Velmanase alfa for treating alpha-mannosidosis: A Highly Specialised Technology Appraisal

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Contributions of authors

Matt Stevenson and Rebekah Pennington critiqued the health economic analysis submitted by the company. Sue Harnan and Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens critiqued the statistical aspects including the elicitation of experts' beliefs. Mark Clowes critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

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Abbreviations

3-MSCT	3-minute stair climb test
6-MWT	6-minute walk test
ADA	Anti-drug antibody
AEs	Adverse events
AIC	Academic-in-confidence
AM	Alpha-Mannosidosis
ANCOVA	Analysis of Covariance
BMT	Bone marrow transplant
BOT-2	Bruininks-Oseretsky test of motor proficiency 2nd edition
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CEV	Comprehensive evaluation visit
CHAQ	Childhood Health Assessment Questionnaire
CI	Confidence interval
CIC	Commercial-in-confidence
CPQ	Cost per quality-adjusted life year gained
CrI	Credible interval
CSt	Cohort study
CS	Company's submission
CSF	Cerebrospinal fluid
CSR	Clinical study report
DB	Double-blind
DSA	Deterministic sensitivity analyses
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
EQ-5D-Y	EuroQol 5-Dimensions-Youth
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GFAp	Glial fibrillary acidic protein
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HST	Highly Specialised Technology
HTA	Health Technology Assessment

HUI3	Health Utility Index-3
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IgG	Immunoglobulin G
IRRs	Infusion-related reactions
ITT	Intention-to-treat
IV	Intravenous
KOLs	Key opinion leaders
LSD	Lysosomal storage disorder
MC	Multicentre
MCID	Minimal clinically important differences
MDT	Multidisciplinary team
MPS IH	Severe mucopolysaccharidosis I
MPS Society	Society for Mucopolysaccharide Diseases
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NICE	National Institute for Health and Care Excellence
NFLp	Neurofilament protein
NMA	Network meta-analysis
OGS	Oligosaccharides
OL	Open-label
PC	Placebo-controlled
PEF	Peak expiratory flow
PFT	Pulmonary function test
PK	Pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PTA	Pure tone audiometry
PTS	Patients
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SC	Single centre
SD	Standard deviation
SHELF	Sheffield Elicitation Framework
SI	Severe immobility

SRT	Substrate replacement therapy
STA	Single Technology Appraisal
UK	United Kingdom
VA	Velmanase alfa
VAS	Visual analogue scale
WC	Wheelchair dependent
WU	Walking unassisted
WWA	Walking with assistance

1 SUMMARY

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

The company's submission (CS) adequately describes the decision problem. The CS assesses the clinical effectiveness of velmanase alfa within its licensed indication for the treatment of patients with alpha-mannosidosis and the cost-effectiveness of velmanase alfa for patients aged six years and older. The comparator of best supportive care (BSC) was appropriate although the company did not include haematopoietic stem cell transplant as a comparator; clinical advice to the ERG suggested that it could be a comparator in some cases. Evidence relating to all outcomes listed in the final scope produced by the National Institute for Health and Care Excellence (NICE) was included within the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence base comprised one 12 month, double-blind, placebo controlled RCT (rhLAMAN-05, n=25) and one long-term, single arm, open label study (rhLAMAN-10, n=33). Some patients were enrolled in both studies. In rhLAMAN-05 participants were treated with velmanase alfa 1mg/kg or placebo infusions once per week.

Both studies used the biomarker serum oligosaccharides as a co-primary outcome, with the clinical outcomes 3-minute stair climb test (3-MSCT) as the second co-primary outcome. 6-minute walk test (6-MWT) and functional vital capacity (FVC) were prioritised secondary outcomes in rhLAMAN-05 and secondary outcomes in rhLAMAN-10. Other outcomes measured in both trials were other pulmonary function tests (PFTs), Bruininks-Oseretsky test of motor proficiency, 2nd edition (BOT-2), Leiter-R (cognition), Pure Tone Audiometry (PTA), Childhood Health Assessment Questionnaire (CHAQ), and the EuroQol five-dimension-five-levels (EQ-5D-5L) quality of life questionnaire. Infections and psychiatric outcomes were not measured as efficacy outcomes.

In rhLAMAN-05, there was a statistically significant decrease in serum oligosaccharides (adjusted mean difference in relative change between velmanase alfa and placebo group −70.47% (95% confidence interval (CI): −78.35, −59.72), p<0.001; adjusted mean difference in absolute change -3.50 µmol/L (95% CI: -4.37; -2.62), p< 0.001**)**. However, there were no statistically significant decreases in the clinical co-primary and prioritised secondary outcomes or on the other secondary outcomes relating to motor function, cognition and hearing. The adjusted mean difference in relative change and adjusted mean difference in absolute change results respectively were: 3-MSCT: 3.01% (95% CI: −9.86, 17.72), p=0.648 and 2.62 steps/min (95% CI: -3.81, 9.05), p=0.406; For 3-MWT estimates were: 1.86% (95% CI: −6.63, 11.12), p=0.664 and 7.35 meters (95% CI: -30.76; 45.46), p=0.692; FVC% 8.40% (95% CI −6.06, 25.08), p=0.269 and 5.91% predicted (95% CI −4.78, 16.60), p=0.278. The company stated that the trial met the endpoint of "*a statistically significant reduction in serum oligosaccharides (at a*

significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis".

In rhLAMAN-10, the relative change from baseline results (SD) at last observation were: serum oligosaccharides -62.8% (33.61), p<0.001; 3-MSCT 13.77% (25.83), p=0.004; 6-MWT 7.1% (22.0), p=0.071; FVC% predicted 10.5% (20.9), p=0.011. Other statistically significant results at last observation were: EQ-5D-5L Index (11.2% (24.7218), p=0.036); BOT-2 total (13.0% (33.9), p=0.035; Leiter-R (visualisation and reasoning) (5.338 (10.45) p= 0.006), and serum IgG levels, a surrogate for infections, 44.07% 95% CI (32.58, 55.57), p=<0.001.

The company also provided pre-planned analyses in rhLAMAN-10 including age subgroups (<18 years vs ≥18 years) and a patient status analysis. Post-hoc analyses included a multi-domain responder analysis in both studies and an evaluation by age (<18 years vs ≥18 years). The multi-domain responder analysis showed more patients were responders in the velmanase alfa arm of rhLAMAN-05 than the placebo arm (87% vs 30% respectively), and more patients <18years were responders than ≥18 years in rhLAMAN-10 (100% vs 71%). The age subgroup analyses showed observed differences between groups, but interaction tests were not performed in rhLAMAN-05 and were only performed for serum oligosaccharides (non-significant interaction) and 3-MSCT (a significant interaction) in rhLAMAN-10.

To address ERG concerns about the omission of infection rates from the trials, the company provided additional post-hoc analyses of serum IgG, use of antibiotics and a questionnaire provided to caregivers. These data were interpreted by the company as indicating improvements in infection rates were likely.

The proportion of patients receiving velmanase alfa and experiencing any AE is high (88%-100%); approximately one half experienced a treatment-related AE and one third a SAE. However, most AEs were reported as being mild or moderate.

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

The ERG believes the CS is complete with respect to evidence relating to velmanase alfa. The ERG judged both studies to be at some, or unknown, risk of bias. The clinical advice provided to the ERG suggested that serum oligosaccharides are a surrogate with pharmacokinetic relevance, but low clinical relevance. They also considered infection rates and psychiatric outcomes (not measured as efficacy outcomes in the studies) as clinically relevant outcomes.

The ERG noted that the patient spectrum of the evidence base is likely to be younger than the population in England due to the inclusion criteria (5-35 years old), and it may be easier to detect an effect in younger patients as disease progression is more rapid. It is unclear whether some of the patients included

in the studies may have been eligible for HSCT in some clinical practices in England. The company provided draft start/stop criteria which, if applied in clinical practice, would be likely to exclude some patients who continued treatment in the studies. In clinical practice, therefore, fewer patients may be eligible for long term treatment, but for those who are, the studies are likely to have underestimated population-level efficacy.

The ERG does not think it is clear whether rhLAMAN-05 met its definition of efficacy as there was no definition given for a "*trend for improvement*". The ERG noted that the observed differences between treatment groups in clinical outcomes in rhLAMAN-05 did not meet the minimal clinically important differences (MCID) defined by the company post-hoc.

Whilst statistically significant differences from baseline were reported at last observation in some outcomes, results from rhLAMAN-10 are difficult to interpret because it is a single arm study and thus it is unclear how patients would have progressed without treatment. The duration of follow-up varied a great deal for patients, with variable numbers, sometimes comprising different patients altogether, at time points beyond 12 months. There are also instances of patients missing from some analyses. The last observation analysis generally included all patients and for the four main outcomes (Serum oligosaccharides, 3-MSCT, 6-MWT, FVC % predicted) there was little difference between the 12 month and the last observation analyses (though the mean length of follow-up in the last observation analysis is unclear).

The ERG had a number of concerns regarding the multi-domain responder analysis including: dichotomising continuous data based on arbitrary cut-off values; the assumption that the domains are of equally importance; the use of a potentially clinically irrelevant surrogate outcome (serum oligosaccharides) with demonstrably poor association with clinical outcomes in the studies; the omission of infection rates and central nervous system outcomes from the domains; and the post-hoc nature of the analysis and MCIDs.

The ERG did not agree with the company's reasons for not conducting interaction tests by age in rhLAMAN-05 and given that only two outcomes were tested in rhLAMAN-10, the ERG conclude that it is statistically unclear if efficacy is different in the chosen age groups for most clinical outcomes.

The ERG was concerned that the data relating to infection rates was not ideal. In rhLAMAN-05 there was a higher observed adverse event rate of infections and infestations in the velmanase alfa arm than in the placebo arm in rhLAMAN-05(48 events (87% of patients), versus 23 events (70% of patients) respectively).

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a health model constructed in Microsoft Excel® that compared treatment with velmanase alfa to treatment with BSC. The primary outcome measure was cost per quality-adjusted life year (QALY) gained using an NHS and personal social services perspective. The model uses a state transition approach with one-hundred yearly time cycles. There are five primary health states: (i) walking unassisted; (ii) walking with assistance; (iii) wheelchair dependent; (iv) severe immobility and (v) death. In addition, patients can experience severe infection, which can result in transition to a short end stage where death occurs four weeks' later, and patients can also undergo surgery, which can result in either death or transitioning to severe immobility health state. Key clinical parameters of the model that were assumed to be influenced by velmanase alfa treatment were informed largely through elicitation of experts' beliefs with, or interviews with, clinical experts. These included: improvement in health state; the additional time in a health state before progression; the reduction in the probability of major surgery; the reduction in surgical-mortality and surgical complications; the reduction in mortality and complications associated with severe infections; and the reduced requirement for ventilation. Resource use and unit costs were populated from published literature. Based on the deterministic version of the company's revised model, post clarification, the incremental cost-effectiveness ratio (ICER) for velmanase alfa versus BSC was estimated to be: £[redacted] per QALY gained for a paediatric cohort; [redacted] per QALY gained for an adolescent cohort; and [redacted] per QALY gained for an adult cohort. Probabilistic estimates were similar to the deterministic estimates.

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

The ERG critically appraised the company's economic analysis. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent of these include: (i) the use of utility data taken from a UK Society for Mucopolysaccharide Diseases survey ([redacted]) rather than those from rhLAMAN-10[1] ([redacted]); (ii) the use of an inappropriate discount rate of 1.5% per annum rather than one of 3.5% per annum; (iii) the assumption of a utility increase of 0.10 for those patients receiving velmanase alfa; (iv) a model implementation error relating to the transition probabilities after treatment discontinuation; and (v) a model implementation error relating to the expected costs after discontinuation of velmanase alfa treatment. In addition to the five issues previously described, there is considerable uncertainty in many key parameters relating to the effectiveness of velmanase alfa.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Given the rarity of the disease, the availability of RCT evidence is commendable.

The ERG considers the general model structure adopted by the company to be appropriate. The company fixed errors identified by the ERG in the clarification process.

1.6.2 Weaknesses and areas of uncertainty

The small number of patients in the studies and the relatively short (for a treatment that will be given life-long) length of follow-up leads to uncertainty around the estimates of efficacy. The lack of statistical significance is perhaps not surprising in some instances given the small sample size, though the small observed differences between treatment arms is still a concern. The company assert that improvements over the natural course of the disease are likely over time, and the biological rationale for this is plausible. However, the available evidence is difficult to interpret because of the small number of patients followed-up for longer than 12 months, and the inclusion of different patients at different time points.

The rationale for some of the assumptions used within the company's model were unclear or contentious. Many of these assumptions could be seen as being favourable to velmanase alfa. In addition, two programming errors were identified by the ERG after the clarification process. Clinical advice received by the ERG suggested that haematopoietic stem cell transplant may be an appropriate treatment for some patients; however, this was not included in the company model as a comparator.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made five changes to the company model. These were: (1) the use of utility data collected in the rhLAMAN-10[1] study ([redacted]) in preference to data taken from the MPS survey ([redacted]); (2) changing the discount rate from 1.5% per annum to 3.5% per annum; (3) removing the company's assumption that patients receiving velmanase alfa treatment have a gain in utility of 0.10; (4) the correction of a model implementation error whereby the transition rates between those patients receiving BSC were different dependent on whether the patient had received velmanase alfa previously; and (5) the correction of a model implementation error whereby the incorrect costs were used after the discontinuation of velmanase alfa. The differences these changes make to the company's base case are shown in Table 1. The amendments made by the ERG within its base case increased the estimated ICERs for velmanase alfa versus BSC to: [redacted] per QALY gained for a paediatric cohort; [redacted] per QALY gained for an adolescent cohort; and [redacted] per QALY gained for an adult cohort.

In addition, the ERG performed multiple sensitivity analyses which are presented in Table 2. These analyses indicated that the ICER was sensitive to the following assumptions relating to velmanase alfa treatment; the duration for which it was assumed that treatment with velmanase alfa could potentially result in an improvement of health state; the benefit associated with surgical outcome; the benefit

associated with serious infection; and any underlying utility gain that may be conferred by velmanase alfa. There are limited data on these parameters. It was also noted that the ICER was sensitive to assumptions made regarding which health state patients were in when receiving velmanase alfa and also the assumed average ages of patients.

The ERG noted four structural assumptions that it could not amend within the timescales of the Highly Specialised Technology appraisal relating to: (i) the prohibition of patients receiving BSC improving health state (although the rate of velmanase alfa would also need to improve by the same amount); (ii) that the model output did not predict the elicited input data regarding time in health state; (iii) that the number of vials required were not based on a distribution but was assumed fixed and known for a patient of given age and sex; and (iv) that patients discontinuing velmanase alfa treatment were assumed to do so at six months rather than at 1 year as would be the case given the proposed stopping rule. It is not known how amending the model to accommodate these changes would impact on the ICER. The ERG did not perform any analyses with haematopoietic stem cell transplant as a comparator.

The ERG highlights that all ICERs contained in this document are based on the list price of velmanase alfa, whereas there is a PAS agreed. The results when the PAS is incorporated are provided in a separate document.

Table 1: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case [redacted])**	**Adolescent (CS base case £[redacted])**	**Adult (CS base case [redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906;[redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; WU – Walking Unassisted; WWA – Walking With Assistance

Table 2: Scenario analyses run on the ERG's base case

	CPQ given individual change		
Analyses	**Paediatric (base case [redacted])**	**Adolescent (base case [redacted])**	**Adult (base case [redacted])**
Assuming 100% in the WU health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WWA health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WC health state	[redacted]	[redacted]	[redacted]
Assuming the average age per age band observed in rhLAMAN-10[1]	[redacted]	[redacted]	[redacted]
Assuming no improvements in health state after 12 months	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to surgery.	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to serious infection.	[redacted]	[redacted]	[redacted]
Assuming the costs of a severe infection are set to £2742	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to ventilation costs.	[redacted]	[redacted]	[redacted]
Assuming the UK MPS survey as the source for caregiver requirements.	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility	[redacted]	[redacted]	[redacted]
Including personal expenditure by the family	[redacted]	[redacted]	[redacted]
Including caregiver productivity losses	[redacted]	[redacted]	[redacted]
Assuming that patients treated with velmanase alfa have a utility gain of 0.05	[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; MPS – Mucopolysaccharidosis; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

2 BACKGROUND

2.1 Critique of company's description of the underlying health problem

The company's submission (CS) (section 6.1)[2] provides a good and comprehensive description of alpha-mannosidosis (AM). AM is an ultra-rare, inherited, lysosomal storage disorder (LSD), a phenotype of which was first identified in the late 1960s.[2] Numbers of patients with AM are unknown but the most frequently-reported prevalence is between one in 500,000 and one in 1 million live births.[3, 4] The number of cases in the UK is also unknown: based on registry data from the Society for Mucopolysaccharide Diseases (MPS Society), the CS[2] reports that there are only [redacted] cases of AM currently registered in England and Wales, and there is [redacted] in those countries (pages 20, 21, 41 and 43 of the CS). There is no known predisposition based on gender or ethnicity.[4]

The disorder is the result of a deficiency of the lysosomal enzyme alpha-mannosidase. This deficiency is caused by mutation of the MAN2B1 gene, which leads to reduced production of alpha-mannosidase; this in turn leads to increased excretion in urine of mannose-rich oligosaccharides, and the accumulation of these un-degraded oligosaccharides in various tissues, especially the central nervous system, liver and bone marrow.[3, 5]

As a disorder, AM is complex: it is characterised by immunodeficiency, facial and skeletal abnormalities (especially scoliosis and deformation of the hips and feet), and impairment of a person's mental and hearing abilities, and their motor function (including muscular weakness, joint abnormalities and ataxia).[3, 4] However, the clinical presentation of the disorder is highly heterogeneous and patients can present with a very wide range in terms of levels of impairment.[3, 4]

The disorder is diagnosed by measuring acid alpha-mannosidase activity in leukocytes or fibroblasts and by analysis to detect mutations in the alpha-mannosidase gene, MAN2B1.[4] Elevated urinary excretion of mannose-rich oligosaccharides is suggestive of AM but is not used for diagnosis.[4] The majority of patients are diagnosed in childhood.[3, 4] The literature has distinguished between mild, moderate and severe 'types' or forms of the condition,[3-5] but there is no universally-accepted typology.[4] It is accepted that the 'severe' form tends to be diagnosed before the age of 5 years and is characterised by rapid and lethal progress and leads to early death (in childhood), while the 'moderate' and/or 'mild' forms are characterised by slow progression (and therefore survival into adulthood), and a very wide range of impairments to a person's mental and hearing abilities, their eyesight, and their mobility. The CS[2] does not accept the distinctions by 'type' (e.g. types I and II) because of the heterogeneous nature of AM, but proposes that the condition be considered as a 'continuum' with extremes of severity. This is consistent with the literature in terms of the clinical presentation of the disease[4] and does not affect

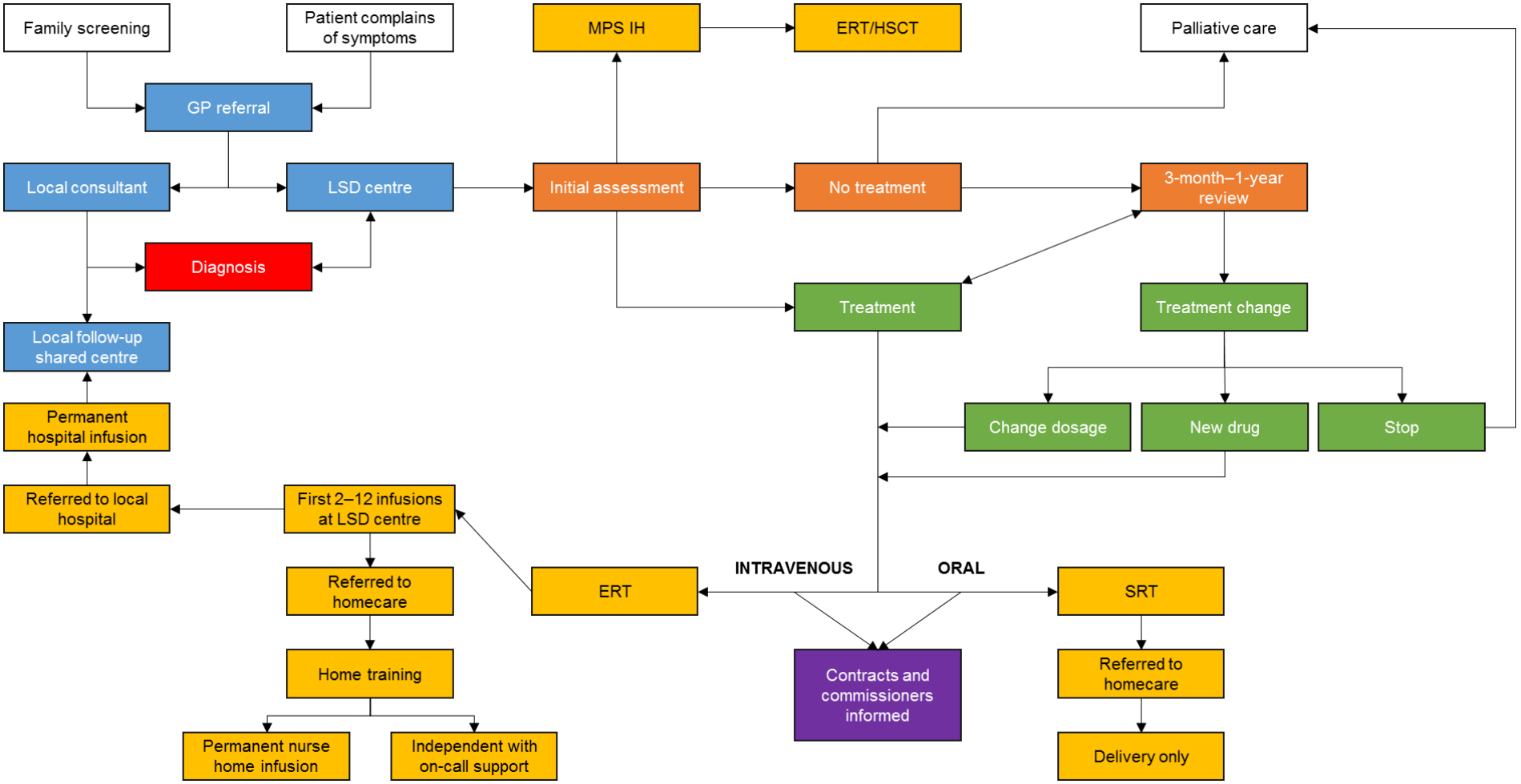
the decision problem because this distinguishes between patients based on treatment options only (CS,[2] Section 2.1).

Given the adverse effect on the immune system, AM patients are pre-disposed to recurrent infections.[3, 4, 6] The disorder also has a major impact on a person's quality of life: they can experience severe impairment to their cognitive ability, mobility, functional capacity, eyesight and hearing,[3, 4] as well as experiencing more pain as the disease progresses.[3] The number and severity of infections, comorbidities and impairments increase with time on account of the progressive nature of the disease. As a consequence of the mental and physical problems experienced by patients diagnosed with AM, they require constant support and are not socially independent, including in adulthood.[4] As a result, there is inevitably a major quality of life burden for carers also, although no published research was presented in the CS to support this (Section 7.1.3.2, page 53 and Section 7.2.3.2, page 57).[2] Given the progressive nature of the disorder, the long-term prognosis is poor and the available data, including unpublished AIC data presented in the CS[2] (page 49), suggest that the disorder is life-limiting.[3, 4]

2.2 Critique of company's overview of current service provision

The CS[2] provides a good overview of current service provision (Section 8.1, 8.2 and 8.3, pages 61-68). The CS[2] states correctly that there is currently no NICE guidance on the management of the condition and no licensed pharmacological or disease-modifying treatments for AM (pages 20, 22-23 and Section 8.3). Patients follow the NHS England lysosomal storage disorder (LSD) services care pathway,[7] as outlined in Figure 1; they are managed at designated LSD service centres in England and specialist hospitals for managing metabolic diseases in Wales (CS[2], page 64). Services depend on a patient's age and location (CS[2], Section 8.3, pages 66-68).

Figure 1: Lysosomal storage disorder (LSD) service care pathway



Source: Reproduced from CS[2], Figure 2 page 63, which was adapted from NHS England Standard Contract for LSD services.[7]
Abbreviations: ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; LSD, lysosomal storage disorder; MPS IH, severe mucopolysaccharidosis I; SRT, substrate replacement therapy

Bone marrow transplant (BMT) and allogeneic Haematopoietic Stem Cell Transplant (HSCT) represent the only treatment options for some patients, but there is substantial morbidity and mortality associated with these procedures.[4, 5, 8] The CS[2] (page 23) states that in the UK, allogeneic HSCT is only clinically indicated for patients aged five years or less, without additional comorbidities/recurrent infections, and who have a matched sibling or umbilical cord donor. However, the CS[2] (Section 8.3.3, pages 67-68) also states that broader clinical criteria might be applied in practice.

Given the lack of treatment options, current service provision principally consists of symptom management for the pain and impairments associated with the disorder. This is represented by best supportive care (BSC) and includes walking aids, physiotherapy, infection management and, where appropriate, surgical intervention (CS, Section 8.2.4 and pages 64-65).[2] Given the highly heterogeneous nature of the disorder, and the highly individual nature of its presentation, patients must be managed on a case-by-case basis.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The remit detailed in the final scope issue by the National Institute for Health and Care Excellence (NICE)[9] is to appraise the clinical and cost-effectiveness of velmanase alfa within its licensed indication for AM. The technology is not yet licensed; the CS[2] (page 38) states that a UK marketing authorisation is expected in April 2018.

The ERG notes that the final NICE scope[9] specified patients aged 6 years or older and that the CS provides clinical trial data on patients aged 5 years or older (CS,[2] Section 9). However, the CS[2] (pages 21 and 33) states that the anticipated licence is now for velmanase alfa as an enzyme replacement therapy (ERT) for the treatment of non-neurological manifestations in patients of any age with mild to moderate AM, who are not clinically indicated for HSCT.

Therefore, there is uncertainty regarding the generalisability of the results to child patients aged less than 5 years, who were excluded from the trials (rhLAMAN-05[10] and rhLAMAN-10[1]) presented in the CS.[2] Given the absence of discrete diagnostic criteria for severe, moderate and mild forms of the disorder, there might also be an issue distinguishing between patients with 'severe' AM and patients with 'moderate or mild AM'. Clinical advice to the ERG suggested that patients diagnosed under 5 years of age tend to be classified as having a 'severe' form of the disorder, with those diagnosed at 5 years or older being considered to have moderate or mild form, which ultimately progresses to 'severe' in later life. Clinical advice received by the ERG also confirmed that the clinical evidence relates to trials of patients with 'moderate or mild' AM.

3.2 Intervention

The intervention evaluated by the company is velmanase alfa (Lamzede®). Velmanase alfa is a white powder that is reconstituted to provide a final concentration of 10 mg/5 ml (2 mg/ml) per vial. The recommended dose of velmanase alfa is 1 mg/kg of body weight, once every week, to be administered by intravenous (IV) infusion at a controlled speed. As velmanase alfa is dosed by weight, (1mg/kg of body weight) dose adjustments are required as/if the patient's weight changes. Velmanase alfa is intended to be used continuously throughout a patient's lifetime, subject to the 'start' and 'stop' criteria described in the CS[2] (pages 182-83). A patient is excluded from treatment if they do not have a confirmed diagnosis of AM; has experienced a severe allergic reaction to velmanase alfa or to any of its excipients; if they are diagnosed with an additional progressive life-limiting condition where treatment would not provide a long-term benefit; or if the patient is unable to comply with the associated monitoring criteria. Treatment may be stopped due to reasons of non-compliance, non-response and/or

deterioration of functional capacity. The list price for velmanase alfa is £866.67 per vial with the number of vials required per week dependent on the patient's weight.

3.3 Comparators

The final NICE scope[9] indicated that the only comparators are BSC or HSCT, where clinically indicated. However, the CS[2] (pages 21 and 33) states that the anticipated licence is for patients for whom HSCT is not indicated, and therefore this therapy does not represent a valid comparator. If this position is accepted, the ERG believes that the rhLAMAN-05[10] and rhLAMAN-10[1] trials, which compared velmanase alfa (plus BSC) with placebo (plus BSC), are appropriate to address the decision problem. For brevity, velmanase alfa in combination with BSC intervention has henceforth been abbreviated to velmanase alfa, and placebo in combination with BSC has been termed BSC.

Clinical advice received by the ERG and submitted to NICE within expert statements suggests that HSCT could present a valid comparator for a minority of these patients, including those aged 5 years or more. The ERG also notes that there are no universally-accepted criteria regarding patients for whom 'allogeneic HSCT is not suitable and/or not possible' (CS[2], pages 23 and 68). The CS[2] (page 23) states that, '*allogeneic HSCT is typically only reserved for AM patients with extensive disease presenting in early infancy (≤5 years), and who do not have additional comorbidities/recurrent infections, and where a matched sibling or matched umbilical cord donor is available … Additionally, the risk of allogeneic HSCT-associated morbidity and mortality increases with age … Therefore, patients over the age of 6 are less likely to have any treatment options'*. The ERG notes that the clinical evidence is drawn from trials of AM patients aged 5 years or older who have never been exposed to allogeneic HSCT (CS[2], pages 97 and 100). There is therefore no comparison of clinical effectiveness or cost-effectiveness of velmanase alfa for patients who are suitable for HSCT.

3.4 Outcomes

Nearly all clinical outcomes listed in the final NICE scope[9] were addressed in the clinical section of the CS;[2] however, infections were only reported as adverse events and language was not measured. The ERG received clinical advice that infections are an important outcome as they are a source of mortality and morbidity and should have been included as an efficacy outcome. The potential status of oligosaccharides as a surrogate outcome for patients' functional outcomes[3] was not demonstrated by the submitted evidence from the only randomised controlled trial (rhLAMAN-05[10]). The company's model aggregates the patients simulated experiences into quality-adjusted life years (QALYs) as stipulated in the final scope.[9] The clinical advisors were further surprised that psychiatric problems such as acute psychosis were missing both from the NICE scope[9] and from the trials, as this is also a problem for many patients.

3.5 Other relevant factors

The company have applied for a patient access scheme which will take the form of a simple discount on the price per vial resulting in a cost of [redacted] (excluding VAT) per 10mg vial rather than the list price of £886.61 (excluding VAT) per 10mg vial. Societal costs are included in a sensitivity analyses.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

Whilst the lack of a registered protocol and poor reporting of methods in the CS[2] introduces the potential for bias, the ERG is satisfied, after clarifications[11] from the company, that the review is conducted to a high enough standard and will have captured all relevant studies relating to AM.

4.1.1 Searches

The company conducted a systematic literature review to identify published and unpublished evidence on the clinical effectiveness of treatments for AM in patients over 6 years. Searches were conducted on 25th January 2017 and then updated 31st October 2017.

Databases searched included all those recommended by NICE (Medline; EMBASE; Cochrane Library, plus a number of additional registers for the cost-effectiveness review – see Section 5.1.1). These were complemented by hand searches of Health Technology Assessment (HTA) publications and relevant conference proceedings listed in full in the CS Appendices (17.1.5.1)[2] and clinical study reports provided by Chiesi; and followed by manual checking of reference lists of included studies to identify any further potentially-relevant studies. The ERG queried whether any "forward" citation tracking (of later publications citing those included) had been conducted, but the company replied that this was not the case (clarification response,[11] Question A1).

There were some minor errors in the reporting of the searches (and specifically the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart) which were resolved via the company's response to the clarification letter (clarification response,[11] Questions A2 and A3). However, the search strategies (reported in Appendix 1 of the CS[11]) are well-designed and the ERG considers them to be unlikely to have missed any relevant studies.

4.1.2 Inclusion criteria for clinical studies

Table 3 provides the inclusion criteria used by the company which is a reproduction of Table 4 of the CS.[2] The selection criteria were in line with the decision problem, but quite broadly defined. The review did not restrict by intervention type, and it was therefore unclear how the final selection of studies was made. The ERG asked for clarification on the inclusion criteria for the review; the company replied that "Only studies that assessed the clinical effectiveness of velmanase alfa in humans were deemed relevant to the decision problem, and therefore presented in Section 9.3 of the CS onwards." (Question A8)[11] The company also listed the excluded studies which comprised seven studies related to HSCT and six studies related to the treatment of the consequences of AM.

