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Velmanase alfa for treating alpha-mannosidosis: A Highly Specialised Technology Appraisal. Critique of the company's response to Technical Engagement

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Rider on responsibility for report

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

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Contributions of authors

Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. Sue Harnan and Matt Stevenson critiqued the new clinical evidence presented by the company. All authors were involved in drafting and commenting on the final report.

1 Introduction

This document is intended to be read alongside the evidence previously submitted by the company and the ERG's critiques. The manufacturer of velmanase alfa (VA) resubmitted evidence related to the clinical and cost-effectiveness of VA in the treatment of people with mild to moderate alpha-mannosidosis (AM) in March 2022.[1] The ERG provided a critique of this evidence, which following revision in the Factual Accuracy Check process, was submitted to NICE in April 2022.[2] The EAG report was then circulated in the Technical Engagement (TE) process where respondents were asked to provide comments related to three key issues, the first two of which were raised within the ERG report. The company[3] and one clinician, who treats patients at a tertiary centre, responded.

The three key issues identified by NICE were:

1) Utility gain associated with VA treatment
2) Disease progression after treatment with VA
3) Appropriate population and inclusion of (the) rhLAMAN-08 study

For information, the third key issue was not included in the ERG report as rhLAMAN-08 was a study in paediatric patients and the ERG had been informed that this was outside of the scope of the appraisal.

In addition to making comments on these three issues, the company commented on the:

4) availability of longer-term data from rhLAMAN-07 and rhLAMAN-09
5) critique of the methodology of the Etoile Alpha study
6) definition of a responder (including the categorisation of super-responders)
7) expert elicitation performed in 2017 / change in the baseline distribution of health states

The company also made changes to its base case economic model, with the principal change being the increase in the assumed utility gain, over and above that for each health state, by being on VA treatment. In the company's submission of March 2022[1], paediatric and adolescents this value was assumed to by 0.10 but this was increased to 0.254 in the company's response to TE.[3] The new base case incremental cost effectiveness ratios (ICERs) presented in terms of cost per quality-adjusted life years (QALY) estimated by the company were £88,912 for a paediatric population, £126,214 for an adolescent population, and £185,872 for an adult population.

The company performed multiple sensitivity analyses, one of which markedly reduced the ICER which was the assumption that VA treatment would permanently stop disease progression in those that respond. Applying this assumption decreased the ICER to £56,162 for paediatric patients, £88,248 for adolescent patients, and £123,986 for adult patients.

Scenario analyses related to super-responders were seen to markedly reduce the ICER: assuming a permanent delay in progression for super-responders remaining on VA treatment and an increased withdrawal rate at year 1, decreased the ICER to £47,545 for paediatric patients, £77,820 for adolescent patients, and £93,241 for adult patients.

When applying the observed utility improvement observed in rhLAMAN-10[4] the ICERs ranged from £141,830 to £216,847 for paediatric patients dependent on the assumed duration for which disease progression would be halted (between 1 and 5 years). Corresponding values were £192,595 to £277,411 for adolescent patients and £244,483 to £370,684 for adult patients.

The evidence review group (ERG) does not believe that compelling evidence has been provided to alter the Appraisal Committee's decision regarding the 0.05 utility gain associated with VA treatment. Similarly, there has been no compelling evidence that treatment with VA would completely halt disease progression in responders for a period of five years.

Considering the results of all analyses performed, the ERG believes that the ICERs will likely be in excess of £150,000 for paediatric patients, and would be considerably higher for adolescent and adult patients.

2 Critique of the responses provided by the company and clinician

This section categorises responses into the key issues highlighted by NICE and the additional issues raised by the company.

