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