There was a mismatch between the reported number of included studies in the text (16 (19 publications)) and in the flow chart (17 (25 publications)). The company clarified that the flow chart total was correct, but that a box detailing the source of the additional studies (an update conducted in October 2017 (1 study, 6 publications)) had been omitted in error (see clarification question A3).[11]

In their clarification response, the company confirmed that study selection was conducted by two independent assessors with recourse to a third reviewer if consensus was not reached after discussion and re-review of discordant decisions (response A6).[11]

Table 3: The Inclusion criteria employed by the company

Inclusion criteria	
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age).
Interventions	Not restricted (see Appendix 1, Section 17.1.6 for details on treatments to include).
Outcomes	Aligned to the outcomes presented in the decision problem (Table 2).
Study design	RCTs, non-RCTs, observational/real-world studies, case series and case reports
Language restrictions	Unrestricted
Search dates	Unrestricted
Exclusion criteria	
Population	Patients aged <6 years with AM (all patients were included at first pass regardless of age).
Interventions	Unrestricted
Outcomes	Publications reporting solely on outcomes outside the NICE scope were not considered relevant.
Study design	Studies not meeting the inclusion criteria for study design.
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: AM, alpha-mannosidosis

4.1.3 Critique of data extraction

In their clarification response, the company confirmed that data extraction was conducted by two independent assessors with recourse to a third reviewer in cases of discordant data (response A6).[11] It was not reported whether a data extraction form was piloted or standardised, and no list of relevant data fields was provided. However, given the data presented, the ERG is satisfied that data was extracted in an acceptable manner.

4.1.4 Quality assessment

The company confirmed that the quality assessment of the studies was conducted in the same manner as data extraction (response A6),[11] and the ERG is satisfied that the process was of an acceptable standard.

However, the ERG does not agree with all the judgements provided by the company, nor the use of an RCT checklist for the assessment of rhLAMAN-10[1] which is a non-controlled study more akin to a cohort study. Table 4 and Table 5 provide the ERG's judgements on the quality of rhLAMAN-05[10] and rhLAMAN-10[1] compared with the company's appraisal. Table 5 also includes responses to a quality assessment checklist for cohort studies provided by the company in their clarification response A5.[11]

Overall, the ERG judges rhLAMAN-05[10] to be of reasonable quality, with some faults. The ERG judged rhLAMAN-05[10] to be at low risk of bias in three domains, compared to six domains judged at low risk by the company. The ERG judged there to be a lack of clarity about randomisation procedure (i.e. how the random sequence was generated), allocation concealment (even after the company's clarification response to A4)[11] and blinding of outcome assessors, whereas the company judged these to be at low risk of bias (see Table 5).

The ERG and company's judgement of risk of bias in rhLAMAN-10[1] differed in three domains. Overall, the ERG judged rhLAMAN-10[1] to be in some respects a well conducted study, but with some key limitations that make the results subject to high risk of bias. The ERG judged an unclear risk for outcome measurement as some measures were subjective (e.g. Childhood Health Assessment Questionnaire (CHAQ)) and the trial was open label. The ERG judged there to be a lack of clarity around attrition as numbers are inconsistent across Figures 18-21 in the CS.[2] The ERG also judged that the results are possibly confounded and inconsistent with other data (CS, page 137-39);[2] there is a lack of consistency across functional outcomes, for example, 3-minute stair climb test (3MSCT) shows significant improvement but 6-minute walk test (6MWT) does not, and there is no quality of life gain despite statistically significant improvements in function; the findings for 6MWT are not correlated with oligossacharide levels as suggested elsewhere (Beck 2013).[3]

Table 4: Critical appraisal of rhLAMAN-05[10] (randomised and controlled trial) (reproduced in part from CS, Table 22)

Study name	rhLAMAN-05[10]			
	CS critical appraisal[2]		ERG critical appraisal	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Randomisation (in a 3:2 ratio) into active and placebo groups was stratified by age and was used to allocate the patients into blocks. Within the blocks, a standard randomisation into active and placebo was performed.	Unclear	CSR: 9.4.6: It is not clear how the randomisation sequence was generated, e.g. by referring to a random number table, using a computer random number generator, etc.
Was the concealment of treatment allocation adequate?	Yes	rhLAMAN-05[10] was double-blind study.	Unclear	Assumption is that vials are identical, but the description provided is not explicit: C.S.R 9.4.2.4[11] (packaging) and 9.4.6 (randomization and blinding): To preserve the blinding no batch number was included, but the batch was identified by the trial reference code (rhLAMAN-05[10]) and the retest date… The subject number, identification and randomization were documented at Larix (a Contract Research Organisation). Three sets of sealed code/label with the randomization number containing information about the treatment for the particular subject were prepared for each subject. One set was kept at the dosing site (during the entire trial period), one set was kept at Larix and one set was kept at the Sponsors Quality Assurance. The randomization code list was kept at Larix and was disclosed to the contract manufacturing organization (CMO) performing the packaging of the trial. The code for a particular subject could be broken in a medical emergency ...

				also clarification response A4[11]: The randomisation code list was kept at the CRO and was disclosed to the contract manufacturing organisation (CMO) performing the packaging of the trial. The code for a particular subject could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject. However, blinding was not broken for any patient in the trial.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Overall, the demographic characteristics were similar between the two groups. In terms of functional capacity (by categorical values arbitrary adopted for 3-MSCT and 6-MWT), PFTs and BOT-2, the two groups were less balanced, with a higher proportion of more compromised patients randomised to the active treatment group.	No	As noted, the patient groups are not balanced for 3MSCT, 6MWT, FVC, BOT-2 or CHAQ Disability Index (CSR, Table 11-1)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Patients and investigators remained blinded to treatment assignment during the study. The blinding for a particular patient could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the patient.	Unclear	Patients and care providers appear to be blinded (see allocation concealment above, CSR[10] sections 9.4.2.4 and 9.4.6), possibly as well as outcome assessors at data review (CSR[10] sections 9.6 and 11.1), but it is not specified if all outcome assessors (e.g. 3MSCT) are blinded. CSR[10] 9.6: After completion of data cleaning, a blinded data review meeting was held to define protocol deviations and patient populations to be analysed. Afterwards, the database was locked, the randomisation codes were opened and the planned statistical analysis was performed.

				CSR[10] 11.1: During the blinded data review, all patients were included in the PK analysis set, but only the 15 patients treated with Lamazym were then analysed.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	NR	No	No reported drop-outs
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	NR	No	However, the following outcomes were not listed in the protocol, but were reported: BOT-2 motor function; Leiter-R cognitive ability; EQ-5D; CHAQ Disability Index and VAS; and PTA hearing loss tests: https://clinicaltrials.gov/ct2/show/record/NCT01681953[12]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety evaluation was based on a modified ITT analysis and included all patients who received ≥1 dose of trial drug and whose efficacy was evaluated post-baseline.	Yes	CSR[10] 9.7.1: statistical analysis of everyone who had at least 1 dose of study drug (CS, 9.6.2, page 154[2]) and protocol deviations did not suggest any patient was not analysed in the correct group (CSR 10.2.1). Appropriate multiple imputation methods were used to account for missing data.

Abbreviations: CS, company submission; CSR: Clinical Study Report; 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency, 2nd edition; ITT, intention-to-treat; PFT, pulmonary function test; PK: Pharmokenetics; PTA: Pure Tone Audiometry; CHAQ: Childhood Health Assessment Questionnaire; VAS: Visual Analogue Scale; EQ-5D: EuroQol five-dimension questionnaire.

Table 5: Critical appraisal of rhLAMAN-10[1] (cohort) using the CASP tool for cohort studies (reproduced in part from clarification response to question A5[11])

	rhLAMAN-10[1]			
Study name	**CS critical appraisal[2]**		**ERG critical appraisal**	
Study question	**Response (yes/no/not clear/N/A)***	**How is the question addressed in the study?**	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Did the study address a clearly-focused issue	NR[2, 11]	NR[2, 11]	Yes	CSR[1], page 3: 'the evaluation of the long-term efficacy of Lamazym treatment in patients with AM who were previously enrolled in trials with Lamazym and were currently receiving the treatment according to the AfterCare Program agreed with the National Authorities'
Was the cohort recruited in an acceptable way	Yes[2]	Patients who were receiving active treatment as part of the compassionate use programme (after-trial study following the Phase I-II and rhLAMAN-05[10] trials) were invited to attend a CEV in order to obtain a long-term data point. These data were combined with the data bases of the Phase I-II trial, rhLAMAN-05[10], rhLAMAN-07 and rhLAMAN-09 to form the integrated data base (see Section 9.4.1.3 for details)[2]	Yes	See CS response in column 3 of this table.
	Yes[11]	Patients were enrolled from the previous rhLAMAN studies[11]		
Was exposure accurately measured	NR[2]	NR[2, 11]	Yes	Full details of different levels of exposure depending on 'parent' trial are reported: CS, section 9.7.2.2, page 157;[2] CSR[1], 12.1, page 150. However, treatment compliance was not assessed as part of this study: CSR[1], 11.3, page 66.
	Yes[11]			
Were outcomes accurately	Yes[11]	A clear definition of all measured outcomes were reported[11]	Unclear	The study measured objective outcomes, e.g. serum oligosaccharides, and subjective outcomes, e.g. CHAQ by 'patients' legally authorized

measured to minimise bias? e.g. same for different groups, are measures subjective / objective				guardians' (CSR[1] 9.5.1.1.4, page 41) and BOT-2 by a physiotherapist and occupational therapist (CSR[1], 9.5.1.1.2, page 38). The measures and outcome assessors were the same for all groups.
Have all confounding variables been identified and taken into account?	Not clear[11]	Identification of potential confounding factors was difficult due to disease heterogeneity, exemplified by variation in severity across the numerous disease manifestations, together with the small population size of the trial. [11]	Unclear	Analyses were conducted by time on treatment and age (CS, pages 139-40 and 148-50).[2] The principal potential confounders were the large variability in range of function etc. at baseline and the small patient numbers (p.103 and 136), as well as possible 'training' (Beck 2013[3]) and potentially 'ceiling effects' for certain outcomes (page 165). It is not possible to control for all of these confounders in small populations with ultra-rare disease.
Was follow-up complete enough and long enough	Yes[11]	The follow-up period ranged from 1 to 4 years[11]	Yes and No	There was no reported attrition and follow-up to 4 years. However, only a small number of patients had 2-year (n=19/33) or 4-year follow-up (n=9/33) (CSR[1], pages 150-51) and exposure is likely to be lifetime in duration. There is some lack of clarity around attrition as n numbers are inconsistent across Figures 18-21 in the CS,[2] and detailed in Table 12 here.
How precise are the results and are they credible?	Yes[11]	For all efficacy outcome results, p-values and variances were reported wherever applicable[11]	Unclear	Results are possibly confounded and inconsistent with other data (CS, page 137-39).[2] There is a lack of consistency across functional outcomes, e.g. 3MSCT shows significant improvement but 6MWT does not, and there is no quality of life gain despite statistically significant improvements in function; the findings for 6MWT are not correlated with oligossacharide levels as suggested elsewhere (Beck 2013[3]).

Can results be applied to the local population?	NR[2, 11]	NR[2, 11]	Yes	The study inclusion criteria potentially led to the recruitment of a more mobile population than reported in other studies (e.g. Beck 2013[3]), but clinical advice suggests the trial data are still applicable to England and Wales.
Do results fit with other available evidence	NR[2, 11]	NR[2, 11]	Unclear	This non-controlled study was recruited from a series of 'parent' trials (rhLAMAN-02[13], 03[13], 04[14] and 05[10]), which currently represent the only other relevant data on velmanase alfa in this patient group. The absence of a clear correlation between oligosaccharides and 6MWT is inconsistent with the findings of a larger, longitudinal study in AM patients (Beck 2013[3]).

Abbreviations: AM: alpha-mannosidosis; CS: company submission; CSR: Clinical Study Report; 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency, 2nd edition; CHAQ: Childhood Health Assessment Questionnaire; VAS: Visual Analogue Scale; EQ-5D: EuroQol five-dimension questionnaire.
*Note, there were two parts to rhLAMAN-10[1]: a) the inclusion of patients already enrolled in ongoing long-term studies and b) the inclusion of patients on compassionate use programmes.

Where applicable, the first row is for a) and the second row for b)

4.1.5 Evidence synthesis

There was no formal synthesis of the data, which the ERG believes was acceptable as there was only a single relevant phase III/IV trial (CS, section 9.8, page 161).[2] The narrative synthesis tabulated results and described these with a good degree of clarity.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The clinical effectiveness review included five studies of velmanase alfa: a Phase I-II trial comprising three individual studies (rhLAMAN-02[13], rhLAMAN-03[15], rhLAMAN-04[14]), and two further Phase III trials, one of which was an RCT (rhLAMAN-05[10]) and the other of which is a long term non-controlled study (rhLAMAN-10).[1] Table 6 details these studies. Of note, patients were eligible to enrol in subsequent trials: patients in rhLAMAN-02[13] could enrol in rhLAMAN-03[15] (and all ten did, exclusively forming the rhLAMAN-03[15] trial); patients in rhLAMAN-03[15] could enrol in rhLAMAN-04[14] (9/10 of whom did, exclusively forming the rhLAMAN-04[14] trial); patients in rhLAMAN-04[14] and -05[10] could enrol in rhLAMAN-07 or -09 (references not provided by the company for either study) or a compassionate use programme (where no efficacy outcomes were assessed). rhLAMAN-07 and -09 were set up to ensure patients could continue treatment in countries that did not want the company to offer a compassionate use programme; -07 was for French patients, and -09 for Norwegian and Polish patients. Both studies include long-term follow-up for safety, with -09 also following-up patients for efficacy (see clarification response Question A18[11]). rhLAMAN-10[1] is an integration of data collected for rhLAMAN -02[13], -03[15], -04[14], -05[10], -07 and -09, and a single efficacy assessment point for patients who enrolled in the compassionate use programme after participating in rhLAMAN-02[13], -03[15] or -04.[14] In this way, all patients had baseline and follow up data. Flow charts of patients through the trials rhLAMAN-02[13], -03[15], -04[14], -07, -09 and -10[1] are provided in Appendix 1.

4.2.1 Description of the design of rhLAMAN-05[10]

rhLAMAN-05[10] was a Phase III multicentre, double blind, placebo-controlled RCT. Patients were randomised to velmanase alfa treatment (1mg/kg by infusion) weekly, or to weekly placebo in a 3:2 ratio stratified by age in a block randomisation. Treatments were administered for 12 months. Inclusion criteria are provided in the footnote to Table 6.

4.2.2 Description of the design of rh-LAMAN-10[1]

rhLAMAN-10[1] was an integrated database(N=33) incorporating data from the Phase I/II trial (rhLAMAN-02[13]/03[13]/04[14]), rhLAMAN-05[10], rhLAMAN-07 and rhLAMAN-09 to form the rhLAMAN-10[1] integrated data set, along with additional patients who entered the compassionate use programme and had a long-term efficacy assessment as part of rhLAMAN-10.[1] The study design is an open label non-controlled study akin to a cohort study as there is no comparator arm and patients are

followed up over time. All patients were receiving velmanase alfa treatment at the standard dose (1 mg/kg); patients who had been treated with placebo in rhLAMAN-05[10] commenced treatment with VA. At the time of analysis, patients were expected to have follow-up times ranging from a minimum of 1 year to a maximum of 4 years. Inclusion criteria were determined by the original studies' criteria (see footnotes to Table 6); of note, the Phase I/II trial included patients aged 5-20 years, whereas rhLAMAN-05[10] included patients aged 5-35 years. Other inclusion criteria are largely similar.

4.2.3 Outcomes in rhLAMAN-05[10] and -10[1]

Outcomes measured in rhLAMAN-05[10] and -10[1] are described in Table 7. Minimal clinically important differences (MCID) were defined post-hoc in response to request from the European Medicines Agency (EMA). These are described on pages 105 to 108 of the CS,[2] and the methods used to define the MCIDs are described in brief in the CS Appendix 2, Section 17.7.3.1.[2] and are summarised in Table 7 of this report. Of note, there were no pre-existing MCIDs defined for alpha mannosidosis; the MCIDs were based on literature review of similar conditions and clinical opinion. Of the outcomes measured in the trials, no MCIDs were provided for motor function (BOT-2), hearing (PTA), cognition (Leiter R), infections (only measured as an adverse event), EQ-5D (though MCID provided for CHAQ) or mortality.

Table 6: Summary of key trials of velmanase alfa

Trial Name	Trial design	Inclusion criteria	N	Duration	Intervention	Comparator	Main outcomes
rhLAMAN-02[13] (NCT01268358) Borgwardt et al, 2013[16] (JA)	Phase I, SC, OL Randomised dose escalation	AM[f] pts aged 5-20[a]	10	1-5 weeks[b]	5 dosing groups (n=2 in each) VA, U/kg: 6.25; 12.5; 25; 50; 100	Baseline	**Safety:** AEs, vital signs, haematology, biochemistry, urinalysis, Anti-drug antibody (ADAs)
rhLAMAN-03[15] (NCT01285700) Borgwardt et al, 2013[16] (JA)	Phase IIa, SC, OL Randomised multiple dose	AM[f] pts aged 5-20 (all from rhLAMAN-02[13])[a]	10	6 months efficacy assessment + 6 months extension[c]	2 dosing groups (n=5 in each), weekly, IV VA, U/kg 25 50	Baseline	**Efficacy:** OGS in serum, urine, CSF; CSF neurodegeneration markers; Brain MRS; Functional capacity; cognitive development; pulmonary function; hearing; PK profile **Safety:** as rhLAMAN-02[13]
rhLAMAN-04[14] (NCT01681940) Borgwardt et al, 2014[17] (CA)	Phase IIb, MC,[d] OL	AM[f] pts aged 5-20 (all from rhLAMAN-02[13]/-03[15])[a]	9	6 months	VA 1 mg/kg	Baseline	**Efficacy (primary):** Serum and CSF OGS; 3-MSCT; 6-MWT; pulmonary function; **(secondary):** mannose-rich OGS by MRS and MRI in white matter, grey matter and centrum semiovale; CSF neurodegeneration markers; BOT-2 and hearing loss; Leiter-R; CHAQ
rhLAMAN-05[10] (NCT01681953) Guffon et al, 2017[18] (CA)	Phase III; RCT, MC,[e] DB, PC	AM[f] pts aged 5-35[g]	25	12 months	VA 1 mg/kg (randomised 3:2, VA: placebo)	Placebo	**Efficacy (primary):** Serum OGS; 3-MWT; **(secondary):** 6-MWT; FVC; PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; EQ-5D
rhLAMAN-10[1] integrated dataset (NCT02478840)	Phase III; NC, SC, OL,	AM[f] Recruited from rhLAMAN-02[13], -03[15], -04[14], and -05.[10] Pts who chose the compassionate	33	Integration of data collected in other rhLAMAN studies, or a one-week assessment for those	VA 1 mg/kg	Baseline	**Efficacy (primary):** Serum OGS; 3-MWT; **(secondary):** 6-MWT; FVC; PFTs; BOT-2; Leiter-R; CSF OGS; CSF

Guffon et al, 2017[18]; Borgwardt 2017a[19]; Borgwardt 2017b[19] ; Borgwardt 2017c[20] ; Lund 2017[21]; Harmatz 2017[19]; Borgwardt 2017d[22]; Cattaneo 2016[23]; Ardigo 2016 [24]; Borgwardt 2016[25] (all CAs)		use programme after rhLAMAN-04[14] were also eligible. Pts enrolled in rhLAMAN-07 or -09 were included in the dataset.[a g]		who joined the compassionate use programme			neurodegeneration markers; PTA; CHAQ; EQ-5D

3-MSCT, 3 minute stair climb test; 6-MWT, six minute walk test; ADA, anti-drug antibody; AEs, adverse events; AM, alpha-mannosidosis;N, number; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; DB, double-blind; MC, multicentre; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NC, non-controlled study; OGS, oligosaccharides; OL, open-label; PC, placebo-controlled; PFT, pulmonary function test; PK, pharmacokinetics; PTA, pure tone audiometry;RCT, randomised controlled trial; SC, single centre; pts, patients; VA, velmanase alfa;

[f] AM confirmed by α-mannosidase activity <10% of normal activity in blood leucocytes

[a] Inclusion criteria: Physical ability to perform 6-MWT, 3-MSCT and PFTs; Ability to mentally cooperate in the cognitive and motor function tests; Ability to hear and follow a request (hearing aids can be worn); signed, informed consent of legal guardian; Exclusion criteria: known chromosomal abnormality and syndromes affecting psychomotor development, other than AM; HSCT; conditions that would preclude participation in the trial including clinically significant cardiovascular, hepatic, pulmonary or renal disease, echocardiogram with abnormalities within half a year, other medical condition or serious intercurrent illness, or extenuating circumstances; pregnancy; psychosis in previous 3 months

[b] Patients in the 6.25U/kg group started in week 1 and continued treatment to week 5. Patients in the 12.5 U/kg started in week 2 and continued treatment to week 5, and so on, with a higher starting dose each subsequent week.

[c] To maintain treatment until enrolment in rhLAMAN-04[14]

[d] Five EU sites in Denmark, UK, France, Spain, and Belgium.

[e] Six countries in the European Union: Denmark, France, Spain, Belgium, Germany and Sweden

[g] Inclusion criteria: ability to physically and mentally co-operate with the tests; echocardiogram without abnormalities that would preclude participation in the trial; ability to comply with protocol; Exclusion criteria: known chromosomal abnormality and syndromes affecting psychomotor development, other than AM; HSCT; conditions/circumstances that would preclude participation in the trial; pregnancy; psychosis (including remission); participation in other interventional trials testing IMP (including VA) within the last three months; Adult patients who would be unable to give consent, and who do not have any legal protection or guardianship; Total IgE >800 IU/ml; Known allergy to the IMP or any excipients (sodium-phosphate, glycine, mannitol)

Table 7: Outcomes listed in the NICE scope,[9] their measurement in rhLAMAN-05[10] and -10[1], MCIDs (defined post-hoc) and inclusion in patient status analysis. Partly reproduced from Table 7 of the CS[2]

NICE Scope[9]	Measure used in rhLAMAN-05[10] and -10[1]	Description of test	MCID (Absolute change)	Based on	Patient status analysis (rhLAMAN-10[1] only)
Not listed	Serum Oligosaccharide	The levels of oligosaccharides in serum are measured to evaluate VA activity and its efficacy in clearing oligosaccharides.	Cut off: ≤4μmol/L	Arbitrary, based on rhLAMAN-05[10] baseline values	Yes
Mobility	3-MSCT	3-MSCT – evaluation of the number of steps climbed in 3 minutes to assess mobility/functional capacity.	Increase ≥7 steps/min	Used MCID defined post-hoc for a trial MOR-004 of elosulfase alfa in patients with MPS IVA (similar condition). Based on 20% of baseline value in MOR-004 (27-35 steps/min at baseline)	Yes
	6-MWT	6-MWT – evaluation of the distanced walked in 6 minutes to assess mobility/functional capacity.	Increase ≥30 meters	Literature review: Chronic lung disease MCID = 54-80 meters; pulmonary hypertension MCID = 33 meters; chronic heart failure MCID = 30.1 meters; Duchenne muscular dystrophy MCID = 28.5-31.7 meters (based on statistical distributions) MPS IV: 22.5 meters, but rhLAMAN-05[10] patients have higher baseline (466 meters vs 20 meters) Pompe disease range MCIDs = 24-54 meters	Yes
Motor function	BOT-2	BOT-2 assessment to evaluate motor skills.	NR	NR	No
Hearing and language	Hearing: PTA Language: NR	PTA to assess hearing loss.	NR	NR	PTA: yes
Cognition	Leiter R test	Leiter-R test to assess cognitive ability.	NR	NR	No

Lung function	FVC	Assessment of FVC (L and % of predicted), FEV_1 (L and % of predicted) and PEF (L/s) to evaluate lung function.	Increase ≥10% of FVC % predicted	FVC >80% considered normal. Systemic scleroma, change of 10% from baseline is a real change not measurement error; idiopathic pulmonary fibrosis MCID = 2-6% of predicted (3-9% relative change from baseline) reflected changes in global health status; Pompe disease reported global health changes at similar levels, though MCIDs were set higher (exact figure not reported in CS[2]).	No
Rates of infections	Adverse event	Not clear how AEs reported to clinical team (see clarification response A32).[11]	NR	NR	No
Mortality	Adverse event	No patients died during follow-up	NR	NR	NA
Quality of life	CHAQ disability index	Evaluation of QoL using CHAQ and EQ-5D (assessments were completed by parent/caregiver on behalf of patient, i.e. indirect measures only).	Decrease ≥0.13 on the 0-3 scale	MCID in Juvenile arthritis -0.13: 35.7% of adult patients in rhLAMAN-10[1] had arthralgia	Yes
	CHAQ pain		Decrease ≥0.246 on the 0-3 scale	MCID for Pain (VAS) ≥8.2% in juvenile arthritis (≥0.246 on the 0-3 scale)	Yes
	EQ-5D	NR	Increase NR	NR	No
Adverse events	NR	Not clear how AEs reported to clinical team (see clarification response A32).[11] Clinical team report directly to CRO within 24 hours	NA	NA	NA

MPS IVA; mucopolysaccharidosis IVA; MCID, minimal clinically important difference; VAS, visual analogue scale; CRO, clinical research organisation in charge of running trial; NR, not reported; CHAQ, childhood health assessment questionnaire; QoL, quality of life; CS, company submission; L, litres; 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; min, minutes; PTA, pure tone audiometry.

4.2.4 Critique of the design of rhLAMAN-05[10] and rhLAMAN-10[1]

4.2.4.1 Population

Impact of patient age on detection of effect: The clinical advisors to the ERG felt that the inclusion and exclusion criteria (see footnotes to Table 6) were acceptable but noted that the trial excluded very young patients (<5 years old) and older patients (>35 years old). This probably biased the cohort towards younger patients, and it is possible that it might have been easier to detect an effect in younger patients, as disease progression is more rapid.

Exclusion of severe disease and licence-indicated population: The exclusion of the very young (<5 years) will mean severe disease (which presents at a younger age) patients are excluded. The exclusion of patients who could not complete 3-MSCT or 6-MWT or could not mentally cooperate will also lead to the exclusion of patients with severe disease, and those with mobility problems at the higher end of the spectrum. As such, the spectrum is likely to comprise patients with mild to moderate disease, in accordance with the population proposed for reimbursement.

It should be noted that the anticipated licence will not restrict treatment by age, as the EMA recognises that early treatment could be beneficial. However, the company are not seeking reimbursement for patients under 6 years of age, and currently there is insufficient evidence in this group to judge the clinical effectiveness.

Generalisability concerns: The ERG asked for clarification about the exclusion criterion of "patients with IgE>800 IU/mL". The company clarified that this was to exclude patients who are at high risk of anaphylactic reactions "*or for whom the high background concentrations of immunoglobulin E (IgE) would make it difficult to clearly identify an increase due to a reaction to velmanase alfa.*" (response A15)[11] This reduces the generalisability of safety findings to patients with IgE>800 IU/mL.

Previous treatment: The ERG asked for clarification about why 3 months was chosen as an adequate time for patients who had been on previous IMP treatments (including velmanase alfa). The ERG was satisfied with the company's response, indicating that "*Given that most ERTs are given as weekly or bi-weekly infusions, a total of 12 weeks since the last infusion would ensure that a time significantly longer than 5 times the longest theoretical half-life would have elapsed, ensuring a complete drug wash out*." (response A14).[11]

4.2.4.2 Intervention

The intervention appears to match the proposed licenced posology and dose.

Start/stop criteria: The company described a set of start/stop criteria for continuation of treatment, which are reproduced in Appendix 1. There is uncertainty around the proposed criteria as a review by key opinion leaders in the UK is ongoing. (see clarification response A11).[11] However, the clinical advisors to the ERG felt that the criteria were largely sensible as treatment would be stopped for those with life-limiting conditions, those who cannot tolerate the treatment, those who cannot not comply with monitoring (either for practical reasons or due to worsening of disease) and those gaining no benefit after one year of treatment.

However, the clinical advisors to the ERG also suggested that advance brain disease might be an additional reason for stopping treatment, though the ERG further note that it is possible that this could result in non-compliance with monitoring, which is itself a stopping criterion.

The ERG asked how application of the stopping criteria to the patients in the evidence base might affect the results of rhLAMAN-05[10] and -10.[1] The company stated that results at 12 months would not be affected as the criteria are only applied at 12 months, but that some patients who continued treatment after 12 months may have met the stopping criteria. The company stated that the stopping criteria are likely to result in more favourable outcomes in the long term than those reported in the studies as patients with lower efficacy are excluded from treatment. However, an analysis excluding these patients was not provided. (Clarification response A13).[11]

Following the clarification response[11] (question B1) the manufacturer confirmed that patients who move into the severe immobility health state would continue to receive velmanase alfa treatment for one year to reflect "*that once a person moves into the severe immobility state, there will be a period where their health status in confirmed by their specialist consultant, and the decision is made in collaboration with the patient and their carer to withdraw active treatment.*" The company further confirmed that treatment with velmanase alfa would be withdrawn if a patient entered the short end stage.

4.2.4.3 Comparator

The placebo comparator in rhLAMAN-05[10] seemed appropriate for some of the patients, but the clinical advisors to the ERG, and the experts who submitted expert statements to NICE expressed a view that HSCT is potentially a valid comparator for a (small) proportion of these patients. Within their submission[2] and clarification response,[11] the company stated that the comparator HSCT is not valid as patients recruited to the trial must have been unsuitable for HSCT in order to be eligible. However, no further details to verify this statement were given (e.g. specific reasons for not giving HSCT to younger patients), and it is assumed that such decisions were made by the individual clinicians treating each patient. The studies largely comprise European patients, and it is unclear if HSCT practice in the European countries that were included in the trials were similar to UK practice. The ERG asked for

clarification on whether any of the patients would be eligible for HSCT according to usual UK practice, but the answer provided did not directly address this issue (clarification response A12).[11] As such, the ERG believes it remains unclear if any patients in the trial would have been deemed eligible for HSCT in clinical practice in England.

Use of HSCT in the UK now and in the future: The clinical advisors to the ERG expressed an opinion that HSCT should be considered more often as a treatment option in the UK as the safety of the procedure is much improved over recent years. One advisor who treats paediatric patients stated that in his clinical practice it is more of a decision not to conduct as HSCT, rather than a decision to conduct one. Both clinical advisors to the ERG agreed with the view expressed in the CS that patients under 5 are most likely to receive HSCT as these patients usually have severe disease.[2] However, their view was that as patients get older (≥5 years), the decision is based on a balance of risk from the procedure, expected benefit in terms of severity of disease, and the availability of a suitable donor (the same list of factors is also provided in the CS[2]). They believed there is no clear age cut-off which would preclude an HSCT. The views expressed in the Expert Statements provided to NICE,[26, 27] where clinicians stated that "*HSCT was not normally performed in those aged 5 years or over*" and "*is not usually performed in older patients*" which suggest that it is an option for a small proportion of patients.

Other data relating to HSCT efficacy: The clinical advisors to the ERG noted that data relating to the efficacy of HSCT in AM patients is likely to be very scarce. The company conducted such a review and found seven studies/case reports related to HSCT, the largest of which included 17 patients, and the remainder of which included 1-4 patients (see Appendix 2, CS).[2] The ERG asked for clarification about HSCT evidence in the UK. The company provided a table (reproduced here as Table 8) detailing three patients, and their current age and status. All received HSCT at age <6 years, and all had a current status of "walking unassisted". The cognitive and mental health of these patients was not provided, however, whereas in the wider literature measurement of cognitive function was a key outcome of HSCT trials.

The company further provided information from their systematic review, relating to patients aged ≥6 years (from any country), and these can be found in Appendix 2 of the CS,[2] Tables 123-125. In summary, HSCT was successfully performed in several patients over 6 years of age (contrary to the company's view that HSCT would not be performed in patients of this age) with reports of improved symptomatology (including cognitive), though no RCT evidence was available and follow-up was sometimes short. The ERG has not conducted a full critique of this evidence.