2.1 Utility gain associated with velmanase alfa treatment

The company has reiterated that it believes that the 0.05 utility value associated with VA treatment preferred by the Appraisal Committee in its withdrawn Final Evidence Document (FED) of October 2019 is too low. In its submission in March 2022[1], the company assumed values of 0.10 for all patients. However, at TE the company states that its preference for the utility gain in paediatrics and adolescents is now 0.254 rather than 0.10.[3]

The key arguments put forward by the company are that:

- The multi-organ health benefits that are associated with VA treatment are not adequately captured in the company's walking ability-based model
- The minimally important difference reported for the EQ-5D was a value of 0.074 and patients and clinicians reported clinically relevant improvements
- The ERG has overstated the level of double counting that may occur in the reduced utility associated with walking ability-based health states
- The level of improvement within a walking ability-based health state are not captured fully in the model
- Surrogates end points mapped to utility values are preferable to directly recorded EQ-5D-5L utility gains

Each point has been expanded upon and critiqued by the ERG in the following sub-sections.

2.2.1 The multi-organ health benefits that are associated with VA treatment are not adequately captured in the company's walking ability-based model

The company cites the following list as benefits of VA treatment that would not be captured in the walking ability-based model: "*within health-state functional improvements (including additional mobility and lung function); reductions in minor infections (including ear, nose, throat and respiratory infections), reductions in minor surgeries; improvements in hearing impairment, non-joint pain, upper extremity and fine motor deficits (upper limb coordination, manual dexterity, running ability, strength and balance), fatigue, mental health (anxiety and depression), cognitive function, psychiatric events and increased independence in activities of daily living.*"

No formal estimation of the comparative benefit associated with VA treatment compared with best supportive care (BSC) in terms of incidence and utility impact has been provided by the company. As such, it is difficult for the ERG to critique the company's position regarding the true benefit provided by VA treatment. The ERG notes that the committee accepted that there is additional gain associated with VA treatment and had written in the withdrawn FED that it "*was not convinced that there were sufficient benefits not otherwise captured to justify an additional utility gain of 0.1. However, it considered that it was plausible that velmanase alfa could provide some additional benefits (for example, reduction in pain) so assuming no additional utility (gain of 0) was not appropriate. The committee concluded that an additional utility gain of 0.05 for people having velmanase alfa was reasonable to use in its decision-making.*". Based on this point the ERG sees no compelling reasons to change from the appraisal committee's original decision. Indeed, the EQ-5D-5L data provided by the company in change in baseline value for patient's in rhLAMAN-10[4] was a value of 0.05 (for all patients) which was formed of a composite of a 0.08 change in children and a 0.03 change in adults. These values are more consistent with the 0.05 value preferred by the appraisal committee than the values of 0.254 and 0.10 preferred by the company.

2.2.2 The minimally important difference reported for the EQ-5D was a value of 0.074 and patients and clinicians reported clinically relevant improvements

The company cites a paper published in 2005 which estimates the minimally important difference (MID) on the EQ-5D.[5] This paper provides a midpoint value of 0.074 (range -0.011–0.140). The company contends that as "*many health improvements were reported with velmanase alfa that were clinically relevant to both patients and clinicians this would suggest that the on-treatment utility benefit with velmanase alfa should be above the MID for EQ-5D.*" which presumably refers to the midpoint value of 0.074. The ERG believes the company is using this paper to support its preferred values of 0.254 and 0.10 utility gains rather than the 0.05 value preferred by the appraisal committee.

The ERG notes that to its knowledge there is no precedent for the use of this paper in NICE appraisals and that this source has not been cited in either the NICE 'Methods Guide' produced in 2013[6], or the most recent Methods Guide (2022).[7] Additionally, the populations studied in the Walters and Brazier paper[5] do not closely resemble that with alpha-mannosidosis and that the MID has a wide confidence interval that spans zero, The ERG therefore believes that using directly reported EQ-5D is much preferable than making inferences from Walters and Brazier.

2.2.3 The ERG has overstated the level of double counting that may occur in the reduced utility associated with walking ability-based health states

Within its critique of the company's submission in March 2022, the ERG stated that applying a "*utility gain over and above health state residency would introduce an element of double counting*" although

the level of such double counting was not stated.[2] The company has referred to the list of conditions provided in Section 2.2.1 and questioned in which condition gains would be included in the health states of the walking ability-based model. The ERG has referred back to the source of the utility values for the walking unassisted and the walking with assistance health states, which comes from rh-LAMAN-10 study.[4] Following this, it agrees that the level of double-counting would be much less (and plausibly zero) compared with when the source for baseline utility was not from a directly relevant study. As such, the ERG believes that this is not a key issue.

