).ti,ab. (1048)
42 ((energy or oxygen) adj cost).ti,ab. (3465)

43 ((energy or oxygen) adj expenditure).ti,ab. (23184)
44 or/41-43 (26805)
45 40 not 44 (1019151)
46 29 or 45 (1102664)
47 3 and 46 (334)
48 animal/ or animal experiment/ or nonhuman/ (6688855)
49 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6090714)
50 48 or 49 (7718796)
51 exp human/ or human experiment/ (16590098)
52 50 not (50 and 51) (5902705)
53 47 not 52 (321)

MEDLINE (Ovid). (1946 to November Week 2 2015)
Date searched: 23.11.15
Records found: 128
1 (non alcoholic steatohepatitis or nonalcoholic steatohepatitis or non alcoholic steato hepatitis or nonalcoholic steato hepatitis).ti,ab,ot,hw. (4036)
2 nash.ti,ab,ot,kw. (4015)
3 1 or 2 (5494)
4 quality-adjusted life years/ or quality of life/ (140584)
5 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (16921)
6 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1079)
7 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (3049)
8 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (494)
9 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (344)
10 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (284)
11 "health related quality of life".ti,ab,ot. (23743)
12 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (6882)
13 "assessment of quality of life".ti,ab,ot. (1230)
14 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (4590)
15 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (11177)
16 (hye or hyes).ti,ab,ot. (60)
17 health$ year$ equivalent$.ti,ab,ot. (38)
18 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (950)
19 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (634)
20 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (1966)
21 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (7681)

22 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (4114)
23 15d.ti,ab,ot. (1227)
24 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (252)
25 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (7299)
26 (utilities or disutili$).ti,ab,ot. (4360)
27 or/4-26 (166604)
28 economics/ (27221)
29 exp "costs and cost analysis"/ (195680)
30 economics, dental/ (1888)
31 exp "economics, hospital"/ (20926)
32 economics, medical/ (9034)
33 economics, nursing/ (3957)
34 economics, pharmaceutical/ (2651)
35 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (469610)
36 (expenditure$ not energy).ti,ab. (19049)
37 (value adj1 money).ti,ab. (25)
38 budget$.ti,ab. (18550)
39 or/28-38 (601211)
40 ((energy or oxygen) adj cost).ti,ab. (2822)
41 (metabolic adj cost).ti,ab. (861)
42 ((energy or oxygen) adj expenditure).ti,ab. (17551)
43 or/40-42 (20482)
44 39 not 43 (596690)
45 27 or 44 (735564)
46 3 and 45 (135)
47 animals/ not (animals/ and humans/) (4055381)
48 46 not 47 (128)

Appendix 2: Sensitivity analyses on budget impact model (based on ERG corrected model; 5 mg vials available from the second year of the model onwards)

Appendix 2.1: Five year net budget impact resulting from sensitivity analyses on diagnosis and treatment rates of the Age 1+ presentation group (based on ERG corrected model; 5 mg vials available from the second year of the model onwards)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates -20% [redacted]	Treatment rates -10% [redacted]	Treatment rates as in base case [redacted]	Treatment rates +10% [redacted]	Treatment rates +20% [redacted]
Diagnosis rates -20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£19,346,891	£23,815,388	£28,283,886	£32,752,383	£37,220,881
Diagnosis rates -10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£26,978,260	£33,903,120	£40,827,981	£47,752,842	£54,677,703
Diagnosis rates as in base case [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£34,609,629	£43,990,853	£53,372,077	£62,753,301	£72,134,525
Diagnosis rates +10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£42,240,998	£54,078,585	£65,916,172	£77,753,759	£89,591,347
Diagnosis rates +20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£49,872,367	£64,166,317	£78,460,268	£92,754,218	£107,048,169

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955).

[2] Rates were varied to a minimum of 0% and a maximum of 100%.

[3] Treatment rates in Year 1 until 5.

[4] Diagnosis rates in Year 1 until 5.

Appendix 2.2: Five year net budget impact resulting from sensitivity analyses on treatment continuation and compliance rates of the Age 1+ presentation group (based on ERG corrected model; 5 mg vials available from the second year of the model onwards)[1,2]

Diagnosis rates\ Treatment rates in Age 1+ presentation group		Treatment rates -20% [redacted]	Treatment rates -10% [redacted]	Treatment rates as in base case [redacted]	Treatment rates +10% [redacted]	Treatment rates +20% [redacted]
Diagnosis rates -20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£29,814,890	£37,304,359	£44,793,827	£52,283,296	£59,772,764
Diagnosis rates -10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£42,265,899	£53,765,270	£65,264,640	£76,764,010	£88,263,381
Diagnosis rates as in base case [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£54,716,908	£70,226,180	£85,735,453	£101,244,725	£116,753,998
Diagnosis rates +10% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£67,167,917	£86,687,091	£106,206,266	£125,725,440	£145,244,615
Diagnosis rates +20% [redacted]	Number (%)[5] of treated patient in the fifth year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-year net budget impact	£79,618,925	£103,148,002	£126,677,079	£150,206,155	£173,735,232

[1] The percentage of patients treated is based on the total number of patients in the fifth year of the budget impact model (n=273.2955).

[2] Rates were varied to a minimum of 0% and a maximum of 100%.

[3] Treatment rates in Year 1 until 5.

[4] Diagnosis rates in Year 1 until 5.