Table 8: Reproduction of Table 2 from the clarification response:[11] UK MPS Society Survey patients in receipt of allogeneic HSCT for AM

MPS Survey patient code	Current age (years)†	Age at diagnosis (years, months)‡	Weight (kg)‡	Walking ability‡	Age at receipt of allogeneic HSCT§
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AM, alpha-mannosidosis; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; UK, United Kingdom.
†At time of survey completion; ‡Responses taken from phase 3 of the survey responses, as they are the most up to date data; §Treatment described as bone marrow transplant in survey responses
Source: Data on file: UK MPS Society patient and carer survey, 2018.[28]

No comparator arm in rhLAMAN-10[1]: Comparisons to baseline in rhLAMAN-10[1] are subject to common drawbacks of single-arm observational studies:

- Regression to the mean: It is possible that patients experience temporary worsening in some of the outcomes measured in the trials due to infections. For example, infections can lead to worsening in pulmonary function tests. If these were present at baseline, subsequent improvements may in part or in totality represent an improvement in these temporary conditions (regression to the mean).
- Placebo effect: The increased number of hospital visits can have a positive effect on wellbeing and general monitoring of health; the hope generated by being on an active treatment may have a strong placebo effect.
- Lack of a comparator arm means it is unclear how patients would have fared without a placebo control, and therefore what the efficacy of the treatment is. This is especially true where the disease is progressive, as is the case for AM.
- Concomitant symptom relief treatments: whilst there are no disease-modifying treatments currently available other than HSCT, patients can start concomitant treatments for symptomatic relief. The clinical advisors to the ERG noted that the introduction of inhaled steroids, which often occurs at some point in management, might improve lung function.
- Training effects: clinical advisors to the ERG indicated that the 3-MSCT, 6-MWT and pulmonary function tests are all subject to patients improving with subsequent tests, as they get used to the expectations of the test.

4.2.4.4 Outcomes

Omission of outcomes relevant to the disease: As stated in Section 3.4, the clinical advisors to the ERG were surprised that infections were not included as a key outcome, as these are a major contributor to mortality and morbidity. This was also an outcome listed in the NICE scope.[9] The clinicians were further surprised that psychiatric problems such as acute psychosis were missing as this is also a problem for many patients. The NICE scope[9] listed language as an outcome, but this was not measured in any trial.

Clinical relevance of serum oligosaccharides: Whilst serum oligosaccharides may have pharmacokinetic relevance, its use as a primary outcome was seen as highly problematic by the clinical advisors to the ERG for a number of reasons:

- The link between oligosaccharide levels and clinical outcomes is poor from a clinical perspective.
- There was no formal assessment of whether oligosaccharide levels were surrogate for clinical outcomes using standard criteria.[29] Correlations between last observation values for serum oligosaccharides and 3-MSCT, 6-MWT and FVC% predicted within rhLAMAN-10[1] were all negligible or marginal (see question A20 in the clarification response[11]). These data were not reported for rhLAMAN-05.[10]
- Serum oligosaccharides are not currently measured in UK practice, and this would have to be implemented as a test on the NHS if it is to be used to monitor response to treatment.
- The cut off of 4µmol/L is arbitrary and has no clinical meaning.

Age matching for outcomes where childhood growth leads to improvement: In cases where outcomes are likely to increase as age increases (e.g. 6-MWT, cognition, motor skills, lung function), age-normalised reference values are usually used. This allows any deterioration due to disease to be observed (in the absence of a control arm) even though such outcomes may improve overall due to growth. The ERG noted that some outcomes were age matched, including lung function, BOT-2 and the Leiter-R test, but that the 3-MSCT and the 6-MWT were not age-matched in the primary analysis.

In their clarification response (response A28),[11] the company explained that there are no reference values for the 3-MSCT and that "*it is of general understanding that the 3-MSCT is less impacted by growth in the scholar age and by the adolescence height burst given that leg length is not a major contributor to staircase climbing performance*" (response A28).[11] They also highlighted baseline data for <18 years and ≥18 years (54 steps/min and 53 steps/min respectively), provided a scatterplot showing the distribution of steps/min by age from rhLAMAN-10[1] baseline data (see Figure 2), and argued that in AM, there is no adolescent growth spurt which might explain there being no noticeable

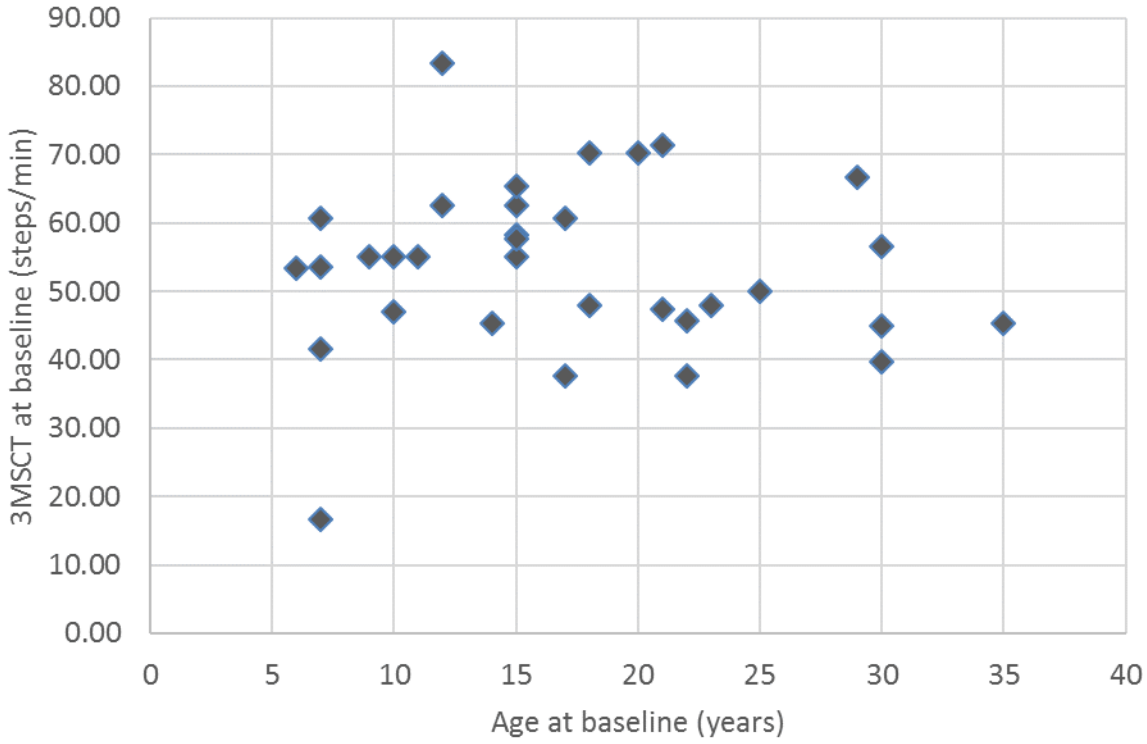
difference between age groups. The ERG note that it was not clear from the clarification response whether a formal assessment of the relationship between 3-MSCT and age was conducted, so it is not possible for the ERG to conclude whether there was, or was not, a correlation.

There are reference values (for age, height and gender) for the 6-MWT, and exploratory analyses using these in rhLAMAN-10[1] were provided in part in the original submission, and in some more detail for data at 12 months and the last observation time in the clarification response A28,[11] and are presented in the results section of this report (Section 4.2.6). The age, height and gender normalised values were generally less favourable than the original non-normalised analysis.

Use of CHAQ in adults: The ERG had initial concerns about the use of CHAQ in adult patients; however, our clinical advisors thought this was appropriate. They explained that CHAQ is filled in by guardians with some questions directed at the patient.

MCIDs and multi domain responder analysis: A critique of the MCIDs and multi domain responder analysis is provided in Section 4.2.7.

Figure 2: Reproduction of Figure 3 from CS: Scatterplot of individual 3-MSCT (Steps/min) and age (years) in rhLAMAN-10[1] at baseline



Source: rhLAMAN-10[1] listings

4.2.5 Description of the analysis of rhLAMAN-05[10] and rhLAMAN-10[1]

4.2.5.1 Analysis of rhLAMAN-05[10]

The statistical plan for rhLAMAN-05[10] is reproduced from Table 12 of the CS,[2] as Table 10 in this report. Follow-up was for 12 months. The co-primary endpoints were serum oligosaccharides and the 3-MWT. The prioritised secondary outcomes were 6-MWT and FVC. The other secondary outcomes were: PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; EQ-5D. Primary outcomes were assessed as the relative change from baseline to month 12. Details of the statistical plan are provided in Table 12 of the CS,[2] and in brief comprised an analysis of covariance (ANCOVA) of log-transformed data. The absolute change from baseline to month 12, the log-transformed relative change from baseline to month 6 and the absolute change from baseline to month 6 were also assessed for these endpoints. Demonstration of efficacy was defined as a statistically significant improvement in both primary outcomes at 6 months, or in serum oligosaccharides with a trend for improvement in the 3-MWT and one prioritised secondary outcome at 12 months. Multiple imputation methods were applied in case of missing data.

Twenty-five patients were recruited but no formal sample size was calculated; the CS[2] states that the number represents a compromise between the total number of patients available who could meet the inclusion criteria and the number required for efficacy assessment.

The company reported a post-hoc analysis of patients aged <18 vs ≥18 years at start of treatment.

4.2.5.2 Analysis of rhLAMAN-10[1]

The statistical plan for rhLAMAN-10[1] is reproduced from Table 13 of the CS,[2] as Table 10 in this report. Data comprises a database of follow-up data from rhLAMAN-07 and -09 (which comprised solely patients from rhLAMAN-04[14] and -05[10] and included long term treatment and follow-up over an unspecified number of years, but probably until treatment becomes available in that jurisdiction) and new data collected from patients who received treatment after rhLAMAN-04[14] and -05[10] on a compassionate use programme (see Table 10 for details of the comprehensive evaluation visit (CEV)).

Absolute and relative change from baseline to each time point were estimated and analysed using paired t-tests, but no sample size calculation was conducted and no data were imputed. Missing values were included in the denominator count when calculating percentages, but only non-missing values were included in analyses of continuous data.

The co-primary outcomes were serum oligosaccharides and the 3-MWT. The secondary outcomes were: 6-MWT; PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; and EQ-5D. Primary outcomes were assessed as the relative change from baseline. The date of the first dose

and the date of the assessment were used to calculate how many days of treatment had elapsed, with the assessment assigned to the nearest designated time point, e.g. 6 months is 183 days, thus any assessment between 1-274 days were assigned to the 6-month time point.

The company provided a table outlining how many patients were available for assessment at each time point. The ERG were not sure if this was the same as the number of patients eligible for assessment at each time point (e.g. did some patients miss assessments), and were further unclear why there were 3 patients at 36 months from the Phase I/II trials and 9 at 48 months; this might be because some patients having been on treatment without assessment (in the compassionate use programme) for 48 months, meaning there was no 36-month data for these patients. The table is reproduced here as Table 9.

Table 9: Number of patients with available data per time point – overall, Phase I/II and rhLAMAN-05[10] (reproduction of Table 14 from the CS)

Study contribution, n (% of total rhLAMAN-10[1])	Total N=33						
	Baseline	Month 6	Month 12	Month 18	Month 24	Month 36	Month 48
rhLAMAN-10[1]	33 (100.0)	24 (72.7)	31 (93.9)	11 (33.3)	10 (30.3)	7 (21.2)	9 (27.3)
Parental study contribution, n (% of total rhLAMAN-10[1])							
Phase I/II‡	9 (27.3)	9 (27.3)	9 (27.3)	9 (27.3)	0	3 (9.1)	9 (27.3)
rhLAMAN-05[10]							
Active	15 (45.5)	15 (45.5)	15 (45.5)	0	10 (30.3)	4 (12.1)	N/A
Placebo→Active	9 (27.3)†	0	7 (21.2)	2 (6.0)	N/A	N/A	N/A

Key: blue cells indicate data derived from rhLAMAN-07 and 09 (baseline to CEV), or rhLAMAN-10[1] data collection.
Abbreviations: N/A, time point not available; VA, velmanase alfa.
†Although 10 patients were included in the rhLAMAN-05[10] placebo group, patient 502 discontinued VA treatment shortly after starting the compassionate use programme. As this patient had no data collected during the active treatment, the patient was excluded from all analyses.
‡Phase I/II trial comprised rhLAMAN-02[13]/03[13]/04.[14]

Pre-planned subgroup analyses included:

- Age group (<18 years vs ≥18 years); this classification is the age of patients at the time of starting treatment
- Parental study (Phase I/II vs rhLAMAN-05[10])
- Anti-drug antibody (ADA) status (positive or negative) for the following outcomes: CSF oligosaccharides, 6-MWT, 3-MSCT and serum IgG
- Patient status analysis: A patient status analysis was also performed for 6-MWT, FVC (% of predicted), FEV1 (% of predicted), CSF oligosaccharides, serum IgG, PTA and CHAQ disability index, where patients were categorised as not impaired/slightly impaired; impaired; seriously impaired. Cut points for this analysis are provided in Appendix 3, and the outcomes listed in Table 7.

Post hoc analyses included:

- *Multi-domain responder analysis,* because AM affects multiple organ systems. Endpoints were classified into one of three domains: Pharmacodynamic: serum oligosaccharide response; Functional: 3-MSCT, 6-MWT and FVC (% of predicted) (FVC is included within the functional domain as muscular effort is required); and quality of life: CHAQ disability index and CHAQ pain (VAS). A patient was classified as a responder in a domain if the MCID was achieved in any one of the component parts. A patient was classified as a responder to treatment if they responded in two domains.

- *analysis of patients according to age* (6-11 years; 12-17 years; ≥18 years)

Table 10: The statistical plans for rhLAMAN-05[10] and rhLAMAN-10[1], reproduced from Tables 12 and 13 of the CS

	rhLAMAN-05[10]	rhLAMAN-10[1]
Duration of follow-up, lost to follow-up information	Patients were followed for 12 months until study end, at which patients were invited to enrol in an after-trial study (rhLAMAN-07 or rhLAMAN-09) or the compassionate use programme. Patients who were receiving placebo in rhLAMAN-05[10] could initiate treatment with VA.	rhLAMAN-10[1] data collection – a one-week assessment visit (the CEV) for patients in the compassionate use programme. • Patients enrolled in the compassionate use programme were not assessed for efficacy. Therefore, patients were invited to enrol in rhLAMAN-10[1] and undergo a CEV, to obtain long-term efficacy data for these patients. • Patients attended a screening visit (Visit 0) on Day 1, at which eligibility was checked and informed consent was signed. After consent was obtained, patients attended the CEV (also on Day 1), at which they underwent pre-infusion evaluations, and then received their infusion of VA. This infusion was the weekly infusion for that week as part of the compassionate use programme. Further evaluations were then carried out over Days 1–6 (Visit 1). Visit 3 (final visit) was held on Day 6 after the evaluations had been completed and before the patient left the trial site. rhLAMAN-10[1] integrated data set analysis • As patients enrolled in rhLAMAN-07 and -09 were subject to annual efficacy evaluations as part of the trial protocol, they were not enrolled in the rhLAMAN-10[1] data collection (as defined by the exclusion criteria). In order to obtain long-term follow-up data, rhLAMAN 07 and 09 were amended to include a CEV. • CEV data from rhLAMAN-07, rhLAMAN-9 and the rhLAMAN-10[1] data collection were pooled and analysed with data from rhLAMAN-02[13], rhLAMAN-03[15], rhLAMAN-04[14], rhLAMAN-05[10], and pre-CEV rhLAMAN-07 and 09 data points. For the integrated data set, details on how the data were aligned to the designated efficacy time points is discussed below this table.

Statistical tests	No formal sample size calculation was performed for this trial. The total of 25 patients represents a compromise between availability of patients who can fulfil the admission criteria and the minimum amount of data that can support an assessment of efficacy and safety of the treatment regimen. The primary analysis of the co-primary endpoints (serum oligosaccharides and 3-MSCT) and prioritised secondary endpoints (FVC [% of predicted] and 6-MWT) was performed on the relative change from baseline to Month 12. Data were log-transformed and then submitted to an ANCOVA with treatment as a fixed factor and corresponding baseline values and age as continuous covariates. The adjusted means in each treatment group, the adjusted mean difference between VA and placebo, their 95% CIs and associated p-values were estimated by the model; however, as no sample size was calculated, p-values should be treated with caution. The absolute change from baseline to Month 12, log-transformed relative change from baseline to Month 6 and absolute change from baseline to Month 6 were also assessed for these endpoints. For primary endpoints, demonstration of efficacy was defined as: • a statistically significant improvement in the two primary endpoints (at significance levels of 0.025 [serum oligosaccharides] and 0.05 [3-MSCT]) at the interim analysis (Month 6), or; • a statistically significant reduction in serum oligosaccharides (at a significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis For the ANCOVA models used in the primary and secondary endpoints, in case of missing data a multiple imputation method was applied before performing the analysis. This approach assumes that measures for withdrawn patients follow the pattern of patients who remained in the study. Imputation was performed by PROC multiple imputation using the Markov Chain Monte Carlo approach by treatment. Each record included baseline, Month 6, Month 12 and the	For each outcome, the absolute and relative changes from baseline to each time point were estimated and analysed using the paired t-test and presented with their p-value and 95% CI; however, as no sample size was calculated, p-values should be treated with caution. Unless otherwise specified, baseline values were defined as the last non-missing value before the first dose of VA (derived from parental Phase I/II and rhLAMAN-05[10] studies). For patients in rhLAMAN-05[10] who were randomised to placebo, the baseline for all scheduled evaluations was the last non-missing value recorded in rhLAMAN-05.[10] Unless otherwise specified, last observation values were defined as the last available value at the end of rhLAMAN trials (derived from the last trial the patient participated in). As such, last observation values presented comprise a range of follow-up times. As the rhLAMAN-07 and rhLAMAN-09 trials were ongoing at the time of the rhLAMAN-10[1] integrated data set, the cut-off date was defined as "the end date of the CEV in rhLAMAN-07, rhLAMAN-09 and rhLAMAN-10".[1] Missing data was not imputed. Unless otherwise specified, missing values were included in the denominator count when computing percentages. When continuous data were summarised, only non-missing values were evaluated for computing summary statistics

	baseline age. One thousand imputations were created and the imputed data sets were then analysed with PROC MIANALYSE.	
Primary outcomes (including scoring methods and timings of assessments)	The co-primary endpoints for rhLAMAN-05[10] were: • Change from baseline to Month 12 in serum oligosaccharides • Change from baseline to Month 12 in the 3-MSCT	The co-primary endpoints for rhLAMAN-10[1] were: • Change from baseline in serum oligosaccharides • Change from baseline in the 3-MSCT
Secondary outcomes (including scoring methods and timings of assessments)	The prioritised secondary endpoints for rhLAMAN-05[10] were: • Change from baseline to Month 12 in 6-MWT • Change from baseline to Month 12 in FVC as a percentage of predicted normal value Additional secondary efficacy endpoints for rhLAMAN-05[10] were: • Change from baseline to other visits in PFTs (FEV_1 [L], FEV_1 [% of predicted value], FVC [L] and PEF [L/s]) • Change from baseline to other visits in BOT-2 (total score and domain scores) • Change from baseline to other visits in the Leiter-R • Change from baseline to other visits in CSF oligosaccharides and CSF biomarkers (tau, NFLp and GFAp) • Change from baseline to other visits in PTA (air conduction left and right ear and bone conduction for the best ear) • Change from baseline to other visits in CHAQ and EQ-5D (total score and domain scores)	• Change from baseline in the 6-MWT (metres and % of predicted) • Change from baseline in PFTs (FEV_1 [L], FEV_1 [% of predicted value], FVC [L], FVC [% of predicted value], and PEF [L/s]) • Change from baseline in BOT-2 (total score and domain scores) • Change from baseline in the Leiter-R • Change from baseline in CSF oligosaccharides and CSF biomarkers (tau, NFLp and GFAp) • Change from baseline in PTA (air conduction left and right ear and bone conduction for the best ear) • Change from baseline in CHAQ and EQ-5D (total score and domain scores)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; ANCOVA, analysis of covariance; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GFAp, glial fibrillary acidic protein; NFLp, neurofilament protein; PEF, peak expiratory flow; PTA, pure tone audiometry; VA, velmanase alfa.

4.2.6 Description of the results of rhLAMAN-05[10] and rhLAMAN-10[1]

The Tables presenting baseline characteristics for each trial are reproduced from the CS in Appendix 4. The results for rhLAMAN-05[10] are presented in Table 11 and from rhLAMAN-10[1] in Table 12.

4.2.6.1 Pre-planned analyses

Serum Oligosaccharides – co-primary endpoint

rhLAMAN-05[10] demonstrated a statistically significant decrease in serum Oligosaccharides at 12 months when considering adjusted mean difference in relative change (−70.47 (95% CI −78.35, −59.72), p<0.001) and adjusted mean difference in absolute change (-3.50 (95% CI: -4.37; -2.62), p< 0.001). Results were also statistically significant at 6 months, Table 11 provides further data including absolute values. The ERG notes that the mean absolute value for the velmanase alfa group was below the (arbitrarily chosen) 4µmol/L MCID cut off but was not for the placebo group.

rhLAMAN-10[1] demonstrated a statistically significant decrease in serum oligosaccharides compared to baseline values at all-time points except 36 months where there was a very low number of patients (n=3) with no imputation conducted. Table 12 provides further data including absolute values. The ERG notes that the mean absolute value for the velmanase alfa group at last observation was below the 4µmol/L MCID cut off.

Pre-planned subgroup analyses in rhLAMAN-10[1]: The CS reports "*treatment with velmanase alfa resulted in an improvement in patient status; only 9.1% were considered to be seriously impaired for serum oligosaccharides at last observation, compared with 81.8% at baseline Appendix 7 (Section 17.7.2.3). When the ADA status of patients was taken into account, both ADA positive and negative patients experienced a reduction in serum oligosaccharides from baseline to last observation (Appendix 7, Section 17.7.2.4).*" (p140 of the CS).[2]

The relative mean (SD) change from baseline to last observation was similar in both age groups: -66.6% (36.1%) for patients aged <18 years and –57.6% (30.5%) for patients aged ≥18 years. The absolute mean (SD) changes from baseline were –5.26 µmol/L (3.74 µmol/L) and –3.68 µmol/L (2.20 µmol/L), respectively. The clarification response to A36 states that a post-hoc analysis indicated there was no interaction between time and age.[11]

3-MSCT - co-primary endpoint

rhLAMAN-05[10] did not demonstrate a statistically significant difference in 3-MSCT at 6 or 12 months (adjusted mean difference in relative change 3.01% (−9.86, 17.72), p=0.648; adjusted mean difference in absolute change 2.62 steps/minute (95% CI: -3.81, 9.05), p=0.406 both at 12 months). See .Table 11

for further data including absolute values. To reach the study definition of efficacy, a trend for improvement in 3-MSCT and in one of the two prioritised secondary endpoints was required. The CS interprets the results as a trend towards improvement.[2] The ERG notes that whilst the observed difference favoured velmanase alfa, the mean difference in absolute change from baseline of 2.62 step/minute at 12 months was small (baseline mean: 54 metres), and below the MCID of ≥7 steps/min.

Table 11: Key clinical results from rhLAMAN-05[10]

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
Serum oligosaccharides(µmol/L unless stated otherwise)						
Actual value (SD)	6.8 (1.2)	6.6 (1.9)	2.4 (1.0)	6.2 (1.8)	1.6 (0.8)	5.1 (1.4)
Absolute change from baseline (SD)			-4.3 (1.4)	-0.4 (2.2)	-5.1 (1.2)	-1.6 (1.7)
Relative (%) change from baseline (SD)			-63.6 (14.5)	-1.6 (32.2)	-75.8 (11.2)	-20.3 (24.0)
Adjusted mean relative change (95% CI)			-65.85 (-72.05, -58.28)	-7.88 (-27.94, 17.77)	−77.60 (−81.58, −72.76)	−24.14 (−40.31, −3.59)
Adjusted mean difference in relative change (95% CI)			-62.93 (-73.03, -49.06**), p<0.001**		−70.47 (−78.35, −59.72), **p<0.001**	
Adjusted mean absolute change (95% CI)			-4.30 (-5.04, -3.55)	-0.47 (-1.38, 0.45)	-5.11 (-5.66, -4.56)	-1.61 (-2.28, -0.94)
Adjusted mean difference in absolute change (95%CI)			-3.83 (-5.01, -2.65), **p<0.001**		-3.50 (95% CI: -4.37; -2.62), **p< 0.001**	
3-MSCT (steps/min unless stated otherwise)						
Actual value (SD)	52.9 (11.2)	55.5 (16.0)	52.9 (13.8)	53.8 (17.2)	53.5 (15.7)	53.1 (15.6)
Absolute change from baseline (SD)			0.0 (5.3)	-1.7 (5.3)	0.6 (8.6)	-2.4 (5.5)
Relative (%) change from baseline (SD)			-0.5 (9.7)	-2.9 (12.9)	0.5 (16.1)	-3.6 (13.1)
Adjusted mean relative change (95% CI)			0.93 (-7.17, 5.72)	-3.78 (-11.15, 4.19)	−1.07 (−9.05, 7.61)	−3.97 (−13.38, 6.47)
Adjusted mean difference in relative change (95% CI)			2.96 (-7.12, 14.14), p=0.562		3.01 (−9.86, 17.72), p=0.648	
Adjusted mean absolute change (95%CI)			0.11 (-2.79, 3.01)	-1.86 (-5.42, 1.70)	0.46 (95% CI: -3.58, 4.50)	-2.16 (95% CI: -7.12, 2.80)

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
Adjusted mean difference in absolute change (95%CI)			1.97 (-2.64, 6.59), p=0.384		2.62 (95% CI: -3.81, 9.05), p=0.406	
6-MWT (meters unless stated otherwise)						
Actual value (SD)	459.6 (72.26)	465.7 (140.5)	464.3 (82.68)	466.4 (126.2)	464.0 (82.51)	461.1 (138.7)
Absolute change from baseline (SD)			4.67 (42.80)	0.70 (37.56)	4.40 (46.12)	-4.60 (40.79)
Relative (%) change from baseline (SD)			1.08 (9.65)	1.65 (9.16)	1.17 (9.78)	-0.82 (10.80)
Adjusted mean relative change (95% CI)			0.62 (-4.15, 5.63)	1.29 (-4.56, 7.50)	0.64 (−4.74, 6.32)	−1.20 (−7.63, 5.68)
Adjusted mean difference in relative change (95% CI)			-0.66 (-8.01, 7.28), p=0.860		1.86 (−6.63, 11.12), p=0.664	
Adjusted mean absolute change (95%CI)			3.79 (-17.52, 25.09)	2.02 (-24.09, 28.13)	3.74 (-20.32, 27.80)	-3.61 (-33.10, 25.87)
Adjusted mean difference in absolute change (95%CI)			1.77 (-31.98, 35.52), p=0.914		7.35 (95% CI: -30.76; 45.46), p=0.692	
FVC% predicted normal value						
Actual value (SD)	81.67 (20.66, n=12)	90.44 (10.39, n=9)	90.38 (18.43, n=13)	91.00 (14.12, n=8)	91.36 (21.80, n=14)	92.44 (18.15, n=9)
Absolute change from baseline (SD)			5.82 (9.56, n=11)	-0.63 (5.50, n=8)	8.17 (9.85, n=12)	2.00 (12.61, n=9)
Relative (%) change from baseline (SD)			9.15 (13.93, n=11)	-1.04 (6.41, n=8)	11.37 (13.13, n=12)	1.92 (15.40, n=9)
Adjusted mean relative change (95% CI)			8.05 (0.3, 16.38)	-2.93 (-14.42, 10.12)	10.11 (1.31, 19.67)	1.58 (−9.48, 13.99)
Adjusted mean difference in relative change (95% CI)			11.30 (-4.10, 29.19), p=0.159		8.40 (−6.06, 25.08), p=0.269	
Adjusted mean absolute change (95%CI)			5.97 (0.11, 11.84)	-2.73 (-11.94, 6.49)	8.21 (1.79, 14.63)	2.30 (-6.19, 10.79)
Adjusted mean difference in absolute change (95%CI)			8.70 (-2.39, 19.78), p=0.124		5.91 (95% CI: -4.78; 16.60),p=0.278	

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
CHAQ disability						
Actual value (SD)	1.37 (0.82)	1.59 (0.64)	1.31 (0.72)	1.75 (0.53)	1.36 (0.76)	1.76 (0.50)
Absolute change from baseline (SD)			-0.06 (0.38)	0.16 (0.41)	-0.01 (0.32)	0.18 (0.36)
CHAQ pain (VAS)						
Actual value (SD)	0.84 (0.86, n=14)	0.40 (0.56, n=9)	1.00 (0.91)	0.63 (0.76)	0.97 (1.02)	0.50 (0.62)
Absolute change from baseline (SD)			0.20 (0.79, n=14)	0.30 (0.80, n=9)	0.19 (0.69, n=14)	0.15 (0.71, n=9)
EQ-5D-5L index score						
Actual value (SD)	0.61 (0.19)	0.61 (0.18, n=8)	0.66 (0.15, n=14)	0.64 (0.16)	0.64 (0.18, n=14)	0.62 (0.15)
Absolute change from baseline (SD)			0.06 (0.12, n=14)	0.04 (0.09, n=8)	0.04 (0.09, n=14)	0.03 (0.16, n=8)
EQ-5D-5L VAS						
Actual value (SD)	66.07 (20.68, n=14)	64.00 (12.87)	71.67 (16.30)	67.00 (13.98)	68.20 (17.34)	67.70 (16.62)
Absolute change from baseline (SD)			5.71 (16.94, n=14)	3.00 (15.85)	2.00 (17.95, n=14)	3.70 (15.71)
BOT2 – motor function						
Actual value (SD)	94.93 (41.68)	109.2 (51.84)	95.13 (38.02)	108.7 (50.02)	101.3 (38.56)	113.4 (50.75, n=9)
Absolute change from baseline (SD)			0.20 (12.80)	-0.50 (12.26)	6.40 (13.38)	-0.33 (9.59, n=9) (as reported)
Relative (%) change from baseline (SD)			2.30 (20.27)	7.98 (33.52)	12.30 (20.55)	3.53 (14.23, n=9)
Adjusted mean relative change (95% CI)					9.99 (3.89, 16.45)	3.73 (–3.39, 11.37)
Adjusted mean difference in relative change (95% CI)					6.04 (–3.21, 16.17), p=0.208	
Leiter R- cognition TEA-VR (years)						
Actual value (SD)	5.73 (1.74)	6.06 (1.61)	5.72 (1.45)	6.16 (1.49)	5.91 (1.45)	6.22 (1.53)
Absolute change from baseline (SD)			-0.01 (0.67)	0.10 (0.52)	0.17 (0.71)	0.16 (0.65)
Relative (%) change from baseline (SD)			1.73 (12.24) 6.16 (	2.10 (8.54)	5.59 (13.66)	3.32 (8.22)
Adjusted mean relative change (95% CI)					4.18 (–0.93, 9.56)	3.89 (–2.33, 10.51)

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
Adjusted mean difference in relative change (95% CI)					0.28 (–7.43, 8.62), p=0.943	
Leiter R- cognition TEA-AME (years)						
Actual value (SD)	6.30 (2.56)	6.63 (1.80)	6.40 (2.42)	6.91 (2.28)	6.32 (2.12)	6.74 (1.38)
Absolute change from baseline (SD)			0.10 (1.33)	0.27 (0.62)	0.02 (1.41)	0.11 (1.02)
Relative (%) change from baseline (SD)			5.22 (22.13)	2.48 (11.35)	5.63 (23.01)	3.82 (14.61)
Adjusted mean relative change (95% CI)					2.10 (–6.61, 11.62)	4.64 (–6.20, 16.74)
Adjusted mean difference in relative change (95% CI)					–2.43 (–15.33, 12.43), p=0.722	
PTA – hearing best ear						
Actual value (SD)	54.45 (11.35, n=14)	51.77 (11.01)	57.66 (10.09, n=14)	51.06 (13.77)	56.35 (8.94)	51.90 (14.25)
Absolute change from baseline (SD)			3.21 (3.49, n=14)	-0.71 (5.46)	2.36 (5.21, n=14)	0.13 (5.89)
Relative (%) change from baseline (SD)			7.09 (9.19, n=14)	-2.30 (11.52)	6.22 (13.71, n=14)	-0.68 (10.83)
Adjusted mean relative change (95% CI)					6.31 (0.16, 12.83)	–1.94 (-8.62, 5.24)
Adjusted mean difference in relative change (95% CI)					8.40 (–1.17, 18.90), p=0.087	
PTA – hearing left ear						
Actual value (SD)	64.81 (16.13)	60.02 (18.52)	65.41 (13.90)	58.93 (20.69)	65.77 (13.22)	60.78 (16.44)
Absolute change from baseline (SD)			0.59 (7.08)	-1.09 (10.74)	0.95 (8.03)	0.76 (7.83)
Relative (%) change from baseline (SD)			2.43 (11.82)	-1.33 (18.39)	3.29 (14.26)	2.95 (16.51)
Adjusted mean relative change (95% CI)					3.44 (–3.70, 11.10)	0.34 (–8.10, 9.56)
Adjusted mean difference in relative change (95% CI)					3.09 (–8.05, 15.57), p=0.583	
PTA – hearing right ear						
Actual value (SD)	65.33 (16.41)	60.78 (16.59)	66.41 (15.13)	59.34 (21.00)	67.27 (17.17)	58.89 (18.28)

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
Absolute change from baseline (SD)			1.08 (9.05)	-1.44 (10.61)	1.94 (11.34)	-1.89 (8.99)
Relative (%) change from baseline (SD)			3.68 (15.73)	-2.81 (17.47)	4.85 (17.38)	-2.78 (14.58)
Adjusted mean relative change (95% CI)					4.42 (–4.47, 14.12)	-5.20 (–15.01, 5.74)
Adjusted mean difference in relative change (95% CI)					10.15 (–4.42, 26.93), p=0.171	

3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AME, attention and memory; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CI, confidence interval;; EQ-5D, EuroQol five-dimension questionnaire; FVC, forced vital capacity; PTA, pure tone audiometry; SD, standard deviation; TEA, total equivalence age; VA, velmanase alfa; VAS, visual analogue scale; VR, visualisation and reasoning

* n=15 for VA and n=10 for placebo at all time points unless indicated otherwise.