2.2.4 The level of improvement within a walking ability-based health state are not captured fully in the model

Due to the company's model structure being based on walking ability, patients in the best health state 'walking unassisted' could not improve without consideration of the other benefits that were listed in Section 2.2.1. The company states that in rhLAMAN-10[4], 70% of patients were in the walking unassisted health state at baseline and thus could not improve utility without the use of an additional gain due to VA treatment. The company provides additional data on within health state improvements and reports details of 1 UK-based patient, who remained within the walking with assistance health state, but had a greater EQ-5D-5L value (0.758) compared with the average for this health state (0.577). The ERG cautions that this is a small sample size, and that other patients in rhLAMAN-10 in the walking with assistance health state must have lower EQ-5D-5L levels to arrive at the average of 0.577. It is anticipated that within health state benefits will be captured, to some degree, by the additional utility gain of 0.05 preferred by the committee. The additional utility gain is uncertain, but the ERG accepts that improvements in EQ-5D-5L values would be an appropriate way to measure such gains.

2.2.5 Surrogate end points mapped to utility values are preferable to directly recorded EQ-5D-5L utility gains

The company had access to EQ-5D-5L data for 24 patients in rhLAMAN-10[4], 10 of which were under 18 years of age and 14 of which were 18 years or older. These data suggested a combined utility gain of 0.05 although potentially differed between age category, being 0.08 for paediatric and adolescent patients and 0.03 for adult patients.

The company has considered utility estimates measured from two surrogate end points (forced vital capacity (FVC) and the six-minute walk time (6MWT)) The company has assumed, based on a previous NICE highly specialised technology appraisal[8] that every litre improvement in FVC was associated with an improvement in utility of 0.20 and that every 10 metres of additional 6MWT was associated with an improvement in utility of 0.02. The company assumes that these gains are additive, which likely over-estimates the utility loss as the same underlying condition can be penalised by both FVC and 6MWT.

Based on the improvements in FVC and 6MWT, the company estimates that for all patients the gain in utility would be 0.125 (0.08 from improvements of FVC (n=28) and 0.045 from improvements in 6MWT (n=33)). This is noticeable bigger than the observed EQ-5D-5L increase of 0.05 (n=24).

The surrogate-based estimate of utility gain was larger for patients under 18 years of age (0.258) which consisted of a 0.180 gain associated with FVC (n=17) and a 0.078 gain associated with 6MWT (n=19) which was markedly larger than the directly observed value of 0.08 (n=10) using the EQ-5D-5L. For adult patients the surrogate-based estimate of 0.04 (all of which came from FVC gains (n=12) and none from 6MWT (n=13)) was similar to the directly observed value of 0.03 (n=14).

Whilst the ERG acknowledges that fewer patients under the age of 18 completed the EQ-5D-5L than completed the surrogate-based tests, the ERG believes that the directly observed values are more appropriate for use in the decision problem. The ERG believes it would be informative to validate the surrogate-based estimates by comparing the estimated gain in utility associated with surrogates with the EQ-5D-5L values, only for those patients who had completed the EQ-5D.

The company decided to use the surrogate-based estimate of utility gain from [redacted] patients in the Etoile Alpha study, which was associated with a utility gain of 0.254, (0.220 from FVC gains and 0.034 from 6MWT gains). [redacted] The ERG additionally notes that adding a 0.25 utility gain to the 0.652 utility value for the walking without assistance would result in a utility value of 0.902, which is on a par for values in people without serious diseases, which may lack face validity.

