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

ERRATUM

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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 forced 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. Outcomes not listed in the NICE scope but measured in both trials included CSF oligosaccharides and CSF biopmarkers (tau, NFLp and GFAp).

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 between velmanase alfa and placebo 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 6-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 rhLAMAN-05 to be at generally low risk of bias and rhLAMAN-10 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 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. rhLAMAN-05 was at generally low risk of bias, though somewhat small.

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, in the opinion of the ERG, 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

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

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 typically 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 was granted a licence in March 2018 as "an enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis".

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) who are not clinically indicated for HSCT. The company has chosen to restrict their positioning of the drug in the treatment pathway to children aged 6 years or older who are not clinically indicated for HSCT. However, it should be noted that the licence does not restrict by age or by indication 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 £886.61 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 positioning of the treatment in the pathway in the UK 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.

However, 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 the patients included in the trials, 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 67). 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. The ERG note that the omission of psychiatric outcomes is because velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on these outcomes for patients, even though they are an important symptom of the disease.

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.

4.1.4 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 did not initially 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 initially judged 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). However, after information provided during the Fact Check by the company, two of these items were scored positively, and whilst the third (allocation concealment) remains somewhat unclear, it is likely allocation concealment was maintained. The ERG concluded that rhLAMAN-05 was at generally low risk of bias.

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 2: 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.	Yes	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. Additional information was provided by the company in their Fact Check (issue 16) of the report which stated "SAS program was used for the creation of the randomisation list. The program was generated by a statistician and validated according to internal procedures" The ERG were consequently able to score this item as "yes"
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.	Yes	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 was only specified during the Fact Check that outcome assessors were also blind. 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. Fact Check issue 17: Patients, investigators and staff (sponsor and clinical CRO) were blinded to treatment allocation (excluding the randomisation statistician who performed the randomisation and the programmer responsible for printing the sealed envelopes at the CRO). The "investigators" were also the "assessors" and were all personnel of the coordinating site (Copenhagen) and not external staff.
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.

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 2.

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

Table 3: 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-MSCT; **(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-MSCT; **(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)

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 [TEXT DELETED] licence does 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 [TEXT DELETED] licenced posology and dose.

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. The ERG note that the omission of psychiatric, language and other central nervous system outcomes is because velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on these outcomes for patients, even though they are an important symptom of the disease.

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

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-MSCT. 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-MSCT 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-MSCT. 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 4: 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

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)	8.20 (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	
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) [Text Deleted]	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)
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)

Table 5: 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), **p=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			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**	

from baseline (SD)																
Relative (%) change from baseline (SD)			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 (35.8), p=0.096		7.1 (22.0), p=0.071	
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	93.1 (21.7)	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			-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 (0.44)	

from baseline (SD)																
Relative (%) change from baseline (SD)			-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 (72.27)		-2.41 (45.03)	
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			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)	

from baseline (SD)															
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			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)	

from baseline (SD)																
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)	8.37 (4.20)	24	11.37(4.99)	15	11.76(4.99)	22	10.35(2.47)	2	12.21(6.23)	10	11.75(3.37)	4	NR	NR	11.42(4.52)	24
Absolute change from baseline (SD)			2.37(1.28), **p<0.001**		3.38(1.65), **p<0.001**		2.10(1.13)		3.33(1.47), **p<0.001**		2.95(2.06)		NR		3.05 (2.39, 3.71), **p=<0.001**	
Relative (%) change from baseline (SD)			34.03(23.26) **p<0.001**		47.03(27.26), **p<0.001**		31.46(27.46)		47.07(29.87), **p<0.001**		47.62(33.29)		NR		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.

(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 *achieved the MCID of ≥0.13 at -0.13 (SD 0.44)*). 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]

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. The ERG note that velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on CNS outcomes for patients, even though they are an important symptom of the disease.
- 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]

In addition, in relation to MCIDs and the interpretation of the trial outcomes:

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.

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 6: 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 placebo group vs

20.0% in the vlemanase alfa group respectively), diarrhoea (30.0% vs 13.3%), pyrexia (50.0% vs 40.0%) and ear discomfort (20.0% vs 0%).

Table 7: 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

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 to be at generally low 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

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-page 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 KOL interview 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]

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 8: 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, [redacted], 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.

Table 9: 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 10: 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]

[redacted]

[redacted] The data obtained within the survey were not used in the cost-effectiveness modelling.

[redacted]The base case and the scenario analyses are detailed below. [redacted]

[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]

[redacted]

[redacted] [TEXT DELETED]

Table 11: 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 – carer-reported	3	0.906 (0.000)	0.758 (N/A)	N/A	N/A
Scenario 1 – patient reported	3	0.918 (0.000)	0.642 (N/A)	N/A	N/A
Scenario 2†	5†	0.906 (0.000)	[redacted])	0.100 (N/A)	-0.011 (0.053)
Scenario 3	5†	0.906 (0.000)	0.503 (N/A)	0.100 (N/A)	-0.011 (0.053)
Scenario 4	5†	0.906 (0.000)	0.345 (N/A)	0.100 (N/A)	-0.011 (0.053)
rhLAMAN-10[1] baseline	24	0.652 (0.149)	0.577 (0.200)	N/A	N/A
rhLAMAN-10[1] Last observation	31	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

Table 12: 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	Interviews with UK KOLs
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	UK Expert Elicitation Panel
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 ventilation 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] five-year period, increasing from £[redacted] million in year 1 to [redacted] 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 therefore 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.

   [redacted] 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. Finally, the ERG believes 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 assumption in the model relating to transition probabilities

After the clarification period, the ERG identified an assumption 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 assumption in the model relating to costs post discontinuation of velmanase alfa

After the clarification period, the ERG identified an assumption 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.

Table 13: 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