Table 12: Key clinical results from rhLAMAN-10[1]

Analysis	Baseline (n=33)		6 months (n=24)		12 months (n=31)		18 months (n=11)		24 months (n=10)		36 months (n=7)		48 months (n=9)		Last observation (n=33)	
		n		n		n		n		n		n		n		n
Serum Oligosaccharides (µmol/L)																
Actual value (SD)	6.90 (2.30)	33	2.60 (0.97)	24	1.61 (1.12)	31	1.59 (1.56)	11	1.45 (0.57)	10	6.20 (5.46)	3	1.57 (0.90)	9	2.31 (2.19)	33
Absolute change from baseline (SD)			-5.01 (2.33) p<0.001		-5.41 (2.87) **p<0.001**		-6.67 (3.83) **p<0.001**		-5.12 (1.12) **p<0.001**		-0.40 (4.19) p=0.884		-7.43 (2.81), **p<0.001**		-4.59 (3.23) , **p<0.001**	
Relative (%) change from baseline (SD)			-64.1 (14.86) **p<0.001**		-72.7 (23.53**) p<0.001**		-76.0 (31.21) **p<0.001**		-77.7 (9.29) **p<0.001**		-13.6 (59.19) p=0.729		-81.8 (11.65), **p<0.001**		-62.8 (33.61) **, p<0.001**	
3-MSCT																
Actual value (SD)	53.60 (12.53)	33	56.56 (14.48)	24	58.48 (14.85)	31	62.58 (17.03)	11	57.33 (18.22)	10	60.67 (18.95)	6	69.70 (15.14)	9	59.98 (16.29)	33
Absolute change from baseline (SD)			3.736 (7.887), p=0.030		4.247 (8.573), p=0.10		11.58 (9.471), p=0.002		1.900 (9.300), p=0.534		11.61 (9.296), p=0.028		17.07 (9.929), **p<0.001**		6.384 (10.54), p=0.001	
Relative (%) change from baseline (SD)			8.315 (18.32), p=0.036		9.317 (19.57), p=0.013		24.48 (18.76), p=0.001		2.487 (16.84), p=0.651		30.88 (32.72), p=0.069		39.11 (31.31), =0.006		13.77 (25.83), p=0.004	
6-MWT																
Actual value (SD)	466.6 (90.1)	33	474.6 (84.1)	24	492.4 (83.7)	31	499.9 (95.6)	11	486.6 (90.7)	10	471.2 (83.5)	6	522.6 (77.1)	9	489.0 (85.7)	33
Absolute change from baseline (SD)			17.6 (62.7), p=0.183		21.9 (65.2), p=0.071		55.5 (66.3), p=0.020		5.0 (58.5), p=0.793		59.3 (85.9), p0.151		69.7 (81.1), p=0.033		22.4 (63.2), p=0.050	
Relative (%)			6.1 (21.1), p=0.169		7.3 (23.3), p=0.090		16.4 (25.7), p=0.061		1.2 (12.3), p=0.766		24.4 (46.1), p=0.252		22.5		7.1 (22.0), p=0.071	

change from baseline (SD)													(35.8), p=0.096			
6-MWT (% predicted for age, height and gender)																
Actual value (SD)	69.04 (11.65)	33	NR		71.8 (10.26)	31	NR		NR		NR		NR		70.20	33
Absolute change from baseline (SD)			NR		2.37 (9.98), p=0.196		NR		NR		NR		NR		1.16 (9.29), p=0.478	
Relative (%) change from baseline (SD)			NR		5.87 (22.14), p=0.150		NR		NR		NR		NR		3.55 (18.30), p=0.273	
FVC % predicted																
Actual value (SD)	84.9(18.6)	29	87.1(18.6)	22	93.2(20.8)	30	84.8(23.6)	8	106.1(18.0)	8	78.8(22.0)	6	98.3(12.4)	7	93.121.7)	31
Absolute change from baseline (SD)			3.5(14.7), p=0.304	20	6.6(12.8, p=0.011	28	4.4(13.9), p=0.403		16.1(14.8), p=0.028	7	5.6(10.3), p=0.243		13.7(19.6), p=0.114		8.1(14.8), p=0.007	29
Relative (%) change from baseline (SD)			6.1(20.3), p=0.194	20	8.5(16.5), p=0.011	28	5.0(20.9), p=0.520		20.7(18.5), p=0.025	7	7.6(15.2), p=0.277		19.8(28.4), p=0.116		10.5(20.9), p=0.011	29
CHAQ disability index*																
Actual value (SD)	1.36 (0.77)	33	1.12 (0.71)	24	1.20 (0.70)	31	1.07 (0.75)	11	1.44 (0.79)	10	1.16 (0.60)	7	0.88 (0.64)	9	1.23 (0.66)	33
Absolute change from baseline (SD)			-0.11 (0.37)	24	-0.10 (0.36)	31	-0.14 (0.41)		0.16 (0.35)	10	-0.32 (0.62)		-0.10 (0.42)		-0.13 (0.440	
Relative (%) change from			-11.2 (44.08)	22	-7.76 (50.68)	29	-7.00 (68.73)		11.83 (23.88)	8	2.28 (76.66)		13.13 (72.270		-2.41 (45.03)	

baseline (SD)																
CHAQ – pain VAS (0-3 scale)*																
Actual value (SD)	0.618(0.731)	32	0.895(0.911)	24	0.761(0.931)	31	0.407(0.409)	9	0.339(0.458)	10	0.390(0.326)	7	0.443(0.644)	9	0.431(0.616)	33
Absolute change from baseline (SD)			0.257(0.776)	23	0.148(0.723)	30	0.060(0.487)	9	-0.393(0.697)	9	-0.249(0.476)		0.063(0.771)	9	-0.173(0.647)	32
Relative (%) change from baseline (SD)			45.77(138.8)	16	3.697(107.3)	20	122.3(380.0)	5	-46.0(60.21)	6	32.61(198.2)		51.69(202.7)	5	-17.0(109.8)	21
EQ-5D-5L Index*																
Actual value (SD)	0.6217(0.1698)	24	0.6596(0.1492)	14	0.6678(0.1785)	21	0.6385(0.1181)	2	0.6437(0.2057)	10	0.7158(0.0743)	4	NR		0.6722(0.1674)	24
Absolute change from baseline (SD)			0.0647(0.1199)		0.0346(0.1044)		0.1950(0.1245)		0.0262(0.1303)		0.0993(0.1422)		NR		0.0505(0.1351)	
Relative (%) change from baseline (SD)			17.2811(32.8088)		6.9320(19.0980)		44.1743(28.6949)		7.2199(21.9332)		21.1495(32.1006)		NR		11.2291(24.7218), p=0.036	
EQ-5D-5L VAS*																
Actual value (SD)	67.9(18.2)	23	71.7(16.3)	15	69.0(16.6)	22	80.0(21.2)	2	70.8(14.3)	10	73.8(18.9)	4	NR		71.6(15.0)	24
Absolute change from baseline (SD)			5.7(16.9)	14	1.6(17.2)	21	6.5(4.9)		9.8(22.7)	9	-2.5(8.7)		NR		3.3(18.1)	
Relative (%) change from baseline (SD)			15.5(30.9)	14	7.7(32.2)	21	8.3(4.9)		26.6(43.3)	9	0.4(16.7)		NR		11.5(33.8)	
BOT-2 total*																

Actual value (SD)	107.0 (47.6)	33	108.5 (47.7)	24	119.1 (44.9)	31	117.3 (66.0)	11	114.3 (33.5)	10	71.8 (27.9)	4	128.3 (59.4)	9	112.1 (46.0)	33
Absolute change from baseline (SD)			3.9 (12.4)		7.5 (16.5), **p=0.017**		12.2 (21.8)		7.3 (24.9)		16.3 (10.4)		7.7 (35.5)		5.1 (23.9)	
Relative (%) change from baseline (SD)			3.8 (17.8)		10.6 (19.3), **p=0.005**		17.9 (32.3)		16.2 (39.8)		31.5 (16.2), **p=0.03**		13.0 (38.3)		13.0 (33.9), **p=0.035**	
Leiter TEA VR*																
Actual value (SD)	5.879(1.565)	33	5.840(1.380)	24	6.296(1.541)	31	5.788(1.574)	11	6.292(1.317)	10	5.131(1.584)	7	5.898(1.437)	9	6.144(1.612)	33
Absolute change from baseline (SD)			0.122(0.577)		0.320(0.717), **p=0.019**		0.333(0.587)		0.308(0.436)		0.333(0.344), **p=0.043**		0.204(0.632)		0.265(0.637), **p=0.023**	
Relative (%) change from baseline (SD)			3.447(10.28)		6.695(12.17), **p=0.005**		6.251(10.75)		6.724(8.951), **p=0.042**		9.037(10.77)		4.140(11.24)		5.338(10.45), **p=0.006**	
Leiter TEA AME*																
Actual value (SD)	6.514(2.176)	24	6.400(2.424)	15	6.860(1.992)	22	3.792(2.180)	2	6.817(1.529)	10	5.250(0.561)	4	NR		6.670(1.757)	24
Absolute change from baseline (SD)			0.100(1.331)		0.167(1.254)		-0.750(1.414)		0.108(1.665)		0.833(1.855)		NR		0.156(1.519)	
Relative (%) change from baseline (SD)			5.219(22.135)		5.849(19.657)		-19.42(34.413)		11.244(33.786)		33.225(47.595)		NR		9.345(32.485)	
Pure tone best ear*																
Actual value (SD)	52.57(12.36)	32	55.44(10.65)	22	53.35(11.41)	31	48.35(16.80)	11	54.76(8.72)	9	56.16(12.86)	7	47.62(13.76)	9	52.16(13.13)	33

Absolute change from baseline (SD)			2.05(4.72)		1.47(6.00)	30	-4.81(9.74)		2.05(6.55)	8	-0.76(8.78)		-3.73(6.21)		-0.49(6.58)	32
Relative (%) change from baseline (SD)			5.76(13.90)		4.26(14.97)	30	-8.89(20.44)		6.85(16.25)	8	-1.71(16.90)		-8.08(12.81)		-0.72(14.54)	32
Serum IgG*																
Actual value (SD)	NR															
Absolute change from baseline (SD)															3.05 (2.39, 3.71), **p=<0.001**	24
Relative (%) change from baseline (SD)															44.07 (32.58, 55.57), **p=<0.001**	

3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AME, attention and memory; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CI, confidence interval;; EQ-5D, EuroQol five-dimension questionnaire; FVC, forced vital capacity; PTA, pure tone audiometry; NR, not reported; SD, standard deviation; TEA, total equivalence age; VA, velmanase alfa; VAS, visual analogue scale; VR, visualisation and reasoning

***** only statistically significant p values reported.

rhLAMAN-10[1] demonstrated statistically significant changes in absolute and relative change from baseline in 3-MSCT at most time points (Table 12). Absolute change from baseline ranged from 1.90 (24 months, n=10) to 17.07 (48 months, n=9). The last observation analysis had an absolute change from baseline of 6.38 steps/min (SD 10.54), p=0.001, which is close to the MCID of ≥7 steps/minute, but not much higher than the outcome at 12 months for this study (4.25 steps/min (n=31)).

Pre-planned subgroup analyses in rhLAMAN-10[1]: The CS reports "*The analysis of 3-MSCT by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in an increase in the proportion of patients considered to have no or minor impairment at last observation (60.6%) compared with baseline (39.4%) (Appendix 7, Section 17.7.2.3). When the ADA status of patients was taken into account, improvements in the 3-MSCT were observed in both ADA negative and positive patients (Appendix 7, Section 17.7.2.4).*"

Absolute mean change from baseline in 3-MSCT was consistently greater in patients <18 years of age than in patients ≥18 years of age (Figure 20 of the CS)[2]. The clarification response to question A36[11] indicated that there was an interaction between time and age in a post-hoc analysis, and that there is a difference between results in those aged <18 and those aged ≥18 years.

6-MWT – prioritised secondary endpoint

rhLAMAN-05[10] did not demonstrate a statistically significant difference in 6-MWT at 6 or 12 months (adjusted mean difference in relative change 1.86% (−6.63, 11.12), p=0.664; adjusted mean difference in absolute change 7.35 metres (95% CI: -30.76; 45.46), p=0.692, both at 12 months). Table 11 provides further data including absolute values. To reach the study endpoint, a trend for improvement in 3-MSCT in one of the two prioritised secondary endpoints was acceptable. The CS interprets the results as a trend towards improvement.[2] The ERG note that the observed difference is considerably lower than the MCID of an increase of ≥30 meters.

rhLAMAN-10[1] reported some statistically significant changes in absolute values from baseline at some time points (18 months; 48 months, last observation, see Table 12). The ERG notes that the observed difference at the last observation of 22.4 meters (n=33) does not reach the MCID of an increase of ≥30 meters and is similar to the 12-month outcome of 21.9 steps (n=31) of the patients.

Pre-planned subgroup analyses in rhLAMAN-10[1]: The company states that "*The analysis of 6-MWT (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in modest reductions in the number of patients considered to be seriously impaired based on the 6 MWT (% of predicted; 6.1% at baseline to 0% at last observation) (Appendix 7, Section 17.7.2.3). When the ADA status of patients was taken into account, improvements in the 6-MWT (metres and %*

of predicted) were observed in both ADA negative and positive patients (Appendix 7, Section 17.7.2.4)" (p143 of the CS)[2]

In the subgroup analysis by age, both velmanase alfa and placebo groups improve in 6-MWT in the <18 years of age group, but to a somewhat greater extent in the velmanase alfa group (2.0 vs 1.2 metres). In the ≥18 years of age group, velmanase alfa patients show a small numerical improvement whilst placebo patients had a decrease in distance walked (0.4 vs -2.8 metres).

Lung function- FVC (% of predicted)

In rhLAMAN-05[10], this was a prioritised secondary endpoint. The results did not demonstrate a statistically significant difference in %FVC predicted at 12 months (adjusted mean difference in relative change 8.40% (−6.06, 25.08), p=0.269; adjusted mean difference in absolute change 5.91% FVC predicted (95% CI: -4.78; 16.60),p=0.278). Table 11 provides further data including absolute values.

The ERG notes that a 5.91% FVC predicted mean difference in absolute change from baseline (baseline 82-90 % FVC predicted) does not meet the MCID of an increase of ≥10% of FVC % predicted.

In rhLAMAN-10[1] the ERG notes that there is some attrition in the analyses of FVC (% of predicted), putting these results at some risk of bias, especially given the small patient numbers. For example, there were only 20 patients at 6 months, where there should be 24, only 28 at 12 months where there should be 31 (Table 12). Statistically significant differences in absolute % predicted data were reported at some, but not all, time points, with absolute changes ranging from 3.5% of predicted at 6 months to 16.1% of predicted at 24 months. The last observation analysis was statistically significant, with 4/33 patients in the absolute change analysis unaccounted for (Table 12). The ERG note that some analyses reached the MCID of an increase of ≥10% of FVC % predicted.

Pre-planned subgroup analyses in rhLAMAN-10[1]: The CS[2] also reported that "The *analysis of FVC (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in a small increase in the number of patients considered to have no or some impairment based on FVC (% of predicted; 58.6% at baseline to 67.7% at last observation); similar results were observed when the analysis was based on FEV1 (% of predicted) (Appendix 7, Section 17.7.2.3).*" (p144 of the CS).[2]

There were consistently greater increases in FVC (% predicted) in patients <18 years of age compared with baseline and patients greater than 18 years of age (CS Figure 22).

Other PFTs

For rhLAMAN-05[10] the CS[2] states:

"*Overall, a trend for improved lung function compared with placebo was apparent in the velmanase alfa group for all additional PFT endpoints. While patients in both the velmanase alfa and placebo group experienced an improvement in pulmonary function, velmanase alfa demonstrated a numerical advantage over placebo for all PFT secondary endpoints, although no statistically significant differences were observed*."

For rhLAMAN-10[1] the CS[2] states:

"*In addition to FVC (% of predicted), lung function was also measured by FVC (L), FEV1 (% of predicted), FEV1 (L) and PEF (L/s); these results are presented in Appendix 7 (Section 17.7.2.1 for overall results and by age class; Section 17.7.2.2 for results by parental study) and are summarised in Table 15. Together, the results from the PFT secondary endpoints demonstrate that velmanase alfa can produce statistically significant improvements in lung function in patients with AM.*" (p144 of the CS).[2] and that "*The analysis of FVC (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in a small increase in the number of patients considered to have no or some impairment based on FVC (% of predicted; 58.6% at baseline to 67.7% at last observation); similar results were observed when the analysis was based on FEV1 (% of predicted) (Appendix 7, Section 17.7.2.3).*" (p 144 of the CS).[2]

The ERG notes that for these other lung function measurements, outcomes were only statistically significantly different from baseline at some time points.

CHAQ and EQ-5D

rhLAMAN-05[10] did not provide comparative or adjusted analyses of CHAQ, EQ-5D or any of the sub-domains. Table 11 provides further data. At 52 weeks, velmanase alfa patients had an absolute change in CHAQ disability of -0.01 (SD 0.32) and placebo patients of 0.18 (SD 0.36) (negative changes indicate an improvement in disability). The CS interpreted these data as demonstrating a trend towards improvement.[2] The ERG considers the data inconclusive as no statistical comparison was provided, though also note that the change (worsening) in the placebo arm is larger than the MCID of ≥0.13. Differences between arms for CHAQ pain VAS, and EQ-5D index and VAS were negligible.

rhLAMAN-10[1] did not demonstrate a statistically significant difference in CHAQ, EQ-5D or any of the sub-domains reported except in the last observation analysis of relative change from baseline (p=0.036) for EQ-5D-5L index, though this analysis only included 24/33 patients with the reason for this unclear. Table 12 provides further detail. The change in CHAQ disability exceeded the MCID of ≥0.13 at -0.17 (SD 0.65). No MCID was reported for EQ-5D-5L index.

The CS[2] also highlights data relating to changes to numbers of patients requiring ambulatory assistance taken from the CHAQ. At baseline, ten patients required help, whereas at last observation, 70% of these patients required less help. Conversely, of the 23 who did not require help, 3 (13%) became dependent on some help by the last observation.

In their clarification response A44,[11] the company provided a further analysis where a "walking with assistance" category was created, to more closely mimic the category defined in the model, by combining CHAQ-defined wheelchair users and those requiring walking aids/assistance. The results of this analysis are presented in Table 13. The company state "*It is only in the velmanase alfa arm that a net effect (20%) was observed for an improvement in walking ability after 12 months of treatment, i.e. a higher proportion of patients treated with velmanase alfa transitioned to an improved walking ability state (40%) compared to the proportion of patients treated with velmanase alfa that transitioned to a worse walking ability state (20%).*" (clarification response to question A44).[11]

The company also provided the following statement about rhLAMAN-10[1]:
"*It should be noted that longer-term data (up to 48 months of treatment) are available from the rhLAMAN-10[1] trial. Overall, ten patients required help from a person, walking aids (cane, walker, crutches), or a wheelchair at baseline according to the CHAQ 'Helps and Aids' responses. Of the ten patients, seven (70%) became device- or third party-independent at last observation: 4/5 (80%) paediatric patients and 3/5 (60%) adults. In particular, two paediatric patients and one adult forced to adopt the wheelchair for long distance mobility/functional capacity at baseline discontinued use at last observation. Overall, three patients out of the 23 (13%) who did not require help from a person, walking aids, or a wheelchair at baseline, did so at last observation (one adult and two paediatric patients).*"
(A44 clarification response).[11]

Table 13: Post-hoc analysis of proportion of patients in health states defined to closely resemble the model health states (walking with assistance and walking unaided) in rhLAMAN-05[10]

	baseline	12 months	Notes
VA group	WWA 5/15 (33%) WU 10/15 (67%)	WWA 5/15 (33%) WU 10/15 (67%)	2/5 (40%) patients moved to WU 2/10 (20%) patients moved to WWA
Placebo group	WWA 5/10 (50%) WU 5/10 (50%)	WWA 5/10 (50%) WU 5/10 (50%)	2/5 (40%) patients moved to WU, 2/5 (40%) patients moved to WWA

WWA, walking with assistance; WU, Walking unaided; VA, velmanase alfa.

BOT2 – motor function

rhLAMAN-05[10] did not demonstrate a statistically significant difference in BOT2 total score, or any of the sub-domains reported Table 11 of this report and Appendix 7 (Section 17.7.1) of the CS provide further data.[2] The CS interpreted these data as demonstrating a trend towards improvement.[2] The ERG considers the data inconclusive.

rhLAMAN-10[1] reported statistically significant differences at some time points (Table 12)

Leiter R- cognition

rhLAMAN-05[10] did not demonstrate a statistically significant difference in Leiter R or any of the sub-domains reported. Table 11 provides further data. The CS concludes there was no significant difference in cognition between groups.[2]

rhLAMAN-10[1] reported statistically significant differences at some time points for the Leiter R total equivalence age VR, including the last observation analysis, but not for the Leiter R total equivalence age AM. Table 12 provides further details.

Hearing – PTA

rhLAMAN-05[10] did not demonstrate a statistically significant difference in Hearing PTA test. Table 11 provides further details. Whilst the CS[2] notes that results numerically favoured the velmanase alfa group, the ERG considers the data inconclusive.

rhLAMAN-10[1] did not demonstrate a statistically significant difference in Hearing PTA test. Table 12 provides further data.

The CS states on page 48[2] "*The analysis of PTA measures by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in modest reductions in the number of patients*

considered to be seriously impaired based on air conduction in left (72.7% at baseline to 63.6% at last observation) and right ear (66.7% at baseline to 57.6% at last observation) (Appendix 7, Section 17.7.2.3). No change in patient status was seen with regards to bone conduction (best ear).”

Infection rates

Infection rates, which are listed in the NICE scope[9] as an outcome of interest, were not formally assessed as an efficacy outcome in the rhLAMAN-05[10] or -10[1] studies. However, they were measured as an adverse event. The results are presented in Table 14.

Table 14: infections and infestation adverse events reported by ≥ 2 patients in rhLAMAN-05[10] and -10[1]

Trial	VA group	Placebo
rhLAMAN-05[10]	13 (86.7%) pts 48 events	7 (70.0%) pts 23 events
rhLAMAN-10[1]	24 (72.7%)	NA

The company also provided additional analyses and evidence relating to infections in their clarification response.[11] All analyses were post hoc. The following were provided:

- Evidence that Serum IgG is a relevant biomarker for infection rates in AM: “*The biomarker of serum IgG is well accepted as a surrogate for humoral deficiency and for patients with hypogammaglobulinaemia. Patients with AM may have serum IgG levels below the normal range. The standard therapy for hypogammaglobulinaemia is replacement with immunoglobulins, a treatment which has been demonstrated to reduce infections. An increase in IgG following treatment with velmanase alfa is therefore considered a positive effect.”*(p22, clarification response).[11] Results for serum IgG are reported in Section 4.2.6.2.
- A post hoc analysis of infections requiring antibiotics in those patients with hypogammaglobulinaemia in rhLAMAN-05.[10] This selected group of patients comprised 5/15 (33.3%) from the velmanase alfa arm, and 4/10 (40%) from the placebo arm. The results are presented in Table 16, reproduced from the clarification response.[11]
- Caregivers questionnaire – In response to the ERG’s request for clarification about why infections were not measured, the company provided an analysis of a questionnaire given to caregivers at the CEV for rhLAMAN-10,[1] which was intended to “*indirectly estimate the occurrence of infections*” (p23 clarification response).[11] Table 5 in the clarification response details the responses of the caregivers. The company summarised the results as *“Although the exact number of infections was not collected, of the 32 patients with completed questionnaires, 22 (68.8%) were reported by their caregivers as having fewer or almost no infections after treatment.”* (p23 clarification response).[11]

Additional secondary outcomes

The CS[2] states that "*Although less relevant to the decision problem, the results for the change from baseline in CSF oligosaccharides, tau, neurofilament protein (NFLp) and glial fibrillary acidic protein (GFAp) at Month 12 are presented in Appendix 7 (Section 17.7.1, Table 131) for completeness.*"

Preplanned subgroup analyses in rhLAMAN-10[1]

Data relating to the subgroup analyses according to parental study are not presented here but can be found in the CS Appendix 7.[2] Data relating to ADA status are presented in part above in relevant sections.

4.2.6.2 Post hoc analyses

Post hoc analysis of patients aged <18 and ≥18 years in rhLAMAN-05[10]

The results of the post hoc analysis are presented in Table 15. The ERG asked if interaction tests to test whether the two age group results were statistically significantly different to each other were performed, to which the company responded that they were not, but that the ANCOVA model included baseline value and subject age (A36 clarification response).[11]

Table 15: Primary and prioritised secondary endpoints by age class (reproduction of Table 25 from the CS) in rhLAMAN-05[10]

Outcome	Mean change from baseline to Month 12 (SD)			
	<18 years		≥18 years	
	VA (n=7)	Placebo (n=5)	VA (n=8)	Placebo (n=5)
Serum oligosaccharides (µmol/L)				
Relative change, %	−70.6 (14.6)	−7.2 (19.3)	−80.3 (4.4)	−33.4 (22.2)
VA - placebo†	-63.4	-	-46.9	-
3-MSCT (steps/min)				
Relative change, %	5.8 (18.0)	−4.4 (10.8)	−4.1 (13.7)	−2.8 (16.4)
VA - placebo†	10.2	-	-1.3	-
6-MWT (metres)				
Relative change, %	2.0 (7.8)	1.2 (9.4)	0.4 (11.7)	–2.8 (12.8)
VA - placebo†	0.8	-	3.2	-
FVC (% of predicted)				
n	6	4	6	5
Relative change, %	20.5 (11.2)	9.5 (5.6)	2.3 (7.5)	–4.1 (18.7)
VA - placebo†	11.0	-	6.4	-

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; FVC, forced vital capacity; SD, standard deviations; VA, velmanase alfa.

†The differences between the VA and placebo group are provided for descriptive purposes only. For serum oligosaccharides, positive values indicate a treatment effect in favour of placebo. For 3-MSCT, 6-MWT and FVC (% of predictive) negative values indicate a treatment effect in favour of placebo.

Post hoc analysis of serum IgG (not in NICE scope)

Serum IgG was not listed in the NICE scope. The CS reports a post-hoc analysis of serum IgG in rhLAMAN-05[10], where an increase in serum IgG indicates an improvement. The company state in their clarification response that serum IgG is a *"well accepted surrogate for humoral deficiency and for patients with hypergammaglobulinaemia"* (response A20).[11] The CS reports: *"Serum IgG mean (SD) values at baseline were 9.00 g/L (5.02) and 7.27 g/L (1.64) for the velmanase alfa and placebo groups, respectively. At Month 12, treatment with velmanase alfa resulted in a statistically significant increase in serum IgG levels compared with placebo. The adjusted (for baseline value and age) mean change from baseline was 3.59 g/L (95% CI: 2.75, 4.43) in the velmanase alfa group and 0.12 g/L (95% CI: –0.91, 1.16) in the placebo group; the adjusted mean difference was 3.47 g/L (95% CI: 2.12, 4.81; p<0.001).*

When expressed in terms of normal range, 5/15 patients in the velmanase alfa group and 3/10 in the placebo group had low serum IgG levels, comparable with hypogammaglobulinaemia, at baseline. At Month 12, 3/5 patients in the velmanase alfa group reverted to normal serum IgG levels, while the other two patients experienced substantial improvements. In contrast, no patients in the placebo group reverted to normal serum IgG levels after 12 months." (p135 of the CS).[2]

Serum IgG is listed in amongst the main results for rhLAMAN-10[1] but not listed in the study plan as an outcome. It is unclear if this is a post-hoc analysis. The results (Table 12) show a statistically significant change from baseline at last observation. Only rhLAMAN-05[10] patients were included in the analysis as serum IgG was not recorded in the rhLAMAN Phase I/II trial. The absolute change from baseline was 3.05 (95% CI 2.39 to 3.71) at last observation.

Table 16: Reproduction of Table 4 from the clarification response:[11] Number of patients with low IgG levels experiencing infections requiring antibiotics during the 12 months of rhLAMAN-05[10]

	Velmanase alfa n=15		Placebo n=10	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Number of patients with low IgG	5/15 (33.3)	-	4/10 (40.0)	-
Low IgG patients with infections requiring antibiotic use				
Overall	2/5 (40.0)†	2	2/4 (50.0)	4
>1 month	0/2 (0)	0	2/2 (100.0)	3
Rate of Infections requiring antibiotics per infected patient				
Overall	1		2	
>1 month	0		1.5	

Source: CSR Study rhLAMAN-05[10], Table 11-19, Appendix 16.2.4. Listing 16.2.4.4
†Patient 518 received Cefazolin on Day 234 for use during genua valga surgery has been excluded as the antibiotic use was preventative and not to treat an infection.
IgG, immunoglobulin G.

Post hoc analysis of patients switching from placebo to VA.

The company also describe a subgroup analysis of patients who switched from placebo to velmanase alfa after the completion of rhLAMAN-05.[10] The results of the analyses are given in Table 17 and Table 18, reproduced from the CS.[2]

Table 17: Reproduction of Table 28 form the CS[2]: Change in 3-MSCT, 6-MWT and serum IgG after switching from placebo to velmanase alfa

Outcome	Mean relative change from baseline value reported in placebo, double blind phase, % (SD)	
	Placebo double blind phase, month 12 (n=10)	Velmanase alfa only phase, last observation (n=9)
3-MSCT	-3.6 (13.5)	9.0 (25.1)
6-MWT	-0.8 (10.8)	2.2 (13.1)
Serum IgG	1.0 (16.9)	37.3 (16.1)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; SD, standard deviation.

Table 18: Reproduction of Table 29 form the CS[2]: Improvement in quality of life after switching from placebo to velmanase alfa

Outcome	Placebo double blind phase		Velmanase alfa only phase
	Baseline (n=9)	Month 12 (n=9)	Last observation (n=9)
CHAQ-DI, mean (SD)	1.56 (0.67)	1.71 (0.50)	1.43 (0.50)
CHAQ pain (VAS), mean (SD)	0.42 (0.59)	0.52 (0.66)	0.36 (0.51)

Abbreviations: CHAQ, childhood health assessment questionnaire; DI, disability index; SD, standard deviation; VAS, visual analogue scale.

Post hoc multi-domain responder analysis in rhLAMAN-05[10] and -10[1]

The results to the multi-domain responder analysis are provided in Table 19. Statistical significance was not reported. The ERG note that 30% of patients in the placebo arm of rhLAMAN-05[10] were classed as responders. A greater proportion of patients in the velmanase alfa arm were classified as responders (87%). More patients in the <18 years of age group in rhLAMAN-10[1] were classified as responders than in the ≥18 years of age group.