2.2 Disease progression after treatment with VA

In its report following the company's March 2022 submission, the ERG suggested that the company "*provide a more robust and transparent analysis (e.g., including all time points for all patients who are classed as responders)*".[2] This was because the ERG believed that the data supplied did not provide compelling evidence that disease progression would be halted for 5 years.

The ERG also noted that it was not clear whether the available data was generalisable to a) responders (as defined by the European Medicines Agency (EMA) responder analysis, that is, responding in ≥2 domains out of pharmacodynamic, function and health related quality of life (HRQoL)) or b) patients who meet the company's proposed starting and stopping criteria. In its technical engagement response[3], the company have provided individual patient data (IPD) for patients from the Etoile Alpha study sub-grouped into those who have received less than 5 years of VA treatment and those that have had 5 years or more of VA treatment. The format of these data does not lend itself to a quick review, or in providing a clear overview of the direction of effect at a population level. The company state that "*Aggregated*

data by specific timepoints have been requested", but this were presumably not available within the time frame of the company's technical engagement response.

The ERG has considered the IPD data, and is of the opinion that the data are not sufficient to either support or refute a claim of no disease progression for 5 years. This does not seem to be an area of dispute, since the company state in its Technical Engagement response that "*Chiesi agree with the ERG that there is some uncertainty in the precise delay in disease progression with the current data, but further data collection in ongoing trials and registry will be able to reduce this uncertainty*".[3] It is not possible to tell which of patients are either a) responders or b) meet the starting and stopping criteria proposed by the company as not all relevant outcomes are reported (HRQoL measures, short physical performance battery (SPPB) test, sniff nasal inspiratory pressure (SNIP) test and data relating to infections are missing). This means the ERG cannot tell whether progression may have been observed in any of these outcomes, in patients who have been treated for more than 5 years.

In the absence of empirical data, the question of whether disease progression will be halted for 5 years (or longer) becomes a qualitative judgement about what the impact would be of the proposed starting and stopping criteria. This is discussed further in Section 4.

The company also cites an interview with a UK clinician as supporting no disease progression for at least 5 years.[9] The ERG was not able to find an explicit question about disease progression, but the clinician did express that the results of Etoile Alpha were consistent with their own experiences, or that theirs were potentially more positive. The ERG also notes that in this interview, the model assumptions presented to the clinician included mean disease progression on VA of 3.48, 4 and 2.68 years respectively for children, adolescents and adults (p7, UK clinical expert interview).[10] The ERG could not find a record of whether the clinician was asked a question about the model assumptions presented.

2.3 Appropriate population and inclusion of (the) rhLAMAN-08 study

The ERG believes that this is a question that needs to be answered by NICE as it directly relates to whether there should be a divergence from the final scope that was issued in November 2017.[11] Changing the scope mid-appraisal would not be accordance with standard process, but NICE may decide, pragmatically, that this would be a reasonable exception. The ERG has not critiqued rhLAMAN-08 at this point.

2.4 Availability of longer-term data from rh-LAMAN-07 and rh-LAMAN-09

The company states that longer-term data from rh-LAMAN-07 and rh-LAMAN-09 will likely be available in late 2022 or early 2023. Across these two trials, an additional 21 patients are included, 13 of whom have follow-up data for longer than 9 years. The company states that the assumption of no

progression for 5 years "*is likely to be strengthened when final rhLAMAN-07/-09 data are available*". The ERG is unable to comment on this assertion.

2.5 Critique of the methodology of the Etoile Alpha study

The ERG has discussed this within sub-sections.

2.5.1 Unclear times of outcome assessment

The company have clarified the timing of outcome assessment for Etoile Alpha. The IPD data from Etoile Alpha is discussed in Section 2.2.

2.5.2 Missing data points

The company clarifies the reasons for some of the missing data, which include difficulties with measuring HRQoL in children, or those with cognitive impairment. The ERG believes it is plausible that these data may not be missing at random, and therefore has the potential to select patients with better outcomes and potentially biasing the observed data. The company states "*In the absence of missing data for specific clinical outcomes in some patients, evidence of clinical improvement can be assessed in the case reports of each patient that were provided in the submission*"; the ERG did not have sufficient time to conduct such analyses, and believes the onus of doing so rests with the company.