Table 19: Reproduction of Table 30 of the CS[2]: Results of multi-domain responder analysis

Responder	rhLAMAN-10[1] (N=33)			rhLAMAN-05[10] (N=25)	
	All (N=33)	<18 (n=19)	≥18 (n=14)	VA (n=15)	Placebo (n=10)
Responder (≥2 domains), n (%)	29 (87.9)	19 (100.0)	10 (71.4)	13 (86.6)	3 (30.0)
Three domains, n (%)	15 (45.5)	10 (52.6)	5 (35.7)	2 (13.3)	0
Two domains, n (%)	14 (42.4)	9 (47.4)	5 (35.7)	11 (73.3)	3 (30.0)
One domain, n (%)	3 (9.1)	0	3 (21.4)	2 (13.3)	3 (30.0)
No domains, n (%)	1 (3.0)	0	1 (7.1)	0	4 (40.0)

4.2.7 Critique of the analyses and results of rhLAMAN-05[10] and rhLAMAN-10[1]

Baseline characteristics of study participants

The clinical advisors to the ERG felt the spectrum of baseline characteristics were acceptable, given the inclusion/exclusion criteria. Given the heterogeneity of the disease, and the small numbers of patients with AM, the UK population probably does not reflect the full spectrum of disease possible.

As noted by the company, the patient groups in rhLAMAN-05[10] were not balanced for 3MSCT, 6MWT, FVC, BOT-2 or CHAQ disability, with a higher proportion of more compromised patients randomised to the velmanase alfa group (CSR, Table 11-1,[11] Appendix 4). It is unclear how this would affect estimates of efficacy, as more compromised patients may provide more scope for improvement, or alternatively may have irreversible deterioration due to the disease.

The ERG asked for clarification about whether patients were balanced for prognostic factors at baseline in rhLAMAN-05[10] (A9, clarification response).[11] The company stated there were no real prognostic factors known except age, for which patients were stratified at randomisation. The company described some of the classifications that have been used in AM, including the Malm classifications[4] based on phenotype (two versions) and classification by genetic mutations, but did not believe these to be prognostic, nor provide any data on whether patients were balanced at baseline for these classifications in rhLAMAN-05.[10]

Definition of efficacy not met in rhLAMAN-05[10]

The definition of efficacy in rhLAMAN-05[10] was:

- a statistically significant improvement in the two primary endpoints (at significance levels of 0.025 [serum oligosaccharides] and 0.05 [3-MSCT]) at the interim analysis (Month 6)).

Or

- a statistically significant reduction in serum oligosaccharides (at a significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis

Whilst a statistically significant improvement in serum oligosaccharides was observed, there is a lack of clarity in the statistical plan as to what should constitute a trend, and consequently it is unclear whether a 2.62 step/minute mean difference in absolute change from baseline (baseline mean: 54 metres) in 3-MSCT and a 7.35 metre mean difference in absolute change from baseline (baseline: 460 metres) in 6-MWT should be considered a trend for improvement. The ERG note that neither outcome met the MCID which was ≥7 steps for 3-MSCT, and ≥30 meters for 6-MWT (see Table 7).

Muti-domain responder analysis and minimal clinically important differences

The ERG and the clinical advisors to the ERG believe the multi-domain responder analysis to be problematic for a number of reasons:

- Dichotomising patients according to arbitrary cut-offs results in a loss of power relative to the original continuous data
- Dichotomising patients according to multiple domains assumes that the domains are equally important
- Serum oligosaccharides may not be clinically important
- Setting aside the fundamental problems with dichotomising continuous outcomes, clinical advisors to the ERG were of the opinion that infection rates and central nervous system effects should have been included in the responder analysis
- If serum oligosaccharides are excluded from the analysis, and only two domains are left [redacted], patients could potentially be considered a responder solely on the basis of improvements in any one of the tests included in the domains.
- Some of the MCIDs were defined after the trials results were un-blinded, and there is the potential for bias in their definition. This was, however, conducted in response to a request from the EMA, quoted in the clarification response to question A19[11] as:

""*The clinical relevance of the various changes compared to baseline or compared to placebo cannot be assessed for all endpoints due to the lack of predefined clinically important changes. Clinically relevant changes based on experience with comparable conditions for the various endpoints should be identified based on relevant literature. For example, 3MSCT and 6MWT might be related to the experience in patients with JIA. Responder analyses based on these clinically relevant differences should be submitted. Also the 3MSTC and 6MWT results should be presented as scatter plots of change (style shown in fig 11-6 in study report rhLAMAN-05[10]) in order to further appreciate the individual responses."*

- The ERG notes that, based on this quote, the EMA did not request a multi-domain responder analysis, only a responder analysis. In addition, the specifics of how the analysis was conducted were specified post-hoc and were not defined by the EMA. There is therefore a high risk of bias in these analyses in addition to concerns regarding the appropriateness of responder analyses.
- The methods used to define MCIDs comprised a literature review of values in conditions with similar clinical characteristics to AM. It appears only one clinical expert was asked to verify the domains selected: "*An expert was consulted and they concurred with the heterogeneity of AM and relevance of the domain response approach given the heterogeneity of disease manifestation and severity, and small patient numbers*." (CS Appendix 2, section 17.7.3.1.)[2]
- There are no MCIDs reported for motor function (BOT-2); hearing; Leiter-R; rates of infections; or EQ-5D.

Attrition in the trials

There is a lack of clarity around attrition in the later months of rhLAMAN-10.[1] Whilst some of this attrition could be down to length of time enrolled, there are some clear examples of missing data in the secondary outcomes (see Table 12). It is unclear what impact this may have, given no imputation was performed in rhLAMAN-10.[1]

Lack of adjustment for age and height

The ERG is satisfied that a lack of reference values for the 3-MSCT and assertion that it is not affected by age mean that the values can be interpreted as they stand. However, the change in rhLAMAN-05[10] was quite small (an absolute difference in change from baseline at 12 months of around 3 steps from a baseline of 53-56 steps), and the changes from baseline observed in rhLAMAN-10[1] were highly variable, possibly due to missing values and patients who had not been on treatment.

6-MWT % predicted for age, height and gender values were only supplied for rhLAMAN-10[1] as an exploratory analysis, and show that the last observation results are somewhat less favourable for the % predicted analysis (relative change from baseline 3.55 (SD 18.30, n=33)) than for the non-normalised analysis (relative change from baseline 7.1 (SD 22.0, p=0.071, n=33)).

Interaction with age

It was not clear if there is evidence of a difference in the effect of treatment depending on age so the ERG requested interaction tests. In response, the company replied that adding additional terms to the ANCOVA analysis in rhLAMAN-05[10] "*might have produced over-parameterisation issues*". Although, with only 25 observations, the test for an interaction lacks statistical power, there would be 1 degree-of-freedom for treatment, 1 degree-of-freedom for age, 1 degree-of-freedom for the interaction between treatment and age, and 21 degrees-of-freedom to estimate residual error. Hence, the ERG considers it reasonable to model the interaction between treatment and the variable continuous age in this trial. In rhLAMAN-05,[10] subgroup analyses were performed for patients aged <18 years of age and those aged ≥18 years. However, the ERG notes that the estimates of treatment effect presented in Tables 24 and 25 of the CS are derived differently.[2] For consistency with Table 24, the correct estimates of treatment effects on serum oligosaccharides are a 68.32% reduction for patients aged <18 years and a 70.42% reduction for patients aged ≥ 18 years. Although the ERG prefers not to perform subgroup analyses based on the dichotomisation of a continuous variable, these results suggest that if there is an interaction between age and treatment it may be small. Interaction tests were not provided for any other outcomes, so the statistical significance of the impact of age on treatment effect remains unknown. Observed differences in clinical outcomes between younger and older patients in both trials are generally greater in the younger patients.

In rhLAMAN-10,[1] the interaction between age (<18 years and ≥18 years) and time was significant for 3-MSCT, but not for serum oligosaccharides.

Long term effects

The duration of follow-up is not long enough to establish whether any treatment effects will be maintained in the long term. The company argue that effects seem to increase over time (see response to clarification question A20[11]), based on the multi-domain responder analysis. The ERG notes that the length of follow-up varied a great deal in rhLAMAN-10,[1] with variable and smaller numbers, sometimes comprising different patients altogether, at the time points beyond 12 months. This makes it difficult interpret data beyond 12 months, especially given the heterogeneity of disease and patient response, and the very small numbers in some analyses. The last observation analysis generally included all patients and for the four main outcomes (serum oligosaccharides, 3-MSCT, 6-MWT, FVC % predicted) there was very little difference between the 12 month (n=31) and the last observation

analyses (n=33). However, it is unclear what the mean follow-up length was for the last observation analysis, and it is possible that this is not much longer than 12 months. There were, however, some differences in other secondary outcomes (Table 12) including EQ-5D-5L and Leiter-R, thought the clinical significance of the size of the changes is unknown, and the lack of a comparator arm makes it difficult to draw conclusions regarding long term efficacy.

Patient status analysis

The patient status analysis was post-hoc and the cut off points defined were arbitrary. Many of the points raised concerning the multi-domain responder analysis apply to this analysis.

Missing data in rhLAMAN-10[1]

No imputation was used in the analysis which could be a problem if only patients who tolerated and responded to treatment continued to be followed up. An analysis of last observation was performed, but this did not always include all patients, and combined data across different times for example, FVC% predicted n=29/33; CHAQ pain VAS, n=21/33, see the final column in Table 12. Analyses were also performed over time but these also did not always account for all patients.

Infection rates

Infection rates were not measured as an efficacy outcome. The company states "*at the time of designing the clinical trials for velmanase alfa the expected size of the trial population was considered too small to envisage the possibility to collect meaningful clinical data on the change of infection rate after treatment.*" (response to clarification question A21).[11]

Infection rates were measured as an adverse event (AE) however, and rates appear higher in the velmanase alfa arm. The ERG asked for clarification of how AEs were reported, but the company response only concerned how the clinicians reported to the trial, not how patients reported to the clinicians, meaning the ERG cannot establish how well AEs were monitored, and therefore how reliable these event rates are.

In response to the ERGs request for clarification, the company provided additional data and analyses relating to infections and immune function. In summary these included:

- a post-hoc analysis of serum IgG in rhLAMAN-05,[10] where a statistically significant improvement was reported: adjusted mean difference vs placebo: 3.47 g/L; 95% confidence interval [CI]: 2.12, 4.81, $p<0.0001$
- a post-hoc analysis of changes in patients with low serum IgG: 9/25 pts had low serum IgG based on age and gender (5 velmanase alfa group, 4 placebo group). 3/5 (60%) of velmanase

alfa patients achieved normal IgG levels and 2/5 improved; 0/4 improved/achieved normal levels in the placebo arm

- An analysis of antibiotic use in the low serum IgG group demonstrated patients receiving velmanase alfa had fewer antibiotic uses than the placebo group after the first month (Table 16)
- An analysis of caregivers reports of infection rates supports a reduction in infections for patients in rhLAMAN-10[1]

The rationale for the importance of serum IgG appears reasonable (it being the standard therapy and a surrogate biomarker in hypogammaglobulinaemia). The ERG notes that the number of patients and events was extremely low and no statistical analysis was provided. Only patients with low IgG were included in the analysis, and it remains unclear what happened to the remaining patients, though the company state "*This sub-group of nine patients is the only group where a potential correlation between an increase in serum IgG due to treatment and improvement in rate and/or severity of infections could be formally demonstrated.*" which may indicate that infections were not improved for other patients. Given the responses presented from patient carers in the clarification response to question A20,[11] which state that infections are common and impact on social life, rates of 4 events for 10 patients over 12 months (in the placebo arm) suggest that not all impactful infections were captured and bring into question the relevance of the results reported.

The results of the analysis of data provided by caregivers are not analysed statistically but indicate that the majority of patients report fewer infections. However, the trial was open label and therefore the results are subject to bias. Also, the analysis relied on caregivers responding retrospectively, which is subject to recall bias. The ERG is also unclear if the questionnaire asked about both infections and social life problems; data presented relate to infection rates or social life problems, and it is unclear if the most favourable response has been selected for presentation. The questionnaire also only had a 69% response rate.

The observed infection rates reported as adverse events show more infections in the velmanase alfa arm than in the placebo arm, which does not match with the IgG analysis or the patient carer reports. It is therefore difficult to draw any firm conclusions as to the impact of velmanase alfa on infection rates.

Ceiling effect in 3-MSCT and 6-MWT

The company argue that baseline values for the 3-MSCT and 6-MWT are relatively high, making it difficult to detect an effect of treatment in such a small sample. The baseline value for the 6-MWT was around 460 meters in rhLAMAN-05[10] and 467 meters in rhLAMAN-10[1], equivalent to 69% predicted for age, height and gender (see Table 11 and Table 12). Given these values are similar, and these patients

appear to have values 30% below the norm for their age, height and gender, there appears to be scope for improvement in these patients. The ERG was not able to identify comparative data for the 3-MSCT to assess whether a ceiling effect was likely. However, the company go on to note that the velmanase alfa arm had more severely disabled patients compared with the placebo arm for both 3-MSCT and 6-MWT, and that this may have confounded results; this appears to be at odds with the argument that ceiling effects may have reduced the ability of the trial to detect an effect, as the velmanase alfa arm would be less prone to ceiling effects in this instance.

Critique of trials identified and included in the indirect comparison and/or network meta-analysis
Not applicable

Critique of the indirect comparison and/or multiple treatment comparison
There was no indirect comparison or network meta-analysis (NMA) conducted. The ERG believes that HSCT could be considered a relevant comparator for a small proportion of patients, in which case an NMA could have been considered to generate a comparison between velmanase alfa and HSCT.

Additional work on clinical effectiveness undertaken by the ERG
No additional analysis of the clinical effectiveness data was undertaken by the ERG.

4.2.8 Safety data

AEs of any type or grade were frequent for patients receiving velmanase alfa. Only data from the rhLAMAN-05[10] phase III trial and the rhLAMAN-10[1] non-controlled study are presented here. These represent the most recent and extensive evidence in terms of numbers of patients and length of follow-up (the integrated data set of rhLAMAN-10[1] includes data from the earlier phase I/II trials rhLAMAN-02[13], -03[15], and -04[14], as well as the rhLAMAN-05[10] phase III trial). All patients in rhLAMAN-10[1] had been exposed to velmanase alfa for at least 12 months. All of the safety concerns raised in the earlier phase I/II trials were reflected in the more recent and more extensive data from the rhLAMAN-05[10] phase III trial and the rhLAMAN-10[1] study.

rhLAMAN-05[10]

In the rhLAMAN-05[10] trial, the patients received between 48 and 55 infusions (1 per week for 12 months), with a mean (SD) of 62.8 (44.2) (CSR[10], p.150). All patients in the treatment-arm of this trial reported at least one AE (Table 20), although nine out of 10 patients in the placebo arm also reported AEs. Approximately half of all patients in the treatment (46.7%) and placebo (50%) arms also reported 'treatment-related AEs'. The CS reported that one patient in the velmanase alfa study arm experienced 11 events categorised as Infusion Related Reactions (IRRs) (chills, nausea, hyperhidrosis and vomiting),[2] but these were all considered to be mild or moderate in intensity (CS, page 155[2] and CSR[10],

p121). As a result of five of these events, the drug was interrupted (n=4) or the infusion rate was reduced (n=1) (CSR[10], p121).

According to the CSR[10] (pages 58-59)[11] a Serious Adverse Event (SAE) was defined as any AE that resulted in one of the following outcomes: death; life-threatening experience; required or prolonged in-patient hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect; or any important medical events that jeopardised the patient or subject and might require medical or surgical intervention to prevent one of the outcomes listed above. Five patients (33.3%) reported experiencing a treatment-emergent SAE: knee deformity (genua valga both sites), joint swelling (swollen ankle), Sjogren's syndrome, sepsis and acute renal failure. Only one patient was considered to have a treatment-related SAE (acute renal failure, CS, p155[2]), although there was no reported SAE in the placebo arm. According to the CS[2] and CSR[10], no patients discontinued treatment due to any AE during the rhLAMAN-05[10] trial, and there was also no death in any arm during the trial. These data were confirmed by the company following a clarification request (clarification response to question A35).[11]

Table 20: Numbers of overall adverse events, severe and treatment-related adverse events, and events leading to treatment discontinuation (rhLAMAN-05[10]) (reproduced from CS, Table 32)

AE	VA (n=15)		Placebo (n=10)	
	n (%)	Events	n (%)	Events
Summary of AEs				
Any AE	15 (100.0)	157	9 (90.0)	113
Treatment-related AE	7 (46.7)	30	5 (50.0)	9
SAE	5 (33.3)	5	0	0
Treatment-related SAE	1 (6.7)	1	0	0
Severe AE*	1 (6.7)	1	0	0
Discontinuations due to AE	0	0	0	0

Abbreviations: AE, adverse event; VA, velmanase alfa. *No definition provided in CS or CSR.

The most frequent AEs experienced by two or more patients receiving velmanase alfa in the 12-month rhLAMAN-05[10] trial were: infections (86.7%), principally nasopharyngitis (66.7%); gastrointestinal disorders (60%), especially vomiting (20.0%); pyrexia (40.0%); headache (33.3%) and arthralgia (20.0%) (Table 21). The reported rates of many adverse events were similar between study arms, but some adverse events were reported more frequently in the velmanase alfa arm than the placebo arm: toothache, syncope, hypersensitivity and the infections of acute tonsillitis, influenza and gastroenteritis were reported in two patients (13.3%) in the velmanase alfa group compared with no patients (0%) in the placebo group. A number of AEs were also reported more frequently in the placebo arm than the velmanase alfa arm: vomiting (40.0% in the velmanase alfa group vs 20.0% in the placebo group respectively), diarrhoea (30.0% vs 13.3%), pyrexia (50.0% vs 40.0%) and ear discomfort (20.0% vs 0%).

Table 21: Numbers of patients experiencing adverse events, >2 patients in any arm (rhLAMAN-05[10]) (reproduced in part from CS, Table 32 and CSR Table 12-2)

AE	VA (n=15)		Placebo (n=10)	
	n (%)	Events	n (%)	Events
Infections and infestations	13 (86.7)	48	7 (70.0)	23
Nasopharyngitis	10 (66.7)	30	7 (70.0)	16
Ear infection	2 (13.3)	2	1 (10.0)	1
Acute tonsillitis	2 (13.3)	2	0	0
Influenza	2 (13.3)	2	0	0
Gastroenteritis	2 (13.3)	2	0	0
Gastrointestinal disorders	9 (60.0)	18	8 (80.0)	24
Vomiting	3 (20.0)	5	4 (40.0)	6
Diarrhoea	2 (13.3)	2	3 (30.0)	3
Toothache	2 (13.3)	3	0	0
General disorders and administration site conditions	6 (40.0)	20	7 (70.0)	18
Pyrexia	6 (40.0)	11	5 (50.0)	11
Musculoskeletal and connective tissue disorders	7 (46.7)	11	5 (50.0)	16
Arthralgia	3 (20.0)	4	1 (10.0)	6
Back pain	2 (13.3)	2	1 (10.0)	1
Nervous system disorders	6 (40.0)	11	5 (50.0)	12
Headache	5 (33.3)	7	3 (30.0)	9
Dizziness	1 (6.7)	1	2 (20.0)	2
Syncope	2 (13.3)	2	0	0
Respiratory, thoracic and mediastinal disorders	4 (26.7)	7	2 (20.0)	4
Immune system disorders	2 (13.3)	5	2 (20.0)	2
Hypersensitivity	2 (13.3)	5	0	0
Ear and labyrinth disorders	0	0	3 (30.0)	3
Ear discomfort	0	0	2 (20.0)	2

Abbreviations: AE, adverse event; VA, velmanase alfa.

rhLAMAN-10[1]

The mean (SD) number of infusions reported in the CSR[1], p.150, for the rhLAMAN-10[1] study was 84.8 (63.1) overall (compared with 62.8 in the rhLAMAN-05 trial[10]), with a higher number reported in patients who participated in the rhLAMAN-02[13] study, and therefore in patients aged <18 years. In this study, the actual exposure of patients to velmanase alfa ranged from 357 to 1625 days, with greater exposure in patients who participated in the earliest phase I/II study, rhLAMAN-02[13] (mean exposure 1585.2 days), than in the more recent rhLAMAN-05[10] phase III study (mean exposure 630.0 days).

Almost all patients in the treatment-arm of the rhLAMAN-10[1] study reported at least one AE (Table 22). The proportions of patients in rhLAMAN-10[1] (n=33) being treated with velmanase alfa and experiencing AEs were similar to the proportions in the treatment arm of the rhLAMAN-05[10] trial (n=15): 17 patients (51.5%) reported 'treatment-related AEs'(weight increase, pyrexia and diarrhoea all affected three or more patients: CSR[1], page 156); 12 patients (36.4%) experienced a SAE; two (6.1%) experienced a treatment-related SAE (sepsis and loss of consciousness, CSR[1], p157-58) and three (9.1%) a severe AE (pyrexia and tremor in one patient, loss of consciousness in one patient and sepsis in one patient: CSR[11], p156). Sepsis was the only SAE common to both rhLAMAN-05[10] and

rhLAMAN-10.[1] The CS,[2] p158, reported that three patients in the velmanase alfa trial arm experienced 19 events categorised as IRRs (14 events for a single patient), but which were all considered to be mild or moderate in intensity.

Table 22: Numbers of adverse events, severe and treatment-related adverse events, and events leading to treatment discontinuation overall, and by age group (rhLAMAN-10[1]) (reproduced from CS, Table 34 and Table 62 from CSR, p.152)

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Any AE	29 (87.9)	546	17 (89.5)	423	12 (85.7)	123
Treatment-related AE†	17 (51.5)	84	12 (63.2)	69	5 (35.7)	15
SAE	12 (36.4)	14	7 (36.8)	9	5 (35.7)	5
Treatment-related SAE	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Severe AE*	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Discontinuations due to AE	0	0	0	0	0	0

Abbreviations: AE, adverse event; VA, velmanase alfa. *No definition provided in CS or CSR †Categorised as adverse drug reaction (ADR) in the CSR

As with the placebo-controlled, phase III trial rhLAMAN-05[10], according to the CS[2] and CSR[10], no patients discontinued treatment due to any AE during the rhLAMAN-10[1] study, and there was also no death during follow-up. These data were confirmed by the company following a clarification request (clarification response to question A35).[11] The proportion of patients experiencing AEs was generally similar across age groups, with the exception of treatment-related AEs and severe AEs. The percentage of patients affected by AEs was higher in the younger age group (<18 years of age) than in the older age group (>18 years of age): 63.2% of the younger patients reported treatment-related AEs compared to 35.7% of older patients; and 10.5% of the younger patients reported severe AEs compared to 7.1% of older patients (Table 21). These latter percentages represent the difference of only a single patient, but the ERG notes that the younger patients did have longer exposure to treatment than the older patients (CSR, p151).[1]

A broader range of AEs were reported as being experienced by two or more patients receiving velmanase alfa in the 12 to 48 month rhLAMAN-10[1] study (n=33) (Table 23). However, the most frequently-reported AEs were similar to the rhLAMAN-05[10] trial and also affected similar proportions patients, that is, nasopharyngitis (69.7% for rhLAMAN-10[1] vs 66.7% for rhLAMAN-05[10] respectively); gastrointestinal disorders (63.6% vs 60.0%), especially vomiting (30.3% vs 20.0%); pyrexia (33.3% vs 40.0%); headache (39.4% vs 33.3%) and arthralgia (21.2% vs 20.0%). Other specific AEs affecting five or more patients (>15%) were diarrhoea (27.3%), ear infections, gastroenteritis, weight increase, contusion and pain in extremity (18.2%), psychiatric disorders, excoriation and rash (15.2%). The ERG notes that the frequency of patients reporting diarrhoea (13.3% compared with 27.3%) was much lower in the velmanase alfa arm in the rhLAMAN-05[10] trial.

The proportion of patients experiencing many AEs was higher in the younger age group (<18 years of age) (n=19) than in the older age group (≥18 years of age) (n=14) in the rhLAMAN-10[1] study. The AEs reported as being more frequently experienced in the younger age group included: most gastrointestinal disorders, especially vomiting (42.1% in the group aged <18 years vs 14.3% in the group aged ≥18 years); diarrhoea (31.6% vs 21.4%) and upper abdominal pain (21.1% vs 0%); pyrexia (47.4% vs 14.3%); headache (47.4% vs 28.6%); contusion (31.6% vs 0%); excoriation (26.3% vs 0%) and wound (31.6% vs 7.1%); weight increase (31.6% vs 0%); pain in extremity (26.3% vs 7.1%); dizziness (15.8% vs 0%); cough (42.1% vs 7.1%); and tooth extraction (21.1% vs 0%). Only peripheral oedema (5.3% in the group aged <18 years vs 14.3% in the group aged ≥18 years), pollakiuria (0% vs 14.3%), rash (10.5% vs 21.4%) and hypersensitivity (10.5% vs 14.3%) were higher in the older age group.

Although the rhLAMAN-10[1] integrated data set included safety data from the earlier Phase I/II trials (rhLAMAN-02[13], rhLAMAN-03[15], rhLAMAN-04[14]), these studies did report higher proportions of patients with the AEs of nasopharyngitis (90%-100% in the phase I/II trials vs 69.7% in rhLAMAN-10[1]), weight increase, headache and pyrexia (60% for each event in the Phase I/II trials vs 18.2%, 39.4% and 33.3% respectively in rhLAMAN-10).[1] These differences might be explained in part by differences in the trial populations: the participants in the earlier Phase I/II trials were aged 5-20 years (CS[2], Table 5, p80) and their higher reported rates of AEs are consistent with the higher reported rates of AEs in the <18 years age group of the rhLAMAN-10[1] study (Table 23), although this might also be due to increased exposure to velmanase alfa.

Table 23: Numbers of patients experiencing adverse events, >1* patients in any arm, overall and by age group (rhLAMAN-10[1]) (reproduced in part from CS, Table 34 and CSR Table 63)

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Blood and lymphatic system disorders	2 (6.1)	2	2 (10.5)	2	0	0
Lymphadenopathy	2 (6.1)	2	2 (10.5)	2	0	0
Ear and labyrinth disorders	4 (12.1)	8	3 (15.8)	7	1 (7.1)	1
Eye disorders	8 (24.2)	18	5 (26.3)	10	3 (21.4)	8
Conjunctival hyperaemia	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Eye infection	2 (6.1)	2	2 (10.5)	2	0	0
Eye pruritus	3 (9.1)	5	2 (10.5)	4	1 (7.1)	1
Gastrointestinal disorders	21 (63.6)	51	13 (68.4)	36	8 (57.1)	15
Abdominal pain	3 (9.1)	3	3 (15.8)	3	0	0
Abdominal pain upper	4 (12.1)	4	4 (21.1)	4	0	0
Diarrhoea	9 (27.3)	11	6 (31.6)	7	3 (21.4)	4
Nausea	3 (9.1)	3	3 (15.8)	3	0	0
Reflux gastritis	2 (6.1)	2	2 (10.5)	2	0	0
Toothache	2 (6.1)	3	2 (14.3)	3	0	0
Vomiting	10 (30.3)	14	8 (42.1)	12	2 (14.3)	2
General disorders and administration site conditions	17 (51.5)	59	11 (57.9)	46	6 (42.9)	13
Chills	2 (6.1)	9	2 (10.5)	9	0	0
Fatigue	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Malaise	2 (6.1)	3	2 (10.5)	3	0	0
Oedema peripheral	3 (9.1)	3	1 (5.3)	1	2 (14.3)	2
Pyrexia	11 (33.3)	26	9 (47.4)	23	2 (14.3)	3
Immune system disorders	4 (12.1)	10	2 (10.5)	5	2 (14.3)	5
Hypersensitivity	4 (12.1)	9	2 (10.5)	4	2 (14.3)	5
Infections and infestations	24 (72.7)	141	15 (78.9)	112	9 (64.3)	29
Acute tonsillitis	2 (6.1)	2	2 (10.5)	2	0	0
Ear infection	6 (18.2)	7	4 (21.1)	5	2 (14.3)	2
Gastroenteritis	6 (18.2)	7	5 (26.3)	6	1 (7.1)	1
Influenza	3 (9.1)	3	2 (10.5)	2	1 (7.1)	1
Laryngitis	2 (6.1)	2	2 (10.5)	2	0	0
Nasopharyngitis	23 (69.7)	89	14 (73.7)	71	9 (64.3)	18
Urinary tract infection	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Otitis media	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Injury, poisoning and procedural complications	15 (45.5)	65	13 (68.4)	63	2 (14.3)	2
Arthropod bite	3 (9.1)	4	3 (15.8)	4	0	0
Contusion	6 (18.2)	10	6 (31.6)	10	0	0
Excoriation	5 (15.2)	18	5 (26.3)	18	0	0
Ligament sprain	2 (6.1)	2	2 (10.5)	2	0	0
Post lumbar puncture syndrome	4 (12.1)	4	3 (15.8)	3	1 (7.1)	1
Wound	7 (21.2)	10	6 (31.6)	9	1 (7.1)	1
Investigations	11 (33.3)	14	10 (52.6)	13	1 (7.1)	1
Weight increased	6 (18.2)	7	6 (31.6)	7	0	0
Metabolism and nutrition disorders	4 (12.1)	4	2 (10.5)	2	2 (14.3)	2
Increased appetite	2 (6.1)	2	2 (10.5)	2	0	0
Musculoskeletal and connective tissue disorders	18 (54.5)	47	11 (57.9)	38	7 (50.0)	9
Arthralgia	7 (21.2)	14	5 (26.3)	10	2 (14.3)	4
Back pain	5 (15.2)	5	3 (15.8)	3	2 (14.3)	2
Myalgia	2 (6.1)	3	2 (10.5)	3	0	0

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Pain in extremity	6 (18.2)	14	5 (26.3)	13	1 (7.1)	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (6.1)	2	2 (10.5)	2	0	0
Skin papilloma	2 (6.1)	2	2 (10.5)	2	0	0
Nervous system disorders	16 (48.5)	43	10 (52.6)	34	6 (42.9)	9
Dizziness	3 (9.1)	4	3 (15.8)	4	0	0
Headache	13 (39.4)	27	9 (47.4)	22	4 (28.6)	5
Loss of consciousness	2 (6.1)	2	2 (10.5)	2	0	0
Syncope	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Psychiatric disorders	5 (15.2)	10	3 (15.8)	4	2 (14.3)	6
Renal and urinary disorders	4 (12.1)	5	1 (5.3)	1	3 (21.4)	4
Pollakiuria	2 (6.1)	2	0	0	2 (14.3)	2
Respiratory, thoracic and mediastinal disorders	15 (45.5)	28	11 (57.9)	20	4 (28.6)	8
Bronchitis	2 (6.1)	2	2 (10.5)	2	0	0
Cough	9 (27.3)	12	8 (42.1)	11	1 (7.1)	1
Rhinorrhoea	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Skin and subcutaneous tissue disorders	14 (42.4)	23	9 (47.4)	13	5 (35.7)	10
Acne	2 (6.1)	2	0	0	2 (14.3)	2
Erythema	4 (12.1)	5	3 (15.8)	4	1 (7.1)	1
Rash	5 (15.2)	5	2 (10.5)	2	3 (21.4)	3
Scar pain	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Surgical / medical procedures	8 (24.2)	11	8 (42.1)	11	0	0
Catheter removal	2 (6.1)	2	2 (10.5)	2	0	0
Ear tube insertion	2 (6.1)	2	2 (10.5)	2	0	0
Tooth extraction	4 (12.1)	4	4 (21.1)	4	0	0
Vascular disorders	3 (9.1)	3	2 (10.5)	2	1 (7.1)	1

Abbreviations: AE, adverse event; VA, velmanase alfa.
* reported as >1 in CSR[1] Table 63, or ≥1 in the CS.[2]

Summary

The proportion of patients receiving velmanase alfa and experiencing any AE is high (88%-100%); approximately one half experienced a treatment-related AE and one third a SAE. However, most AEs were reported as being mild or moderate. No patient in either of the rhLAMAN-05[10] or rhLAMAN-10[1] studies discontinued treatment due to AEs, although three patients in other studies did so: one from the Phase I/II trial rhLAMAN-03[15] but who entered the rhLAMAN-05[10] trial; one in the compassionate use programme, and one patient who ultimately chose not to re-enrol for the rhLAMAN-10[1] study (clarification response to question A35[11]). No deaths were reported. The safety data were well-reported and comprehensive and, for a small number of patients, represented follow-up of 24 months (n=19) and 48 months (n=9), respectively (CSR[1], pages 150-51). However, the number of patients is small, treatment would be received, in practice, for very many years (life-long), and there is possible correlation between increased exposure and higher rates of AEs.

4.3 Conclusions of the clinical effectiveness section

The ERG believes the CS[2] is complete with respect to evidence relating to velmanase alfa. The evidence base comprised one double-blind, placebo controlled RCT (rhLAMAN-05,[10] n=25) and one long-term, single arm, open label study (rhLAMAN-10,[1] n=33).

The patient spectrum of the evidence base is likely to be younger than the population in England due to the inclusion criteria (5 to 35 years old), and it may be easier to detect an effect in younger patients if disease progression is more rapid. It is unclear whether some of the patients included in the studies may have been eligible for HSCT in some clinical practices in England. The company provided draft start/stop criteria which, if applied in clinical practice, would be likely to exclude some patients who continued treatment in the trials. In clinical practice, therefore, fewer patients may be eligible for long term treatment, but for those who are, the studies are likely to have underestimated population-level efficacy.

The ERG were concerned about serum oligosaccharides being the co-primary outcome as this is a surrogate biomarker with pharmacokinetic relevance, but low clinical relevance and which has not been assessed as a surrogate using standard criteria. 3-MSCT, 6-MWT and FVC were the co-primary and prioritised (rhLAMAN-05)[10] secondary outcomes. Quality of life was measured using CHAQ and EQ-5D-5L. These are other secondary outcomes appeared relevant, but infections, which have a big impact on patients and which were listed in the NICE scope, were not measured.

rhLAMAN-05[10] appears reasonably well conducted, though some elements are at unclear risk of bias. The small numbers (n=25) are to be expected given the rarity of the condition. There was a statistically significant decrease in serum oligosaccharides, but no statistically significant decreases in the clinical co-primary and prioritised secondary outcomes or on the other secondary outcomes of motor function, cognition and hearing. It is unclear if the study met its definition for demonstrating efficacy. No comparative analyses of quality of life outcomes were provided. The observed differences for most outcomes did not meet MCIDs where these were provided. The lack of statistically significant results for the clinical outcomes means it is unclear whether the effect of velmanase alfa on the biomarker translates to an impact on clinical outcomes.

rhLAMAN-10[1] is a non-controlled, experimental study akin to a cohort study. The design has some risk of bias and due to the lack of a control arm the results are difficult to interpret. The length of follow-up varied a great deal for patients (12 months to 48 months), with variable and smaller numbers, sometimes comprising different patients altogether, at the time points beyond 12 months. The last observation analysis generally included all patients and for the four main outcomes (serum oligosaccharides, 3-

MSCT, 6-MWT, FVC % predicted) there was very little difference between the 12 month and the last observation analyses (though the mean length of follow-up in the last observation analysis is unclear).

Post-hoc analyses of the interaction between age groups in rhLAMAN-10[1] indicate that whilst there is no difference between younger (<18 years of age) and older (≥18 years of age) patients in serum oligosaccharides, there is in the clinical outcome of 3-MSCT. No other interaction tests were reported. Observed differences in clinical outcomes between younger and older patients in both trials are generally greater in the younger patients.

Adverse events were frequent in both studies, but mostly mild to moderate. The safety of treatment over a lifetime is unknown.

5 COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.[2]

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The CS[2] includes a review of cost-effectiveness evidence related to the decision problem, essentially based on the same broad searches as the review of clinical effectiveness with the addition of EconLit specifically for the purpose of identifying economic studies.

As noted in Section 4.1.1, these included all the databases usually recommended by NICE (Medline; EMBASE; Cochrane Library and EconLit); a selection of relevant conference proceedings and HTA reports; and an additional list of registers specifically designed to identify cost-effectiveness evidence (all detailed in CS Appendix 17.3.5.1).[2]

The search strategies (reproduced again in CS Appendix 3, Section 17.3)[2] were highly sensitive and designed to retrieved all published studies related to the disease area (AM), without applying any restrictive filters to limit the types of evidence retrieved. Results were then manually sifted for inclusion or exclusion in the parallel reviews looking at clinical effectiveness, cost-effectiveness, cost and resource use and health-related quality of life, with PRISMA flowcharts provided for each review.

The inclusion criteria for the economic and HRQoL reviews are provided in Table 24, which is a reproduction of Table 46 from the CS.[2] The eligibility criteria for inclusion in the HRQoL review is provided in Table 25 which is a reproduction on Table 38 of the CS.[2]

Table 24: Inclusion criteria for health economic studies

Inclusion criteria	
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age).
Interventions	Not restricted (see Section 17.1.6 for details on treatments to include).
Outcomes	**Economic evaluation SR** • Main outcomes: o ICERs: cost per QALY, cost per DALY, cost per event avoided • Additional outcomes: o Range of ICERs as per sensitivity analyses o Assumptions underpinning model structures o Key cost drivers o Sources of clinical, cost and quality of life inputs o Discounting of costs and health outcomes o Model summary and structure **Cost of illness/resource use SR** • Direct costs • Direct medical and pharmacy healthcare costs per patient per year (interventions, concomitant medications, treatment of AEs/co-morbidities) • Method of valuation • Indirect costs o Productivity loss costs o Presenteeism: at work productivity level (also from patients' viewpoint) o Short- and long-term sick leave (absenteeism) o Withdrawal from labour force o Method of valuation (Human capital or friction cost approach or contingent valuation) o Costs of special schooling for patients o Costs of adapting home settings to account for progressive disability • Patient and family/caregiver costs o Travel, co-payments o Annual loss of income o Formal and informal care • Caregiver burden
Study design	**Economic evaluation SR** • Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses **Cost of illness/resource use SR** • For studies to be eligible: o Epidemiological approach should be specified for the design o Perspective of the study should be clear o Objectives of the study must include an assessment of costs of illness or an assessment of interventions in management of AM o Studies reporting predictors of costs were considered for inclusion
Language restrictions	Unrestricted
Search dates	Unrestricted

Exclusion criteria	
Population	Patients aged <6 years with AM (all patients were included at first pass regardless of age).
Interventions	Unrestricted
Outcomes	Restricted to those stated in the eligibility criteria.
Study design	Restricted to those stated in the eligibility criteria.
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: AE, adverse events; AM, alpha- mannosidosis; CSF, cerebrospinal fluid; DALY, Disability-adjusted life year; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SR, systematic review.

Table 25: Eligibility criteria for inclusion in the HRQoL review

Criteria	Include
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age)
Treatments	No restriction
Outcomes	HSUV/QoL SR • Utilities values directly elicited using TTO/SG techniques • Utility values derived using generic preference-based instruments for relevant health states (e.g. EQ-5D, SF-6D, HUI3) • Mapping studies allowing generic or disease-specific measures to be mapped to preference-based utilities • Generic or disease-specific measures reporting the QoL associated with AM
Setting/study design	HSUV/QoL SR, no limitation and to include: • HSUV elicitation studies • Interventional studies • Observational studies e.g. cohort studies
Language of publication	No restriction. On completion of citation screening on the basis of title and abstract, a list of foreign-language publication was forwarded to Chiesi. A decision was then taken on whether the studies were conducted in a country of interest.
Date of publication	No restriction
Countries/global reach	No restrictions

Abbreviations: AM, alpha-mannosidosis; EQ-5D, EuroQol five dimensions questionnaire; HUI3, health utilities index Mark 3; HSUV, health-state utility value; QoL, quality of life; SG, standard gamble; SF-6D, short form 6D; SR, systematic review; TTO, time-trade-off.

5.1.2 Results produced from the company's systematic review of cost-effectiveness evidence

The company's initial search initially identified 1556 unique publications, which were reduced to 100 following screening of titles and abstracts. The full texts of these 100 studies were reviewed with the company determining that no studies reported an economic evaluation or cost/resource use. In the updated search, 65 unique records were identified; all of these were excluded following screening of title and abstract.

5.2 Description of the company's model

5.2.1 Model scope

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's economic analysis is summarised in Table 26. The ERG notes that this covers the outcomes contained in the final NICE scope.[9]

Incremental health gains, costs and cost-effectiveness of velmanase alfa are evaluated over a 100-year time horizon from the perspective of the UK NHS and Personal Social Services (PSS). All costs and health outcomes are discounted at a rate of 1.5% per annum. Unit costs are valued at 2016 prices.

Table 26: Summary of company's health economic model scope

Population	Patients aged six years and over with AM. This is subdivided into a paediatric cohort (6 to 11 years), an adolescent cohort (12 to 17 years) and an adult cohort (18 years and over)
Intervention	Once weekly treatment with velmanase alfa, administered intravenously, at a dose of 1mg/kg of body weight. Treatment is intended to be lifelong although the company propose both start and stop criteria that are described in this section.
Comparator	BSC†
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	100 years
Discount rate	1.5% per year
Price year	2016

BSC – Best Supportive Care; NHS – National Health Service; PSS – Personal Social Services; QALY – Quality-Adjusted Life Years.

† Note Haematopoietic Stem Cell Transplant was not included despite being in the final scope.

Population

The population considered within the company's economic analysis relates to patients aged six years and over with AM. These patients are divided into a 'paediatric cohort' (6 to 11 years of age), an 'adolescent cohort' (12 to 17 years of age) and an 'adult cohort' (aged 18 years and older). Within the company's clarification response[11] (question A9) it was stated that '*The European Medicines Agency (EMA) has adopted a positive opinion to velmanase alfa with a therapeutic indication not restricted by age, so as to no longer exclude patients aged under 6 years.*' However, the company also state that '*no clinical trial data concerning the efficacy and safety of velmanase alfa are available for patients aged 5 years and under; therefore, a clinical and economic case is put forward in this highly specialised technology (HST) evaluation for an AM population aged 6 years and older*.'

The company have proposed the following criteria, which if any are met, means that a patient would not be eligible for velmanase alfa treatment. Collectively these criteria have been termed the 'start criteria'.

- The patient does not have a confirmed diagnosis of AM; or

- The patient has experienced a severe allergic reaction to velmanase alfa or to any of the excipients (disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol and glycine); or
- The patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- The patient is unwilling or unable to comply with the associated monitoring criteria, i.e. that all patients are required to attend their appointed clinics two times per year for assessment

Intervention

The intervention under consideration is velmanase alfa (given alongside BSC). Velmanase alfa is assumed to be administered intravenously at a dose of 1mg/kg of body weight with the intended duration of treatment being lifelong.

The company have proposed the following set of criteria, which if any are met, would result in the cessation of velmanase alfa treatment. Collectively, these criteria are termed the 'stop criteria'.

- the patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 18-month period); or
- the patient fails to meet two of the three criteria as defined in multi-domain responder analysis at their Year 1 assessment (see Sections 9.4.1.4 and 9.6.1.3 of the CS[2])
- the patient is unable to tolerate infusions due to infusion related severe AEs that cannot be resolved; or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g. due to repeated recurrent chest infection or progressive and sustained lack of mobility; or
- the patient misses more than four infusions of velmanase alfa in any 12-month period, excluding medical reasons for missing dosages.

Comparator

The comparator included in the company's model is BSC. The company consulted key opinion leaders (KOLs) who stated that BSC was defined as a "*needs based approach to treatment, dealing with symptoms as they arise*" which may include the following treatments, amongst others.

- Provision of walking aids and wheelchairs, and home adaptations
- Aggressive management of infections

- Major surgical interventions (ventriculoperitoneal shunts, cervical spine decompression, joint replacement)
- Minor surgical intervention (tonsillectomy/adenoidectomy, grommet surgery [insertion and removal], umbilical/inguinal hernia repair, carpal tunnel release surgery, feeding tube insertion)
- Physiotherapy, including hydrotherapy
- Ventilation support
- General treatment of comorbidities
- Supportive measurements at home (hoists etc.)

In addition, monitoring and preventative measures would be necessary to detect or manage emerging problems which could include the following.

- MRI of brain and spine
- Skeletal surveys and respiratory function testing (routinely done in paediatric patients)
- Cardiac echo/ECG (typically done in older/adult patients)
- Prophylactic use of antibiotics

BSC is typically provided by a multidisciplinary team (MDT). In the UK, it is the metabolic consultant who is likely to be the primary physician.

The ERG notes that HSCT was not included in the model by the company despite being contained in the final scope.[9] Clinical advice received by the ERG and submitted to NICE suggests that HSCT may be an appropriate intervention for a small proportion patients. The clinical effectiveness and cost-effectiveness of velmanase alfa in patients who are suitable for HSCT are unknown.

5.2.2 Description of the company's health economic model structure and logic

Within this appraisal, the clarification process worked efficiently and many of the errors and/or limitations identified by the ERG in the initial two-week period were corrected by the company. See the clarification response by the company[11] and Table A in the revised results section presented after clarification,[30] for further details, Only the latest version of the model, and the revised results received by the ERG on the 23rd of February 2018 are discussed in this report unless it is imperative to detail those in a previous version. The net result of the amendments was to improve the cost-effectiveness of velmanase alfa compared with the company's reported base case.

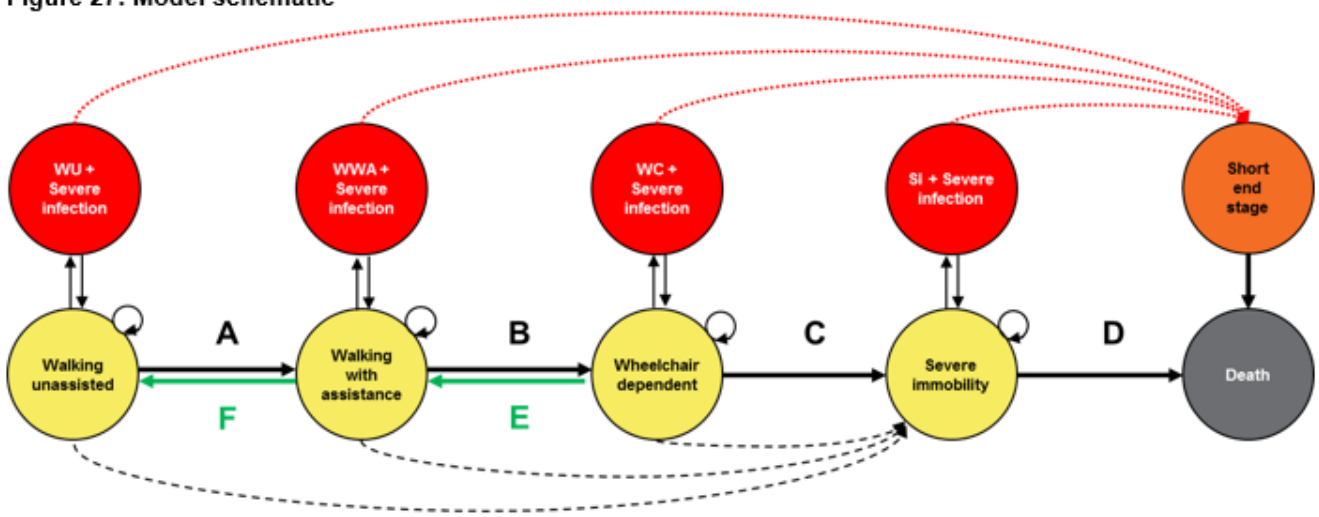
The general structure of the company's model is presented in Figure 3. The model is a state transition model with a time cycle of 1 year and a time horizon of 100 years.

The model has five primary health states: (i) walking unassisted; (ii) walking with assistance; (iii) wheelchair dependent; (iv) severe immobility and (v) dead. For patients on BSC, there is a probability that the condition will worsen and that the patient moves to the next most severe primary health state (equivalent to arrows A, B, C and D in Figure 3). These transitions are also relevant for patients on velmanase alfa treatment, although the company has assumed that it is possible for a patient on velmanase alfa treatment to improve health status (as shown with arrows E and F in Figure 3) but not for patients receiving BSC to improve.

In addition to the primary health states there are four tunnel states that patients enter when experiencing a severe infection. At the end of the time cycle a patient returns to the primary health state in which they were in before the severe infection, unless they are simulated to not recover from the severe infection, in which case they enter the short end stage health state. Once in the short end stage, the patient is assumed to die within four weeks.

Figure 3: Company's model structure (reproduced from CS, Figure 27)

Figure 27: Model schematic



Each health state accounts for the key drivers of disutility and costs due to the functional impairment, hearing impairment, cognitive impairment and pain experienced by patients with alpha mannosidosis

- Tunnel state: accounts for the cost, disutility and mortality risk associated with a severe infection
- Primary health state: patients start in the model in one of the four primary health states
- Short end stage: patients can only transition to short end stage from a severe infection tunnel state
- Death: patients can transition to death due to background mortality or surgery-related mortality from any health state
- Green arrow designates a disease improvement transition due to treatment with velmanase alfa
- Dashed arrow designates a transition to severe immobility as a result of a post-surgical complication
- Dashed arrow designates a transition to short end stage as a result of a severe infection that leads to death

Abbreviations: SI, severe immobility; WC, wheelchair dependent; WWA, walking with assistance; WU, walking unassisted

Surgical complications can move a patient from any of the walking unassisted, walking with assistance, and wheelchair dependent states to the severe immobility state or to death. Death from causes unrelated to AM or the treatment of AM can occur at any time point, with the background rate of mortality taken from UK life tables.[31]

Each health state in the model has an associated cost per cycle and utility. These are detailed in Sections 5.2.3.8 and Sections 5.2.3.16 respectively.

The assumed functional status associated with the four living states is provided in Table 27.

Table 27: Clinical features of the primary health states defined by the company

State	Clinical features
Walking unassisted	• Patient is able to walk and go upstairs unassisted • Patient may have radiological skeletal abnormalities, but these may not present as clinical symptoms • Ataxia may be present but it does not greatly impact the patients' mobility
Walking with assistance	• The patient requires any form of assistance to walk (e.g. help from another person, footwear to support stability, a walking cane, wheelchair for long distances, hand rails etc.) • Patient may have radiological skeletal abnormalities presenting as clinical symptoms • Ataxia may be present and it may impact a patients' mobility
Wheelchair dependent	• Endurance is reduced; the patient is wheelchair-bound, but can still operate walking aids/use assistance to traverse short distances • Patient has some joint destruction that impacts mobility, however the patient can still transfer themselves without carer support (e.g. the patient can transfer from the wheelchair into bed independently) • Patient presents with some joint weakness and loss of joint flexibility
Severe immobility	• Patient requires a wheelchair/mobility device continuously and cannot transfer independently (i.e. requires hoists and other assistive equipment) • Joint destruction is present in weight-bearing joints (cervical spine, hips and/or knees), which severely restricts movement • Patient presents with poor muscle function and manual dexterity; for example, dressing unaided is impossible

5.2.3 Assumptions and evidence used to inform the model parameters

The parameters are detailed in the forthcoming sections. For ease of reference, Section 5.2.3.21 provides a summary of the sources used for parameters to which the ICER is particularly sensitive. The majority of these parameters are populated either through data obtained in an elicitation session or interviews with UK KOLs and are not informed by data observed in clinical studies. Details of the elicitation session and interviews are provided in Sections 5.2.3.1 and 5.2.3.2.

5.2.3.1 Details of the elicitation exercise.

The company described the elicitation process in Section 12.2.5 of the CS.[2] Additionally the company provided a 174 document extensively detailing the elicitation process. In brief, five clinical experts (out of ten contacted) participated, representing four LSD centres in the UK. The Sheffield Elicitation Framework (SHELF) methodology was followed which is appropriate. All experts received honoraria (funded by Chiesi) to cover the time required to prepare for the elicitation exercise (pre-reading of the evidence dossier) and attendance at a one-day elicitation panel.

5.2.3.2 Details of the interviews with KOLs.

The company described the elicitation process in Section 12.2.5 of the CS.[2] In brief, the interview process had three stages. The company stated that the first (18 questions) supported the early scoping / design stages of developing the model, the second (29 questions) generated and validated key assumptions in the model, and the third (36 questions) generated and validated key model parameters for which published data in AM patients did not exist. Ten KOLs were contacted of which five participated in at least one stage of the interview process. All five KOLS had experience of treating AM with BSC, although only one had experience of treating AM with an ERT. However, all five had experience of using an ERT in LSD. Pre-reading was supplied to KOLs before each interview. In each interview, questions and data were displayed to KOLs via teleconference and a WebEX link. Each KOL had to confirm in writing that the minutes and summary were an accurate reflection of the discussions and their responses provided during the interview.

Each KOL received honoraria (funded by Chiesi) to cover the time required to prepare for the interviews (pre-reading of the interview brief and questions) and time to attend at each interview.

5.2.3.3 The population being modelled

The company designated three cohorts: (i) a paediatric cohort; (ii) an adolescent cohort and (iii) an adult cohort.

The starting age of patients within each cohort and the assumed distribution between primary health states assumed by the company are reproduced in Table 28. The company assumed that all patients were at the lowest age within each age band, and the distribution of patients' functional status across primary health states was taken from rhLAMAN-10.[1]

Table 28: Characteristics of the modelled population assumed by the company

Parameter	Age (years)	WU	WWA	WC	SI
Paediatric	6	78%	22%	0%	0%
WWA to WC	12	73%	27%	0%	0%
WC to SI	18	62%	38%	0%	0%

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

Paediatric and adolescent patients on model entry were assumed to incur the costs associated with adult patients once they became 17 years of age.

5.2.3.4 Disease progression whilst treated with BSC

The company undertook a UK Expert Elicitation Panel to provide information regarding the number of years it was expected that a patient would reside in each of the primary health states before progressing to the next more severe health state when treated with BSC. These disease progression data, which are marked as academic in confidence (AIC) are reproduced with slight amendments in Table 29.

Table 29: Assumed time to disease progression whilst treated with best supportive care

Parameter	Value	95% Credible Interval
Years in State: Best Supportive Care		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

5.2.3.5 Disease progression whilst treated with velmanase alfa

Three further elicitation exercises were undertaken assessing the additional years in each health state that treatment with velmanase alfa would provide divided into results for the paediatric cohort, the adolescent cohort and the adult cohort. For the adult cohort, the company also state that the rhLAMAN-10[1] responder analysis was used, although the ERG did not know how. These disease progression data, which are marked as AIC are reproduced with slight amendments in Table 30.

Table 30: Assumed time to disease progression whilst treated with velmanase alfa

Variable	Value	95% Credible Interval
Additional years in state associated with velmanase alfa treatment: Paediatric cohort		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]
Additional years in state associated with velmanase alfa treatment: Adolescent cohort		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]
Additional years in state associated with velmanase alfa treatment: Adult cohort		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

The ERG notes that the company stated in response to clarification question A44[11] that of those patients in the walking unassisted health state in rhLAMAN-05[10] that 20% (2/10) of people in the velmanase alfa arm deteriorated to the walking with assistance health state whilst 40% (4/10) of people in the placebo arm deteriorated to the walking with assistance health state. Thus, a relative reduction in deterioration was observed for velmanase alfa treatment compared with BSC.

5.2.3.6 Disease improvement

The company assumed that disease improvement, in terms of primary health states was not possible for patients receiving BSC alone. In contrast, for those patients receiving velmanase alfa in the Walking With Assistance and Wheelchair Dependent health states, the company assumed that improvement was possible. These values were informed by the interviews with UK KOL, who were aware of the results from rhLAMAN-10.[1] The assumed yearly transition probabilities are shown in Table 31. The ERG comments that as this is a cohort model that on average, one in 25 patients would move from Wheelchair Dependent to Walking Unassisted in the initial two years. The plausibility of this value is not known.

Table 31: Assumed probability of disease improvements when treated with velmanase alfa

Variable	Value	95% Credible Interval
Transition Probabilities associated with velmanase alfa in years 1 and 2		
WWA to WU	20%	0% to 70%
WC to WWA	20%	0% to 70%
Transition Probabilities associated with velmanase alfa in years 3 and beyond		
WWA to WU	2.5%	0% to 5%
WC to WWA	2.5%	0% to 5%

WC – Wheelchair dependent; WU – Walking unassisted; WWA – Walking With Assistance

The ERG notes that the company stated in response to clarification question A44[11] that of those patients in the walking with assistance health state in rhLAMAN-05[10] that 40% (2/5) of people in both the velmanase alfa and the placebo arm improved to the walking unassisted state. Thus, no relative gain in improvement was observed for velmanase alfa treatment compared with BSC.

5.2.3.7 Velmanase alfa treatment discontinuation

The company assumed that patients would be assessed at the end of 12 months of velmanase alfa treatment and those that did not have an adequate response would have treatment discontinued. Adequate response for a patient was defined as the response criteria being reached in at least two of the three domains, with a patient considered a responder in a domain '*if they showed a response for at least one efficacy parameter within that domain by achieving the adopted MCID for that outcome.*' Based on data from rhLAMAN-05,[10] it was assumed that 86.67% of patients would be classified as responders, and that 13.33% would discontinue at one year. This value was assumed for all age groups and primary health states, with an arbitrary credible interval (CrI) of 10.0% to 16.7%, which was assumed to follow a Beta distribution. The model assumed that there would be no further discontinuation based on response criteria in future years.

The model assumed an underlying discontinuation rate, for reasons including infusion-related reactions, non-compliance, patient preferences and/or occurrence of life limiting conditions (e.g. cancer) of 10% based on interviews with UK KOL with an arbitrary CrI of 7.5% to 12.5%, which was assumed to follow a Beta distribution.

Furthermore, the company state that treatment with velmanase alfa would be discontinued after one year when a patient enters the severe immobility state '*This is to reflect that once a person moves into the severe immobility state, there will be a period where their health status in confirmed by their specialist consultant, and the decision is made in collaboration with the patient and their carer to withdraw active treatment.*' (clarification response,[11] question B1). Treatment with velmanase alfa would be discontinued once a patient entered the short end stage health state.

5.2.3.8 The underlying costs associated with each health state

In Table 65 of the CS,[2] the company provide a summary of the assumed annual costs by health state for patients receiving BSC. These are comprised of costs associated with consultations and costs associated with surgery. The type and frequency of consultations were summarised in Table 66 of the CS, and the unit costs of consultations and surgery were summarised in Table 67 of the CS.[2] For reasons of brevity, neither table is reproduced. The company assumed that the costs reported in Table 32 are applicable independent of whether the patient was receiving velmanase alfa or whether the patient was receiving

BSC. It should be noted that the values reported in the CS do not match those used in the model although the numbers were similar[2] Table 32 reports the values used in the model.

Table 32: Assumed annual costs by health state

	Year 1		Year 2 and beyond	
Health State	**Paediatric**	**Adult**	**Paediatric**	**Adult**
WU	£4395	£4361	£4108	£4042
WWA	£4089	£4069	£3802	£3750
WC	£3739	£3720	£3453	£3400
SI	£2156	£2145	£1888	£1875
WU + S Inf	£13,040	£16,038	£12,753	£15,718
WWA + S Inf	£12,957	£15,968	£12,670	£15,649
WC + S Inf	£13,029	£16,040	£12,742	£15,721
SI + S Inf	£13,244	£16,264	£12,977	£15,994
SES*	£46.782	£36.603	£46.782	£36.603

SI – Severe Immobility; S Inf – Severe Infection; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
* four weeks' cost only.

5.2.3.9 The additional costs associated with velmanase alfa treatment

The largest cost component of velmanase alfa treatment is that associated with purchasing the intervention, which has a list price of £886.61 (excluding VAT) per 10mg vial. The company have applied for a PAS which will take the form of a simple discount on the price per vial resulting in a cost of [redacted] (excluding VAT) per 10mg vial. Dosing is weight-based with one vial required for patients weighing up to 10kg, two vials required for patients weighing between 10kg and 20kg and so on. For information, this would result in patients weighing between 60 and 70kg having an annual drug acquisition cost of [redacted] (excluding VAT).

The company assumed that the drug would be initiated in a LSD centre for the first three infusions, before the patient moves on to having an infusion in the home setting (98%) or at a local hospital (2%). These proportions were stated by the company to '*capture the minority of patients that may revert to hospital briefly for the management of Infusion-Related Reactions (IRRs), before returning to homecare once the IRRs are resolved.*' Costs associated with infusions at either an LSD centre or a local hospital were assumed to be £213 based on the Outpatient procedure tariff for vascular access except for renal replacement therapy without complication and comorbidity based on NHS National prices and national tariff 2015-16.[32] Home infusions were assumed to be associated with no additional costs. The number of infusions before leaving the care of the LSD centre, and the proportion of patients receiving home infusions were estimated through interviews with UK KOLs.

The weights for each age group were assumed to be fixed by the company as 'clinical data were not available to derive a population distribution from which to estimate an expected number of vials.' The use of fixed weights is likely to produce inaccurate answers, but it is not clear whether this would favour or disadvantage velmanase alfa.

5.2.3.10 The probability of undergoing major surgery and associated risks and costs

The company assumed that the annual probability of major surgery for patients with AM were as detailed in Table 33. These data, which are marked as AIC, were informed by the elicitation exercise undertaken with UK experts. It was assumed that these rates were applicable irrespective of whether the patient was treated with BSC or with velmanase alfa.

Table 33: Assumed yearly probability of major surgery

Health State	Value	95% Credible Interval
WU	[redacted]	[redacted]
WWA	[redacted]	[redacted]
WC	[redacted]	[redacted]
SI	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking unassisted; WWA – Walking With Assistance

Major surgery is associated with potential mortality and potential complications, which the company assumed would leave the patient in the severe immobility health state. Data on the probability of these events were obtained through interviews with UK KOLs (Table 34); each parameter had an assumed CrI that was +/- 50% of the base case value, which was characterised by a Beta distribution. Based on interviews with UK KOLs, the company further assumed that treatment with velmanase alfa would reduce the risk surgery mortality by 50%, reduce the risk of surgical complications by 50% and reduce the recovery time required after surgery by 50%. All of these values had an arbitrary CrI relating to the reduction of 37.5% to 62.5%, which was assumed to follow a Beta distribution.

Table 34: Assumed probability of surgical-related mortality and surgical-related complications

Health State	Surgical-related mortality	Surgical-related complications†
WU	5.00%	10.00%
WWA	5.00%	10.00%
WC	10.00%	20.00%
SI	10.00%	20.00%

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

† Assumed independent of mortality rate.

The costs related to major surgery were assumed by the company to be the mean costs associated with: ventriculoperitoneal shunt; cervical fusion, complex; cervical fusion, very complex; hip replacement; and knee replacement using NHS Reference costs 2015-2016. This resulted in a value of £11,097 per major surgery. More details are provided in Table 67 of the CS.[2]

5.2.3.11 The probability of minor surgery and associated costs

The probabilities of a patient undergoing minor surgery in a year assumed by the company was informed by the interviews with UK KOLs. The values were: 100% (95% CrI: 75% - 100%) for the Walking Unassisted state, 50% (95% CrI: 37.5% - 62.5%) for both the Walking With Assistance and the Wheelchair dependent state, and 0%, with no allowance for uncertainty for the Severely Immobile state.

The costs related to minor surgery were assumed by the company to be the average costs associated with: tonsillectomy; carpal tunnel surgery; and grommet surgery using NHS Reference costs from 2015-2016. This resulted in a value of £1711 per minor surgery. More details are provided in Table 67 of the CS.[2]

5.2.3.12 The probability of severe infection and associated risks and costs

In the elicitation session with UK experts previously described elicitation was undertaken to form probability distributions related to the annual probability of severe infection for patients receiving BSC. These data, which were marked as AIC, are shown in Table 35. Based on interviews with UK KOLs, the company assumed that treatment with velmanase alfa would reduce the risk of severe infection by 50%.

Table 35: Assumed yearly risks of severe infection

Health State	Value	95% Credible Interval
WU	[redacted]	[redacted]
WWA	[redacted]	[redacted]
WC	[redacted]	[redacted]
SI	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

It was assumed that severe infection was associated with a risk of mortality where the patient spent four weeks in the short end stage health state. The probability of this was elicited from UK experts with the data, that is marked as AIC, reproduced in Table 36. Based on interviews with UK KOLs, the company assumed that treatment with velmanase alfa would reduce the risk of mortality following a severe infection by 50%; this value was arbitrarily assumed to have a 95% CrI ranging from a 37.5% reduction to a 62.5% reduction, characterised by a Beta distribution. Finally, also based on KOL interviews, the company assumed that a patient receiving velmanase alfa would recover in 50% of the time that it takes a person treated with BSC to recover; this value was arbitrarily assumed to have a 95% CrI ranging from a 37.5% reduction to a 62.5% reduction, characterised by a Beta distribution.

Table 36: Assumed probability of mortality following a severe infection

Health State	Value	95% Credible Interval
WU	[redacted]	[redacted]
WWA	[redacted]	[redacted]
WC	[redacted]	[redacted]
SI	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

The costs associated with severe infections were estimated based on the time spent required in an intensive care unit and a general ward multiplied by their respective unit costs per day. This calculation was undertaken separately for paediatrics and adults (see Table 37). The duration of hospital stay was assumed equal to that required for patients with sepsis, with the values for children being those reported in Paul *et al*.[33] and those for adults being taken from Levy *et al*.[34] The costs per intensive care unit (ICU) stay were a weighted average of multiple NHS Reference costs for paediatrics and multiple NHS Reference costs for adults. Further details are provided in Table 67 of the CS.[2]

Table 37: The costs associated with severe infection

Health State	Patients aged 16 years or younger	Patients aged 17 years or older
ICU length of stay	6.25	7.80
Unit cost per day in ICU	£1671	£1307
General ward length of stay	2.98	15.00
Unit cost per day in a general ward	£273	£273
Total costs	£11,255	£14,286

ICU – Intensive Care Unit

5.2.3.13The requirement for, and the costs of ventilation

The company report the UK KOLs indicated that patient with AM typically require ventilator support as their disease severity worsens. The KOLS also '*suggested that velmanase alfa may help to reduce the need for ventilatory support, due to the positive effects of treatment on lung function*'. The company also reported that '[redacted]' The company assumed that patients on velmanase alfa had 50% of the ventilation requirements associated with BSC, with no allowance for uncertainty. The ventilation costs associated with BSC are provided in Table 38.

Table 38: Assumed costs of ventilation by health state for patients on best supportive care

Health State	Overnight ventilation	24-hour care ventilation at home	24-hour care ventilation at institution	Total ventilation cost per year
Annual Cost *	£95,448	£285,176	£358,930	-
WU	0%	0%	0%	£0
WWA	0%	0%	0%	£0
WC	20%	0%	0%	£19,090
SI	50%	25%	25%	£208,751

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
* Taken from Noyes *et al.*[35] and inflated to 2016 prices

5.2.3.14 The requirement for caregiver time and associated costs

The company assumed that data included in Hendriksz et al.[36] relating to the hours of caregiver time required per day in patients with Morquio A syndrome were appropriate for patients with AM. An assumption (without further explanation), was used to estimate the proportion of care delivered by professionals in each primary health state. The estimated carer cost per year was calculated by multiplying the proportion of professional carer time by the anticipated hours of care provided by year. These calculations are reproduced in Table 39.

Table 39: Assumed annual costs of professional care by health state

Health State	Hours of Care required per day (95% Credible Interval) [36]	Proportion of care provided by professionals (95% Credible Interval) †	Cost per Year *
WU	1.3 (0.98 – 1.63)	10% (7.5% - 12.5%)	£1139
WWA	3.9 (2.93 – 4.88)	20% (15% - 25%)	£6833
WC	13.8 (10.35 – 17.25)	50% (37.5%- 62.5%)	£60,444
SI	13.8(10.35 – 17.25)	80% (60% - 100%)	£96,710

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
† Assumption (no further details provided).
* Assuming a cost per hour of £24.00 for professional care[37]

During the clarification period, the company commissioned a survey that assessed the caregiver requirements for patients with AM.[38] This report was marked as AIC in its entirety. [redacted] The data obtained within the survey were not used in the cost-effectiveness modelling.

5.2.3.15 The frequency of adverse events and associated costs

The only adverse event included in the model was IRRs. The rate of IRRs reported in rhLAMAN-10[1] (9.1% per annum 95%CrI 6.82% to 11.36%) were assumed by the company to be generalisable were velmanase alfa used in UK practice. The company assumed that IRRs were associated with zero costs. The company state that this is based on White et al. that reports that '*that IRRs in patients with LSDs receiving ERT requires minimal intervention*'.[39] On examination of the reference provided, the ERG did not find the sentence quoted, but believes that the inclusion of the costs of the treatments received, intravenous hydrocortisone only (2%) and combination intramuscular adrenaline, intravenous hydrocortisone and intravenous antihistamine (3%), are unlikely to influence the incremental cost-effectiveness ratio (ICER).

5.2.3.16 The utility assumed in each health state

In the CS,[2] the utility associated with each health state was estimated using clinicians as a proxy using the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire. The estimated values (which are marked as AIC) are shown in Table 40. Disutilities associated with caregivers were estimated by expert clinicians 'mapping' each primary health state onto an expanded disability status scale and using published data relating to patients with multiple sclerosis.[40] The disutilities assumed for a caregiver is apparently for only one person, and were assumed fixed. It was assumed that the utilities associated with the Short End State were equal to those who were severely immobile.

Table 40: Assumed utility associated with each health state

Health State	Utility of the patient – original submission	Utility of the patient – revised submission	Disutility of the caregiver	Cost per year *
WU	[redacted]	0.906	0.01	£1139
WWA	[redacted]	[redacted]	0.02	£6833
WC	[redacted]	0.100	0.05	£60,444
SI / SES	[redacted]	-0.011	0.14	£96,710

SES – Short End State; SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

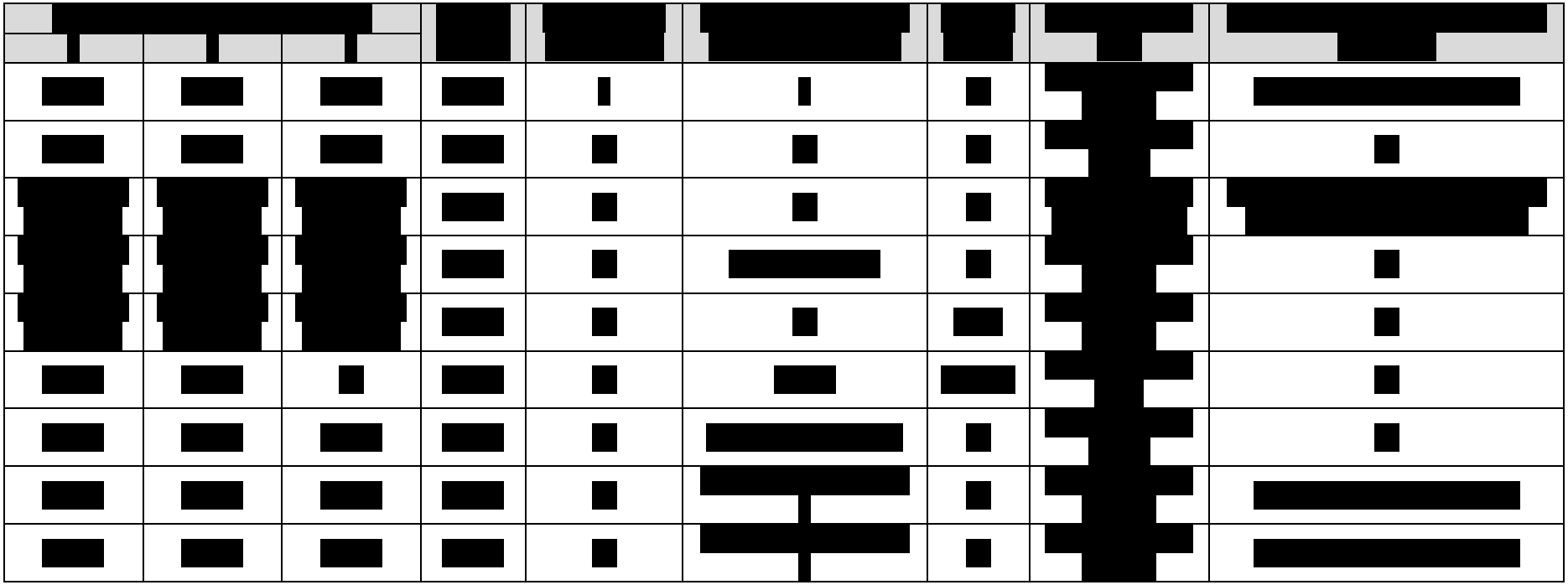
During the clarification process, the ERG commented that these values lacked face validity with respect to the ordering of the values, and the absolute value of one health state ([redacted]) in particular. To address these concerns, the company commissioned a survey with the objective of providing additional data on the utility within each health state. Mucopolysaccharidosis (MPS) Commercial (a wholly owned, not for profit subsidiary of the UK MPS Society) was commissioned to design the survey questionnaires and to conduct the survey. The company provided the results in a full report, which was marked as AIC in its entirety.[38]

[redacted]

[redacted]

Whilst it was not stated clearly in the documentation, the ERG believes that the values presented are EQ-5D-5L values crosswalked to the EQ-5D-3L values using the method detailed by van Hout et al.[41]

Table 41: Patient characteristics of those patients responding to the survey regarding utility



Abbreviations: AM, alpha-mannosidosis; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; NR, non-response; UK, United Kingdom.
†At time of survey completion; ‡Responses taken from phase 3 of the survey responses, as they are the most up to date data, except for CH006 who did not consent to completing the phase 3 survey; §Treatment described as bone marrow transplant in survey responses; §The patient-reported age at diagnosis of CH004; ¶The carer-reported age at diagnosis of CH004

The base case and the scenario analyses are detailed below. [redacted]Base case: Patient utility as reported by the carer (by proxy) regardless of prior treatment

Scenario 1: Comparison of patient utility reported by the carer (by proxy) and by the patient (by self-report). This analysis is only applicable for the three patients with both carer-reported and patient-reported patient utilities.

Scenario 2: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC, i.e. patients who had received stem cell transplant or velmanase alfa were excluded from the pooled analyses. A resulting missing data point for the 'walking with assistance' health state was imputed using the EQ-5D-5L utility for this health state as in the CS^2 by use of KOL input.

Scenario 3: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC. A resulting missing data point for the 'walking with assistance' health state was imputed using the mean of the utility values calculated for the 'walking unassisted' and 'wheelchair dependent' states.

Scenario 4: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC. A resulting missing data point for the 'walking with assistance' health state was imputed using a ratio of utility for 'walking with assistance' relative to 'walking unassisted' determined through KOL input.

[redacted]

Table 42: Utility estimates (standard deviation) by primary health state produced by the company

Health State	n	WU	WWA	WC	SI
Base case	9	0.794 (0.200)	0.758 (N/A)	0.100 (N/A)	-0.011 (0.053)
Scenario 1	3	0.794 (0.000)	0.758 (N/A)	N/A	N/A
Scenario 2†	5†	0.906 (0.000)	[redacted]	0.100 (N/A)	-0.011 (0.053)
Scenario 3	4†	0.906 (0.000)	0.503 (N/A)	0.100 (N/A)	-0.011 (0.053)
Scenario 4	4†	0.906 (0.000)	0.345 (N/A)	0.100 (N/A)	-0.011 (0.053)
rhLAMAN-10[1] baseline	15	0.652 (0.149)	0.577 (0.200)	N/A	N/A
rhLAMAN-10[1] Last observation	25	0.702 (0.171)	0.635 (0.085)	N/A	N/A

N/A – Not Available; SES – Short End State; SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

† Plus one value in the WWA state estimated from UK KOL estimates

† Used in the model

5.2.3.17 The assumed utility benefit associated with velmanase alfa treatment

Of note, the company has assumed that any patient treated with velmanase alfa would receive a utility gain of 0.1. This value was stated to have been validated with UK KOLs, with the company further stating in the clarification response[11] (question B15) that there were many aspects of AM that were not completely accounted for in the model including: 'reducing rates of minor infections; reducing rates of psychiatric problems with investigators noticing that in '[redacted]'; reduced ventilator dependency; providing intra-ambulatory health state improvements', for example, moving from multiple aids/assistance for walking to only requiring one minimal aid for walking (e.g. footwear for stability); and the provision of a structured homecare visit programme with regular (weekly) nurse visits [redacted]. Four UK KOLs confirmed that '*applying an 'on-treatment utility increment' was appropriate, to account for these additional benefits that treatment with velmanase alfa may incur, which are not formally accounted for in the model by other existing parameters.*' The company report that a value of 0.1 was chosen with reference to the improvements of 0.05 and 0.058 in the Walking Unassisted and Walking With Assistance states that had been seen in the EQ-5D analyses using data from the rhLAMAN-10[1] trial and the possibility that some benefits of velmanase alfa '*will only be apparent after a number of years of treatment*.'

5.2.3.18 The assumed disutility associated with severe infection

The disutility associated with severe infection for patients receiving BSC was assumed to be approximated by that reported for patients with sepsis by Drabinski et al.[43] which was a value of 0.18 for a period of six months. This resulted in an undiscounted quality-adjusted life year (QALY) loss of 0.09 per severe infection. The company assumed that this disutility would be halved for patients

receiving velmanase alfa based on interviews with UK clinical experts with an arbitrary CrI relating to the reduction of 37.5% to 62.5%, which was assumed to follow a Beta distribution.

5.2.3.19 The assumed disutility associated with major surgery

For the disutility associated with major surgery the company chose to use a value previously reported by BioMarin in a Highly Specialised Technology Appraisal and which was said to be accepted by NICE in a related mucopolysaccharidosis condition.[44] This disutility was 0.25 and was applied for a period of 6 months resulting in an undiscounted QALY loss of 0.125 per patient receiving major surgery. The company assumed that this disutility would be halved for patients receiving velmanase alfa based on interviews with UK clinical experts with an arbitrary CrI relating to the reduction of 37.5% to 62.5%, which was assumed to follow a Beta distribution.

5.2.3.20 The assumed disutility associated with minor surgery and adverse events

No disutility was assumed for either minor surgery or IRRs.

5.2.3.21 Summary of the evidence sources used for key parameters within the model.

A summary of the sources associated with parameters to which the ICER is particularly sensitive is provided in Table 43. This allows the committee to distinguish which values are populated with observed data, which are populated with data from elicitation sessions with clinical experts and which are populated via interviews with KOLs. For conciseness, the values assumed are not repeated in Table 44.

Table 43: The data sources for key parameters within the company model

Parameter	Source for company base case analysis
Age of population	Assumption
Starting health state of population	Taken from data observed in rhLAMAN-10[1]
Time to disease progression when treated with BSC	UK Expert Elicitation Panel
Additional time to disease progression when treated with velmanase alfa	UK Expert Elicitation Panel
Improvement in health state associated with velmanase alfa treatment	Interviews with UK KOLs
Treatment discontinuation due to lack of efficacy	Data from the multi-domain responder analysis conducted in rhLAMAN-05[10]
Treatment discontinuation due to other reasons	Interviews with UK KOLs
Probability of major surgery conditional on health state	UK Expert Elicitation Panel
Probability of mortality and complications associated with major surgery	UK Expert Elicitation Panel
Reduction in the risks of mortality and complications associated with surgery due to velmanase alfa treatment	Interviews with UK KOLs
Probability of severe infection conditional on health state	Interviews with UK KOLs
Probability of mortality associated with severe infection	UK Expert Elicitation Panel
Reduction in the risks of mortality and complications associated with severe infections due to velmanase alfa treatment	Interviews with UK KOLs
Requirement for ventilation conditional on health state	Interviews with UK KOLs
Reduction in the requirement for velmanase alfa due to the use of velmanase alfa	Interviews with UK KOLs
Utility in each health state	Survey conducted by the UK MPS Society.
Utility gain associated with being on velmanase alfa	Assumption

BSC – Best Supportive Care; KOLs – Key Opinion Leaders; MPS - mucopolysaccharidosis

5.2.4 Model evaluation methods

The CS presents the results of the economic analysis in terms of the incremental cost per QALY gained for velmanase alfa versus BSC.[2] The base case results are presented deterministically using the base case estimate for each parameters. The CS[2] also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSA) and scenario analyses. The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The results of the DSA are presented in tabular form with an additional tornado diagram which is limited to the ten most influential model parameters. The distributions applied in the company's PSA are summarised in Table 63. These values have been provided in the relevant sub-section of Section 5.2.3.

5.2.5 Company's model results

Table 44 presents the estimates of cost-effectiveness derived from the company's revised model following the clarification process. Based on the probabilistic versions of the model, in the paediatric cohort velmanase alfa is expected to generate an additional 2.50 QALYs at an additional cost of [redacted] per patient: the ICER is [redacted] per QALY gained. In the adolescent cohort these values were an additional 2.64 QALYs at an additional cost of [redacted] per patient: the ICER is [redacted]

per QALY gained. In the adult cohort, these values were an additional 2.61 QALYs at an additional cost of [redacted] per patient: the ICER is [redacted] per QALY gained.

The deterministic version of the model produces similar ICERs of: [redacted] per QALY gained for velmanase alfa versus BSC in the paediatric cohort; [redacted] per QALY gained for velmanase alfa versus BSC in the adolescent cohort; and [redacted] per QALY gained for velmanase alfa versus BSC in the adult cohort. The undiscounted incremental QALY gain for the paediatric cohort was stated by the company to be 3.13 with the discounted value being 2.53. According to the Methods Guide for Highly Specialised Technology Appraisals[45] a value below ten QALYs would have a weight of 1 with respect to a £100,000 cost per QALY gained threshold. As such, all the base case ICERs reported by the company, using the list price of velmanase alfa, are in excess of the appropriate threshold.

The ERG comments that the ICERs are more favourable to velmanase alfa in the paediatric group due to the smaller doses of interventions required as the treatment has weight-based dosing.

Table 44: Company's estimates of cost-effectiveness – velmanase alfa versus BSC

Paediatric cohort					
Probabilistic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	9.90	[redacted]	2.50	[redacted]
BSC	[redacted]	7.40	-	-	-
Deterministic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	10.32	[redacted]	2.53	[redacted]
BSC	[redacted]	7.79	-	-	-
Adolescent cohort					
Probabilistic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	9.65	[redacted]	2.64	[redacted]
BSC	[redacted]	7.02	-	-	-
Deterministic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	10.04	[redacted]	2.66	[redacted]
BSC	[redacted]	7.39	-	-	-
Adult cohort					
Probabilistic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	8.82	[redacted]	2.61	[redacted]
BSC	[redacted]	6.21	-	-	-
Deterministic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	9.17	[redacted]	2.67	[redacted]
BSC	[redacted]	6.51	-	-	-

BSC – best supportive care; inc – incremental; QALY - quality-adjusted life years;
VA – velmanase alfa

CEACs and scatterplots are presented in the CS[2] but, for brevity are not reproduced here. The ERG notes that by inspection the CEACs the ICERs did not appear to be below £[redacted] per QALY gained for any of the three cohorts in any of the PSA iterations conducted by the company. Therefore the probability of the ICER being below [redacted] per QALY gained was estimated to be [redacted]%.

Table 45 presents the results of the company's DSAs for the paediatric cohort, with the corresponding results for the adolescent and adult cohorts shown in Table 46 and Table 47, respectively. Across all analyses, the ICER for velmanase alfa versus BSC remains greater than [redacted] per QALY gained, with this value marked as commercial-in-confidence (CIC) by the company as it relates to the cost of a vial of velmanase alfa. The ERG comments that the price of velmanase alfa is directly under the control of the company and should not be entered into the DSA. Excluding this variable, the lowest ICER is greater than £[redacted] per QALY gained.

Table 45: The company's deterministic sensitivity analyses – velmanase alfa versus BSC in the paediatric cohort

Parameter	Value			Cost per QALY gained		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10%	8%	13%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Progression (added years in state) – VA – Paediatric – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

Table 46: The company's deterministic sensitivity analyses – velmanase alfa versus BSC in the adolescent cohort

Parameter	Value			Outcome		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10%	8%	13%	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	[redacted]	[redacted]	23.23	[redacted]	[redacted]	[redacted]
Progression (added years in state) – VA – Adolescent – WU to WWA	[redacted]	[redacted]	2.59	[redacted]	[redacted]	[redacted]

Abbreviations: VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

Table 47: The company's deterministic sensitivity analyses – velmanase alfa versus BSC in the adult cohort

Parameter	Value			Outcome		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10%	8%	13%	[redacted]	[redacted]	[redacted]
Progression (added years in state) – VA – Adult – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; TE, treatment effect; VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

The company performed extensive scenario analyses that were reported in Table 111 of the appendix submitted post clarification response.[11] This table is reproduced in Table 48.

Table 48: Company's scenario analyses – velmanase alfa vs best supportive care (adapted from CS Table 111)

Model parameter (base case)	Scenario analysis	Results (£) ICER (incremental cost, incremental QALYs)		
		Paediatric cohort	Adolescent cohort	Adult cohort
Base case results	-	[redacted]	[redacted]	[redacted]
Utilities (UK MPS Society Survey)	Morquio A proxy utility values adjusted for complications using minimum method and age-adjusted	[redacted]	[redacted]	[redacted]
	rhLAMA N-10[1] trial data for WU and WWA states	[redacted]	[redacted]	[redacted]
	rhLAMA N-10[1] trial data for WWA state only	[redacted]	[redacted]	[redacted]
Time horizon (Lifetime)	10 years	[redacted]	[redacted]	[redacted]
	20 years	[redacted]	[redacted]	[redacted]
	30 years	[redacted]	[redacted]	[redacted]
	50 years	[redacted]	[redacted]	[redacted]
Patient age (lowest cohort age (6, 12, 18))	rhLAMA N-10[1] average age (8, 15, 25)	[redacted]	[redacted]	[redacted]
Discount rates for costs and QALYs (1.5%)	0.00%	[redacted]	[redacted]	[redacted]
	3.50%	[redacted]	[redacted]	[redacted]
Discontinuation (13.3% at year 1, 10% annual, and discontinue at severe immobility	No discontinuation at all	[redacted]	[redacted]	[redacted]
	Annual discontinuation of 20%	[redacted]	[redacted]	[redacted]
	Discontinue once in wheelchair	[redacted]	[redacted]	[redacted]

Caregiver disutility (Gani et al, 2008 (109)). SES state has full year disutility	Acaster et al, 2013 (110)	[redacted]	[redacted]	[redacted]
	No caregiver disutility	[redacted]	[redacted]	[redacted]
	Caregiver disutility in SES applied for 4 weeks	[redacted]	[redacted]	[redacted]
VA on-treatment utility increment (0.1)	0	[redacted]	[redacted]	[redacted]
	0.2	[redacted]	[redacted]	[redacted]
VA on-treatment utility increment post discontinuation (0.0)	0.01	[redacted]	[redacted]	[redacted]
	0.05	[redacted]	[redacted]	[redacted]
Reduction in probability of major surgery in patients on VA (0.0%)	50%	[redacted]	[redacted]	[redacted]
VA monitoring (included in routine BSC specialist appointment	Monitoring not part of BSC	[redacted]	[redacted]	[redacted]
Societal costs (not included)	Include personal & caregiver expenditure	[redacted]	[redacted]	[redacted]
	Include caregiver productivity loss	[redacted]	[redacted]	[redacted]

	Include both personal & caregiver expenditure and productivity loss	[redacted]	[redacted]	[redacted]
Ventilation costs from Noyes (2006) study and VA patients assumed to have 50% lower rate of ventilation/ 24-hour ventilation in WC and SI health states	Double the costs of ventilation	[redacted]	[redacted]	[redacted]
	Remove the cost of ventilation	[redacted]	[redacted]	[redacted]
	VA ventilation equal to BSC ventilation	[redacted]	[redacted]	[redacted]
	No 24-hour care ventilation required for VA patients	[redacted]	[redacted]	[redacted]

Abbreviations: AM, alpha-mannosidosis; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

5.2.6 Budget impact analyses

The company report a budget impact analysis, should velmanase alfa be recommended for use by NICE, in Table 21 of the CS.[2] This predicts a total cumulative budget impact of £8.93 million over a five-year period, increasing from £1.48 million in year 1 to £2.16 million in year 5. The ERG has no reason to believe these values are likely to be significantly inaccurate.

5.3 Critique of the company's model and exploratory and sensitivity analyses undertaken by the ERG

The ERG has endeavoured to produce an ERG base case ICER subject to the constraints of the model submitted by the company, detailed at the end of this section. Within the ERG base case changes are only made to the company's base case where the ERG has a strong preference for a different assumption to the one made by the company. Where the ERG believes that the means of the parameters values are open to debate, but the ERG does not have a preferred value scenario analyses have been undertaken.

The ERG reiterates that many parameters are not populated with observed data but are instead populated by using distributions elicited from experts or estimated from interviews. The values from the interviews and arbitrary distributions used by the company do not benefit from using a formal elicitation process. The ERG is concerned that the parameter estimates may not reflect genuine beliefs which leads to questions regarding the appropriateness of both the company's and the ERG's base case analysis.

Five changes were made to the company's base case ICER:

1) Using the utility values for the Walking Unaided and Walking With Assistance states that were reported at baseline in the rhLAMAN-10[1] study.

   Fifteen patients recruited to rhLAMAN-10[1] provided baseline utility values for the Walking Unaided and the Walking With Assistance health states. This is greater than the number ([redacted]) that responded to the MPS Survey used in the company base case. The baseline value has been chosen rather than the last observation value as [redacted]

2) Using a discount rate value of 3.5% per annum rather than 1.5% per annum

   In their clarification response[11] (Question B30) the company stated that '*NICE recommends that a discount rate of 1.5% can be used for costs and QALYs in treatments where patients would otherwise not survive, patients suffer from severely impaired life conditions or when the condition is sustained for over 30 years.*' The ERG notes that in the latest methods guide to highly specialised technology appraisals[45] it is stated that '*In line with the Guide to the Methods of Technology Appraisal, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered.*' The ERG does not think that velmanase alfa meets these criteria as the intervention does not restore a patient to full or near full health.

3) Using a utility increase associated with velmanase alfa treatment of 0.00 rather than 0.10

   The company's rationale for using a utility increase of 0.10 associated with velmanase alfa treatment is reported in Section 5.2.3.15. The ERG comments that the gain shown between the baseline and the last observation n rhLAMAN-10[1] is non-comparative (as no patient received BSC) and that the values could be confounded by different patient numbers, with different disease severities. The ERG comments that utility gains would be double-counted if a patient improved health state as there would be an increase related to the health state and also a utility increase

associated with being on velmanase alfa treatment. Further double-counting would exist when patients have been maintained in the same health state rather than progressing due to velmanase alfa treatment. The ERG comments that the additional years in each state elicited from the clinical experts (Table 30) are not sufficiently high to support evidence of clear ongoing utility gain for patients receiving velmanase alfa.

4) Amending an implementation error in the model relating to transition probabilities

After the clarification period, the ERG identified an error in that patients who had received velmanase alfa treatment but had discontinued and were receiving BSC, did not have the same transition probabilities as those patients who were on BSC. This discrepancy was amended by the ERG setting these probabilities equal to the values for patients in the comparator arm.

5) Amending an implementation error in the model relating to costs post discontinuation of velmanase alfa

After the clarification period, the ERG identified an error in that patients who had received velmanase alfa treatment but had discontinued and were receiving BSC, did not have the same ventilation costs as patients on BSC. The model has been amended so that patients who have discontinued treatment have the ventilation costs associated with BSC.

The following scenario analyses were run adapting the ERG's base case. These have been run to provide additional potentially informative data to the committee. These are ordered in terms of the headings in Section 5.2.3 and not in order of perceived importance.

1) Assessing the cost-effectiveness of velmanase alfa in each of the primary health states

The ERG explored whether the ICER was sensitive to the distribution of patients in each starting health state by setting 100% of patients to each of the primary health states in turn.

2) Using the mean age of patients in the three age groups observed in rhLAMAN-10[1] rather than setting this to the lowest age

The company set the starting age of patients to be the lowest age for each age band. In response to clarification question[11] B31 the company stated that '*The lowest age of each band was selected to reflect UK KOLs comments that the earlier the intervention with an ERT (such as velmanase alfa), the more potential for a treatment benefit to be realised, and to reflect the reality that future patients with AM are likely to be diagnosed as an incident population in childhood, rather than the rhLAMAN clinical programme which identified patients from a prevalent cohort of patients with AM*' Whilst a case could be made for setting the youngest age to 6 years, there seems no reason to believe that had a patient with AM not been diagnosed at early childhood then they

would be diagnosed at 12 rather than at 11 or 13. As such, the average values from rhLAMAN-10[1] were used in an exploratory analysis.

3) Assuming that improvements in health state were only possible in the first 12 months

The company used values from UK KOLs to assume that there was a 20% chance of improvement from the Wheelchair Dependent health state to the Walking With Assistance Health state, and a 20% chance of improving from the Walking With Assistance health state to the Walking Unassisted state for the initial 2-year period. For each year thereafter, the company assumed a probability of 2.5% for both improvements. The ERG has explored the impact on the ICER if it was assumed that there were no improvements after the initial year, which is the duration of the randomised rhLAMAN-5[10] study.[46] The ERG highlights that the transition probabilities for patients on velmanase alfa are still preferable to those of BSC, and that only improvements in health states beyond 12 months are prohibited. The impacts on surgical and severe infection remain as in the base case.

4) Assuming that velmanase alfa had no beneficial effect on the risks, and the recovery times, associated with surgery

The company assumed that treatment with velmanase alfa would reduce the risk of surgery mortality by 50%, reduce the risk of surgical complications by 50% and reduce the recovery time required after surgery by 50%. These values were produced based on interviews with UK KOLs and could have some element of double-counting as patients also have reduced risks in better health states. Given that there are very few data to populate these parameters, the ERG has performed exploratory analyses to assess the impact of removing these benefits on the ICER.

5) Assuming that velmanase alfa had no beneficial effect on the risks, and the recovery times, associated with severe infection

The company assumed that treatment with velmanase alfa would reduce the risk of severe infection by 50%, reduce the risk of mortality given a severe infection by 50% and reduce the recovery time required after severe infection by 50%. These values were produced based on interviews with UK KOLs and could have some element of double-counting as patients also have reduced risks in better health states. Given that there are very few data to populate these parameters, the ERG has performed exploratory analyses to assess the impact of removing these benefits on the ICER.

6) Assuming that the costs of severe infections were set to £2742

The company used published literature to estimate the costs associated with severe infection, using severe sepsis as a proxy, resulting in costs of £11,255 for a paediatric patient and £14,286

for an adult population. Based on NHS Reference costs (using non-elective long stay codes WJ05A, WJ05B, WJ06A, WJ06B, WJ06C, WJ06D, WJ06E, WJ06F, WJ06G, WJ06H, WJ06J[32]) weighted by the number of finished consultant episodes the ERG estimated that the cost was £2742 which has been used in the exploratory analyses.

7) Assuming that velmanase alfa had no beneficial effect on the costs associated with ventilation

The company assumed, based on interviews with UK KOLs, that the ventilation requirements for patients treated with velmanase alfa would be reduced by 50%. The model could have some element of double-counting as patients also have reduced ventilation requirements in better health states. Given that there are very few data to populate these parameters, the ERG has performed exploratory analyses to assess the impact of removing these benefits on the ICER. It should be noted that a minor coding error in the company's model was amended in order that the company's functionality to select this option could be used.

8) Assuming the values on caregiver time reported in the UK MPS survey

The UK MPS survey produced alternative estimates for the amount of caregiver time required in each health state. The ERG explored the impact on the ICER if it were assumed that [redacted]

9) Removing the impact on caregiver utility from the model

The ERG explored the impact on the ICER of removing caregiver disutility from the model to ascertain the sensitivity of the ICER to this parameter.

10) Including personal expenditure by the family within the model

The ERG explored the impact on the ICER of including personal expenditure by the family within the model.

11) Including the loss of caregiver productivity within the model

The ERG explored the impact on the ICER of including the loss of caregiver productivity within the model.

12) Assuming the chronic utility gain associated with velmanase alfa treatment was 0.05

For reasons previously described, the ERG has set the chronic gain associated with being on velmanase alfa treatment to zero. However, noting that UK KOLs expect a utility increase with velmanase alfa treatment the ERG has performed a scenario analysis using a utility increase of 0.05 based on the improvements seen in rhLAMAN-10[1] ([redacted] for the Walking Unaided state and [redacted] for the Walking With Assistance state).

Combinations of the scenario analyses have not been performed due to the large number of permutations, but specific scenarios can be provided quickly at the Appraisal Committee meeting if desired.

The following limitations in the model were also noted, although no formal changes were made by the ERG as these were not possible within the time frame of the HST.

1) The prohibition of improvement in the BSC arm

The company do not allow any improvement in health state for those patients modelled to have BSC alone. In their clarification response[11] (question B3), the company described this as a simplifying assumption and for the velmanase alfa arm used the level of improvement associated with velmanase alfa over and above BSC. The ERG comments that this simplification is likely to change the ICER, although the direction is not known. A more accurate ICER would be obtained by using the absolute values of improvement for both velmanase alfa and for BSC rather than setting BSC to zero and velmanase alfa to the difference between the treatments.

2) The model output will fail to match the input data elicited from clinicians

   The elicitation with clinicians asked the additional time in each health state a person would be in were they provided with velmanase alfa treatment. These values are used directly in the model. However, logically the model will not produce the answers elicited from the expert clinicians for two reasons: (i) where patients improve health states in the velmanase alfa arm, they would have to progress from the improved state to the original state and then would have a further additional time in the original health state, and (ii) events such as reaching the Short End Stage through infection or the severe immobility state through surgical complications will change the life expectancy of each patients. While a formal analysis of this has not been conducted, the ERG believes that the actual increase in life expectancy will be higher than that predicted by the clinicians.

3) Using fixed weights rather than a distribution of weights may not provide an accurate answer or reflect the true uncertainty

   The use of fixed weight within a model can produce inaccurate answers.[47] In the company's model, it is assumed that all 1-year old females have a weight of 10.27kg, and all 5-year-old females have a weight of 19.91kg. As one vial of velmanase alfa is required for every 10kg, both 1 year old and 5-year-old females will require 2 vials per week. In reality, many 1-year old females will only require one vial, whereas many 5-year olds females will require 3 vials. It is not clear whether the limitations associated with using fixed weights will be favourable or unfavourable to velmanase alfa.

4) Patients who discontinue treatment due to lack of efficacy are assumed to do so at the midpoint of the first year rather than at 12 months

   This is an implementation issue which will be marginally unfavourable to velmanase alfa as the full 12 months' benefit relating to surgery, or severe infection would not be captured, and any assumed utility increase due to velmanase alfa treatment would not be fully realised.

Despite observed data in rhLAMAN-05[10] showing no relative improvement in health state for velmanase alfa treatment compared with BSC, see response to clarification question A44,[11] this was not removed within the ERG base case as the value used in the company base case had been elicited from five clinical experts.

Finally, the ERG did not perform any analyses with HSCT as a comparator. As such, the clinical effectiveness and cost-effectiveness of velmanase alfa in patients who are suitable for HSCT are unknown.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has presented ICERs for a most plausible ERG base case ICER, subject to the caveats that some limitations relating to the model could not be fixed within the time frames of the appraisal. Table 49 details the differences between the components of the company's base case ICER and that of the ERG. This table also provides the deterministic ICER associated with each individual change in the base case. Deterministic ICERs were calculated for computational time reasons given that the model has been shown in Table 44 to be relatively linear, and because the ERG base case ICER was significantly above the thresholds reported in the HST Methods guide.[45] Additional scenario analyses relating to key uncertainties have been undertaken on the ERG base case ICER and are presented in Table 50.

In the ERG base case the undiscounted QALY gains were 1.89 for paediatric patients, 2.00 for adolescent patients and 2.00 for adult patients; the discounted QALYs gained were 1.08 for paediatric patients, 1.14 for adolescent patients 1.17 for adult patients. In the scenario analysis where an ongoing 0.05 utility gain associated with velmanase alfa treatment was assumed the undiscounted (discounted) QALY gains were 2.24 (1.36) for paediatric patients, 2.35 (1.43) for adolescent patients and 2.35 (1.45) for adult patients, which was the scenario analysis with the highest QALY gains associated with velmanase alfa treatment.

Table 49: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case [redacted])**	**Adolescent (CS base case £[redacted])**	**Adult (CS base case [redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906; [redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; CS – company submission; WU – Walking Unassisted; WWA – Walking With Assistance

It is seen that the changes made within the ERG base case result in considerable increases in the ICERs. The increase observed when removing an ongoing utility gain for receiving velmanase alfa treatment, over and above any changes in health state, show the results are particularly sensitive to this parameter. As previously detailed, the ICERs are more favourable in paediatric patients due to the smaller doses of velmanase alfa required.

Table 50: Scenario analyses run on the ERG's base case

	CPQ given individual change		
Analyses	**Paediatric (ERG base case £[redacted])**	**Adolescent (ERG base case £[redacted])**	**Adult (ERG base case [redacted])**
Assuming 100% in the WU health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WWA health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WC health state	[redacted]	[redacted]	[redacted]
Assuming the average age per age band observed in rhLAMAN-10[1]	[redacted]	[redacted]	[redacted]
Assuming no improvements in health state after 12 months	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to surgery.	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to serious infection.	[redacted]	[redacted]	[redacted]
Assuming the costs of a severe infection are set to £2742	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to ventilation costs.	[redacted]	[redacted]	[redacted]
Assuming the UK MPS survey as the source for caregiver requirements.	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility	[redacted]	[redacted]	[redacted]
Including personal expenditure by the family	[redacted]	[redacted]	[redacted]
Including caregiver productivity losses	[redacted]	[redacted]	[redacted]
Assuming that patients treated with velmanase alfa have a utility gain of 0.05	[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; MPS – Mucopolysaccharidosis; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

7 OVERALL CONCLUSIONS

The clinical evidence base comprised one double-blind, placebo controlled RCT (rhLAMAN-05[10], n=25) and one long-term, single arm, open label study (rhLAMAN-10[1], n=33). The patient spectrum was largely representative mild to moderate disease, though likely with a higher proportion of young patients than in England. The ERG noted that some patients included in these studies may have been eligible for HSCT in England. Some patient in the studies may have had their treatment halted if the draft start/stop criteria produced by the company had been applied; for those who would have continue treatment, the studies are likely to have underestimated population-level efficacy.

The ERG had concerns about the use of serum oligosaccharides as the primary outcome. This outcome has low clinical relevance and has not been assessed as a surrogate using standard criteria.[29] Other outcomes, including 3-MSCT, 6-MWT, FVC, cognition, hearing and quality of life, appeared relevant, but infections, which have a big impact on patients and which were listed in the NICE final scope[9], were not measured.

rhLAMAN-05[10] reported a statistically significant decrease in serum oligosaccharides, but no statistically significant decreases in other outcomes (where statistical tests were conducted). The ERG was unclear if the study met its definition for demonstrating efficacy. The observed differences for most outcomes did not meet MCIDs where these were provided. It is unclear to the ERG whether the effect of velmanase alfa on the biomarker translates to a useful impact on clinical outcomes. rhLAMAN-10[1] provided longer term data, but the ERG noted variable and smaller numbers, sometimes comprising different patients altogether, at time points beyond 12 months making results difficult to interpret. Further, there was often little difference between 12 month and last observation data, though the mean length of follow-up at last observation was not reported. Interaction tests showed a difference in effect based on patient age (<18 years of age compared with ≥18 years of age) in 3-MSCT in rhLAMAN-10[1], but not for serum oligosaccharides. No other interaction tests were reported in either study, though observed differences between age groups were generally more favourable in those ages <18 years. Adverse events were frequent, but mostly mild to moderate. The safety of treatment over a lifetime is unknown.

The ERG comments that key clinical parameters of the model that were assumed to be influenced by velmanase alfa treatment were informed largely through elicitation of experts' beliefs with, or interviews with, clinical experts. There were large differences in the base cases ICERs produced by the company and those produced by the ERG, with the values produced by the ERG approximately double that of the company estimates. The cause of the differences were five changes made by the ERG to the company model. These were: (1) the use of utility data collected in the rhLAMAN-10[1] study ([redacted]) in preference to data taken from the MPS survey ([redacted]); (2) changing the discount rate from 1.5% per annum to 3.5% per annum; (3) removing the utility gain of 0.10 that was assumed by the company to be gained when being on velmanase alfa treatment; (4) the correction of a model implementation error

where the transition rates between those patients receiving BSC were different dependent on whether the patient had received velmanase alfa initially; and (5) the correction of a model implementation error where the incorrect costs post discontinuation of velmanase alfa were used. The ERG's base case ICERs were greater than [redacted] per QALY for the paediatric group, the adolescent group and the adult group.

In addition, the ERG performed multiple sensitivity analyses which indicated that the ICER was sensitive to the following assumptions relating to velmanase alfa treatment: the duration of potential improvement of health state; the benefit associated with surgical outcome; the benefit associated with serious infection; and any underlying utility gain that may be conferred by velmanase alfa. There are limited data on these parameters and thus the estimated ICER is uncertain. It was also noted that the ICER was sensitive to assumptions made regarding which health state patients were in when receiving velmanase alfa and also the assumed average ages of patients.

The ERG noted four structural assumptions that it could not amend within the timescales of the HST appraisal relating to: the prohibition of patients receiving BSC improving (and the rate of velmanase alfa also improving by the same amount); that the model output would not predict the elicited input data regarding time in health state; that the number of vials required were not based on a distribution; and that patients discontinuing velmanase alfa treatment were assumed to do so at six months rather than 1 year. It is not known how amending the model to accommodate these changes would change the ICER.

The ERG highlights that all ICERs contained in the main text of this document are using the list price of velmanase alfa. The results when the PAS is incorporated are provided in Appendix 5.

7.1 Implications for research

In order to estimate the ICER accurately additional evidence, with multiple years follow up, are needed on

- The improvement in health states associated with velmanase alfa compared to BSC
- The benefit of velmanase alfa compared to BSC in relation to surgical outcomes
- The benefit of velmanase alfa compared to BSC in relation to serious infection and outcomes after serious infection
- The benefit of velmanase alfa compared to BSC in relation to ventilation requirements
- Any gain in utility associated with velmanase alfa that are not captured by the health state, surgical outcomes and serious infection outcomes.

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9 APPENDICES

Appendix 1: Eligibility for velmanase alfa and start/stop criteria

Reproduction of section 10.1.16 of the CS.[2]

10.1.16.1 Eligibility

To receive treatment, patients must be made aware of the start and stop criteria for treatment with velmanase alfa. Patients are required to attend appointed clinics two times per year for assessment. There may be patients, e.g. those with cognitive impairment or other behavioural issues or challenges, who are not able to complete a full set of assessments at the appointed visits. In such cases, clinicians will be expected to make all possible efforts to gather as much of the required data as possible.

Patients will not be eligible to receive treatment with velmanase alfa if any of the following apply:

- the patient does not have a confirmed diagnosis of alpha-mannosidosis; or
- the patient has experienced a severe allergic reaction to velmanase alfa or to any of the excipients (disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol and glycine); or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient is unwilling or unable to comply with the associated monitoring criteria, i.e. that all patients are required to attend their appointed clinics two times per year for assessment

10.1.16.2 Start criteria

All of the following are required before treatment with velmanase alfa is started:

- Patient eligibility criteria must be met as defined in Section 10.1.16.1
- A full set of baseline biochemical, functional and QoL assessments have been obtained

10.1.16.3 Stop criteria

Patients will cease treatment with velmanase alfa if any of the following apply:

- the patient is non-compliant with assessments for continued therapy (noncompliance is defined as fewer than two attendances for assessment in any 18-month period); or
- the patient fails to meet two of the three criteria as defined in multi-domain responder analysis at their Year 1 assessment (Section 9.4.1.4 and 9.6.1.3)
- the patient is unable to tolerate infusions due to infusion related severe AEs that cannot be resolved; or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or

- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g. due to repeated recurrent chest infection or progressive and sustained lack of mobility; or
- the patient misses more than four infusions of velmanase alfa in any 12-month period, excluding medical reasons for missing dosages.

Patients whose treatment with velmanase alfa is discontinued due to stop criteria will continue to be monitored for disease progression and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

Appendix 2: Study Flow Charts

Reproduction of Figures from the CS relating to patient flow through the trial.

Figure 4: reproduction of Figure 6 from the CS:[2] rhLAMAN-02[13] patient disposition

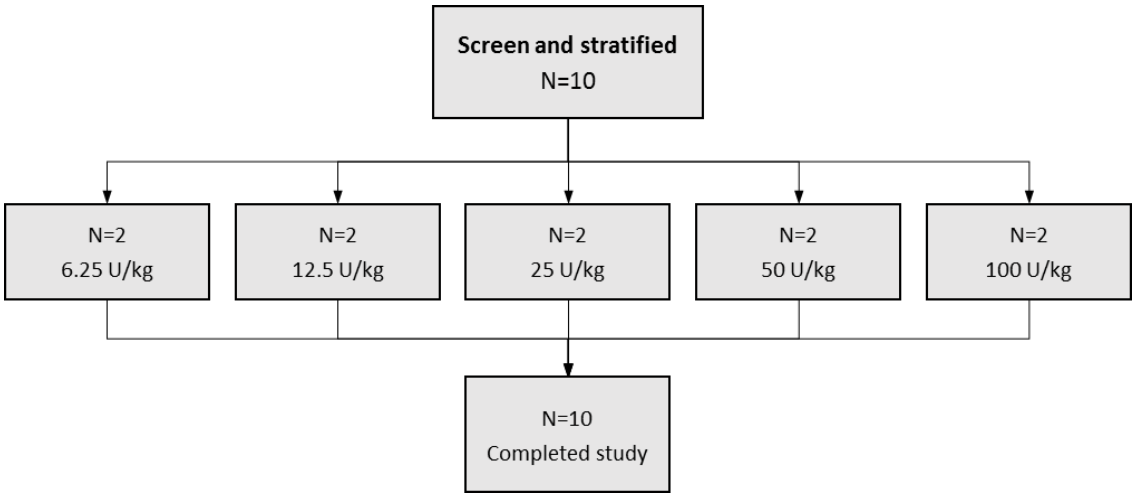
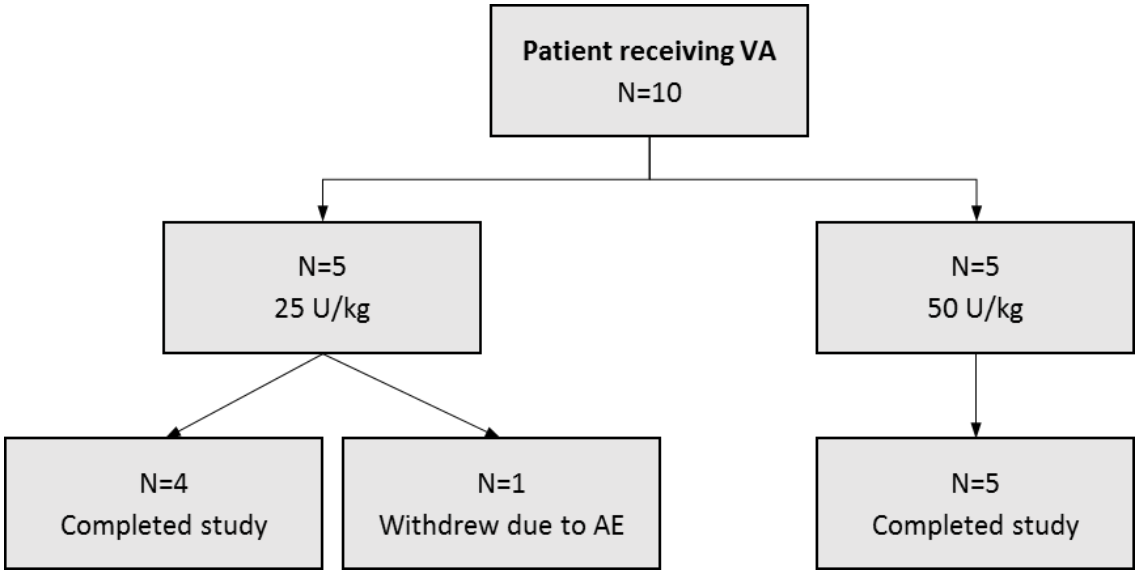
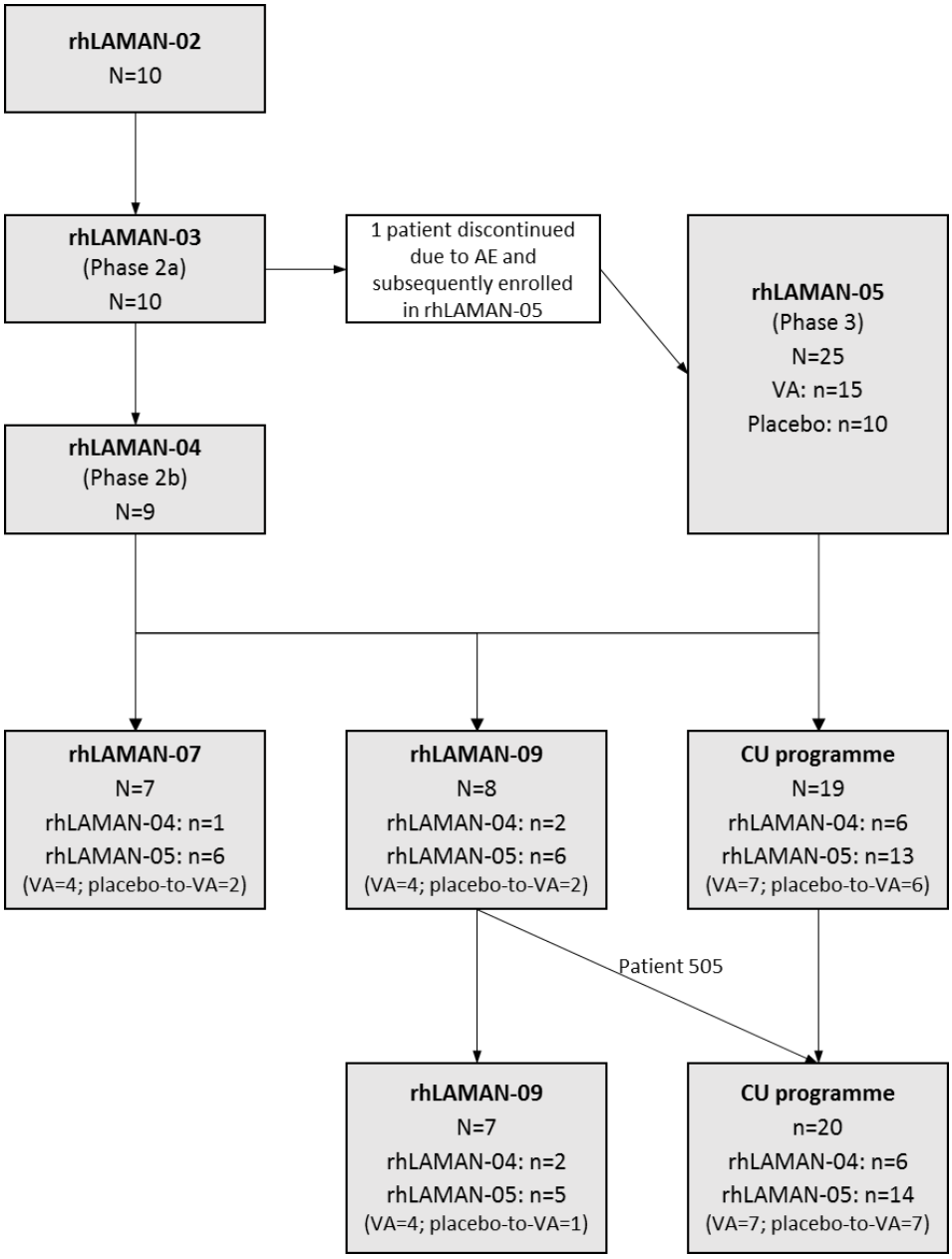


Figure 5: reproduction of Figure 7 from the CS:[2] rhLAMAN-03[15] patient disposition



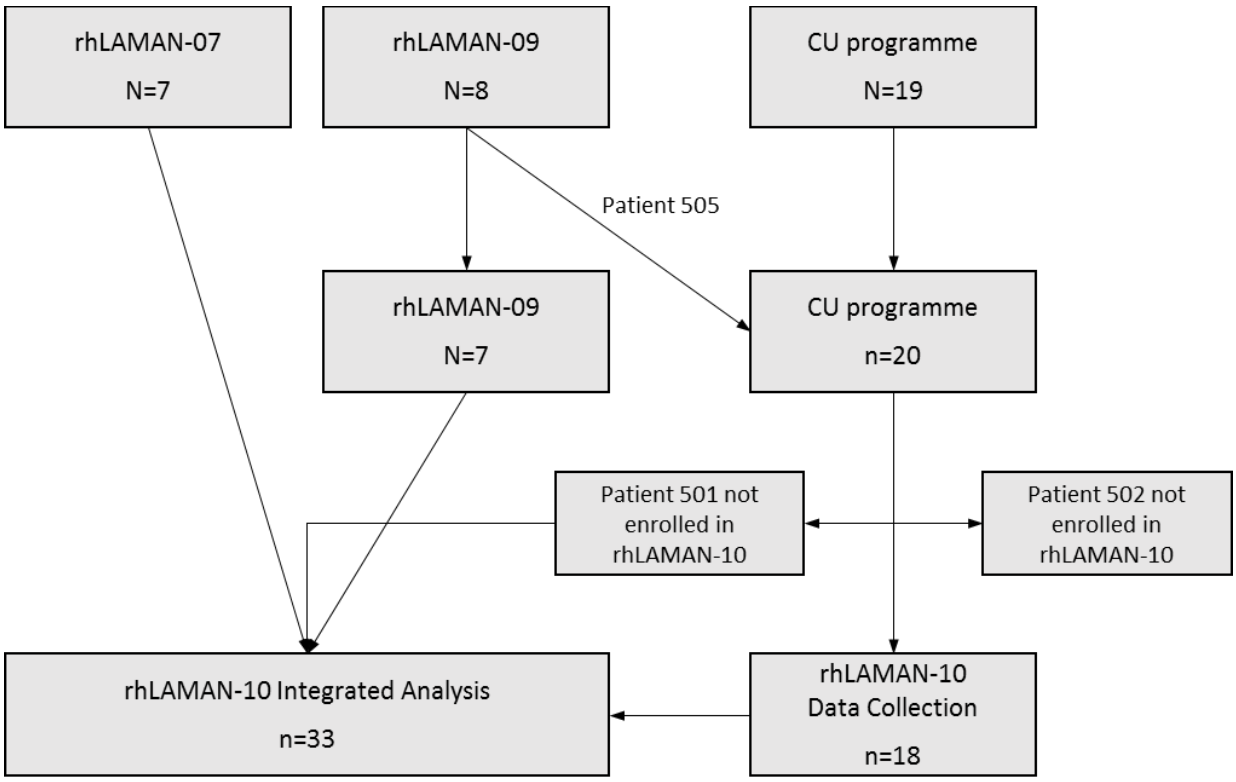
Abbreviations: AE, adverse event; VA, velmanase alfa.

Figure 6: reproduction of Figure 8 from the CS:[2] Patient disposition from Phase I to after-trial studies and compassionate use programme



Abbreviations: AE, adverse event; CU, compassionate use.

Figure 7: reproduction of Figure 9 from the CS:[2] Patient disposition from after-trial studies and compassionate use programme to rhLAMAN-10[1] data collection (CEV) and integrated data set analysis



Abbreviations: CU, compassionate use.
Note: See text for description.

Appendix 3: Patient status analysis: cut off points

Table 51: Reproduction of Table 18 from the CS[2]: Criteria for level of impairment per outcome

Outcome	Not/slightly impaired	Impaired	Seriously impaired
Serum oligosaccharide, µmol/L	0–1.5	>1.5–4.9	≥5
CSF oligosaccharides, µmol/L	0–2	2–7	≥7
Serum IgG, mg/mL	Reference range according to reference range in Cassidy (1974) (98)	4 to normal range	<4
3-MSCT, steps/min	>55	45–55	<45
6-MWT, % of predicted	>80–120	>50–80	≤50
FVC, % of predicted	>80–120	>50–80	≤50
FEV_1, % of predicted	>80–120	>50–80	≤50
PTA air conduction left ear, dBHL	≤25	26–55	≥56
PTA air conduction right ear, dBHL	≤25	26–55	≥56
PTA bone conduction best ear, dBHL	≤25	26–55	≥56
CHAQ disability index, score	0–1	>1–2	>2–3
CHAQ pain (VAS), score	0–1	>1–2	>2–3

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PTA, pure tone audiometry.

Appendix 4: Baseline characteristics of rhLAMAN-05[10] and rhLAMAN-10[1]

Table 52: reproduction of Table 16 from the CS[2]: Baseline characteristics of rhLAMAN-05[10]

Characteristic	VA (N=15)	Placebo (N=10)
Age, n (%)		
<12	4 (26.7)	2 (20.0)
12–<18	3 (20.0)	3 (30.0)
≥18	8 (53.3)	5 (50.0)
Female, n (%)	6 (40.0)	5 (50.0)
Male, n (%)	9 (60.0)	5 (50.0)
Race (white)	15 (100.0)	10 (100.0)
Weight, kg		
Mean (SD)	60.2 (21.5)	64.2 (12.2)
Height, metres		
Mean (SD)	1.51 (0.19)	1.61 (0.14)
BMI, kg/m^2		
Mean (SD)	25.1 (4.9)	24.7 (2.7)
3-MSCT, steps/min		
Mean (SD)	52.9 (11.2)	55.5 (16.0)
35–45, n (%)	1 (6.7)	3 (30.0)
45–55, n (%)	9 (60.0)	2 (20.0)
55–65, n (%)	3 (20.0)	1 (10.0)
≥65, n (%)	2 (13.3)	4 (40.0)
6-MWT, metres		
Mean (SD)	460 (72.3)	466 (140)
200–400, n (%)	2 (13.3)	3 (30.0)
400–500, n (%)	11 (73.3)	3 (30.0)
≥500, n (%)	2 (13.3)	2 (40.0)
FVC		
% of predicted, mean (SD)	81.7 (20.7)	90.4 (10.4)
L, mean (SD)	2.5 (1.1)	3.3 (0.9)
FEV_1		
% of predicted, mean (SD)	80.3 (19.6)	85.9 (18.2)
L, mean (SD)	2.3 (1.0)	2.9 (0.9)
PEF, L/s		
Mean (SD)	4.6 (2.2)	5.7 (1.6)
Leiter-R, years		
TEA-AME mean (SD)	6.3 (2.6)	6.6 (1.8)
TEA-VR mean (SD)	5.7 (1.7)	6.1 (1.6)
Serum oligosaccharides, µmol/L		
Mean (SD)	6.8 (1.2)	6.6 (1.9)
CSF oligosaccharides, µmol/L		
Mean (SD)	11.4 (3.0)	10.3 (2.9)
BOT-2 Total Score, points		
Mean (SD)	94.93 (41.68)	109.2 (51.84)
CHAQ disability index, score		
Mean (SD)	1.37 (0.82)	1.59 (0.64)
EQ-5D index, score		
Mean (SD)	0.61 (0.19)	0.61 (0.18)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation; TEA-AME, total equivalence age for attention and memory; TEA-VR, total equivalence age for visualisation and reasoning; VA, velmanase alfa.

Table 53: reproduction of Table 17 from the CS[2]: Baseline characteristics of patients included in the rhLAMAN-10[1] integrated data set, overall, by age and by parental study

Characteristic	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)	Phase I/II trial (N=9)	rhLAMAN-05[10] (N=24)
Age of starting treatment, years Mean (SD)	17.1 (7.8)	11.6 (3.7)	24.6 (5.3)	12.4 (3.8)	18.9 (8.3)
Female, n (%)	13 (39.4)	6 (31.6)	7 (50.0)	2 (22.2)	11 (45.8)
Male, n (%)	20 (60.6)	13 (68.4)	7 (50.0)	7 (77.8)	13 (54.2)
Race (white)	33 (100.0)	19 (100.0)	14 (100.0)	9 (100.0)	24 (100.0)
Weight, kg Mean (SD)	58.8 (18.6)	49.8 (19.7)	70.9 (6.2)	49.5 (17.5)	62.3 (18.1)
Height, metres Mean (SD)	1.53 (0.18)	1.46 (0.20)	1.63 (0.08)	1.46 (0.19)	1.55 (0.17)
BMI, kg/m^2 Mean (SD)	24.3 (4.3)	22.4 (4.2)	26.9 (2.9)	22.2 (3.9)	25.1 (4.3)
3-MSCT, steps/min Mean (SD)	53.60 (12.53)	54.04 (13.34)	53.00 (11.82)	52.63 (14.25)	53.96 (12.14)
6-MWT, metres Mean (SD)	466.6 (90.1)	454.2 (86.3)	483.4 (95.6)	452.8 (106.7)	471.8 (85.0)
FVC n % of predicted, mean (SD) L, mean (SD)	 29 84.9 (18.6) 2.65 (1.08)	 17 79.6 (16.4) 2.24 (0.93)	 12 92.5 (19.4) 3.23 (1.05)	 9 81.7 (14.1) 2.20 (0.87)	 20 86.4 (20.4) 2.86 (1.13)
FEV_1 n % of predicted, mean (SD) L, mean (SD)	 29 83.8 (17.6) 2.44 (1.00)	 17 79.0 (15.0) 2.06 (0.83)	 12 90.5 (19.3) 2.98 (1.00)	 9 82.2 (12.8) 2.05 (0.79)	 20 84.5 (19.6) 2.62 (1.05)
PEF, L/s n Mean (SD)	 29 4.85 (2.04)	 17 3.90 (1.58)	 12 6.20 (1.90)	 9 3.89 (1.50)	 20 5.29 (2.14)
Leiter-R TEA-VR, years Mean (SD)	5.88 (1.57)	5.40 (1.40)	6.53 (1.59)	5.69 (1.29)	5.95 (1.68)
Leiter-R TEA-AME, years n Mean (SD)	 24 6.51 (2.18)	 10 5.93 (2.11)	 14 7.03 (1.92)	 - -	 24 6.514
Serum oligosaccharides, µmol/L Mean (SD)	6.90 (2.30)	7.63 (2.52)	5.91 (1.54)	9.00 (2.74)	6.11 (1.53)

Characteristic	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)	Phase I/II trial (N=9)	rhLAMAN-05[10] (N=24)
CSF oligosaccharides, µmol/L Mean (SD)	10.64 (3.53)	10.65 (3.84)	10.62 (3.20)	10.33 (4.66)	10.75 (3.11)
BOT-2 total score, points Mean (SD)	107.0 (47.6)	101.9 (53.8)	113.9 (38.6)	120.7 (54.1)	101.9 (45.1)
CHAQ disability index, score Mean (SD)	1.36 (0.77)	1.22 (0.89)	1.55 (0.55)	0.97 (0.80)	1.51 (0.73)
EQ-5D index, score n Mean (SD)	 24 0.62 (0.17)	 10 0.70 (0.18)	 14 0.57 (0.14)	 - -	 24 0.62 (0.17)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five dimension; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation; TEA-AME, total equivalence age for attention and memory; TEA-VR, total equivalence age for visualisation and reasoning.

Appendix 5: PAS Results

Within the main document all cost-effectiveness analyses were undertaken using the list price of velmanase alfa. The company have agreed a patient access scheme (PAS) which takes the form of a simple discount, which reduces the list price from £886.61 (excluding VAT) per 10mg vial to [redacted] (excluding VAT) per 10mg vial.

This document contains the analyses conducted by the ERG using the PAS price of velmanase alfa. Table 49 contains the ERG's base case, subject to caveats described in the main report. Table 50 contains the scenario analyses performed.

Table 54: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case [redacted])**	**Adolescent (CS base case_[redacted])**	**Adult (CS base case [redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906;_[redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa			[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; WU – Walking Unassisted; WWA – Walking With Assistance

Table 55: Scenario Analyses run on the ERG's base case

	CPQ given individual change		
Analyses	**Paediatric (base case [redacted])**	**Adolescent (base case [redacted])**	**Adult (base case [redacted])**
Assuming 100% in the WU health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WWA health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WC health state	[redacted]	[redacted]	[redacted]
Assuming the average age per age band observed in rhLAMAN-10[1]	[redacted]	[redacted]	[redacted]
Assuming no improvements in health state after 12 months	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to surgery.	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to serious infection.	[redacted]	[redacted]	[redacted]
Assuming the costs of a severe infection are set to £2742	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to ventilation costs.	[redacted]	[redacted]	[redacted]
Assuming the UK MPS survey as the source for caregiver requirements.	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility	[redacted]	[redacted]	[redacted]
Including personal expenditure by the family	[redacted]	[redacted]	[redacted]
Including caregiver productivity losses	[redacted]	[redacted]	[redacted]
Assuming that patients treated with velmanase alfa have a utility gain of 0.05	[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; MPS – Mucopolysaccharidosis; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
Dominant refers to producing more health at fewer costs.