2.5.3 Age adjustment of results

In relation to age-adjustments for the 6MWT and the three-minute stair climb test (3MSCT) the company stated that only five patients were under 10 years of age. The ERG notes that a further four patients were adolescents, resulting in a total of 9/16 (56%) who had the potential for growth to affect outcomes. The company cites an expectation that the 6MWT would decline over time in patients, rather than increase, but does not state if this is an expectation in children, or adults, or both. The company also cites natural history data that show in patients under 18 years of age that FVC declines over time, and that untreated children grow slowly, only reaching the 3rd percentile (or lower) of height. These data are supportive of the FVC improvements seen in the Etoile Alpha study not being due to growth, but do not refute entirely the possibility that growth could account for some improvements in the 6MWT and the 3MSCT.

2.5.4 Severity of disease at baseline

The company explains that there are three types of AM, with type 1 and 2 being eligible for treatment even when their disease has progressed to a severe state. The ERG was not able to consult with their clinical advisors regarding this explanation, or how widely accepted the cited system of classification is, within the timescales of the TE process. The company stated that "*some patients in Etoile Alpha may not be eligible for velmanase alfa according to any starting criteria that are agreed; however, the*

definition of patients who are "severely impaired" included in this study is not the same as the "severe" type 3 phenotype that is not indicated for treatment with velmanase alfa according to the label". The impact of these patients on the outcomes reported in the Etoile Alpha study is unclear.

2.6 Definition of a responder (including the categorisation of super-responders)

Within the base case model, patients who are responders at one year, as defined by the EMA responder analysis criteria, remain on treatment. Responders are those who meet the minimum clinically important difference in at least one endpoint in ≥2 domains (Pharmacodynamic domain: serum oligosaccharides; Functional domain: 3MSCT, 6MWT, FVC%; HRQoL domain, the childhood Health Assessment Questionnaire (CHAQ) – disability index, CHAQ – pain visual analogue scale). This definition means that responders can show no response (or indeed, deterioration) in all the other endpoints within a domain, which could conceivably constitute disease progression. A value of 10% discontinuation of VA treatment per year was applied, but was not assumed to be directly related to efficacy but "*due to reasons including IRRs, non-compliance, patient preferences and/or occurrence of other life-limiting conditions (e.g., cancer)*". This may underestimate discontinuation rates if patients also discontinued treatment due to the proposed stopping criteria. Further discussion of the implications of the starting and stopping criteria proposed by the company is contained in Section 4.

The company performs scenario analyses relating to a subgroup of patients who are classed as "super-responders". Super-responders have to have a response in all three of the following domains:

- Pharmacodynamic (serum oligosaccharides)
- Functional: 3MSCT or 6MWT or FVC (% predicted)
- QoL: CHAQ disability index or CHAQ pain visual analogue scale

When comparing the super-responder criteria to the proposed starting and stopping criteria it appears that a patient could be a super-responder, but not meet the criteria, since the super-responders only have to meet 3 criteria (oligosaccharides plus 2 clinical), whilst for the continuation criteria they must meet 5 criteria (oligosaccharides plus 4 clinical). Furthermore, the criteria for the categories do not always use the same outcome measures and thus, a super-responder could have a response in the 3MSCT endpoint, which is not in either the starting or stopping criteria). Equally, a patient could be a responder by having a response in SPPB, SNIP, ejection fraction and antibiotic use but not meet the criteria to be a super-responder, since these outcomes are not related to the definition of super-responder.

In the scenario analyses, 47% of children and 64% of adult patients would not continue with VA treatment beyond the first year, compared with 13% in the model base case. The company assume that the discontinuation rate per year in super-responders remains at 10% as in its base case.

2.7 Expert elicitation performed in 2017 / change in the baseline distribution of health states

The company highlights that the elicitation exercise was performed in 2017 before there was experience of long-term use of VA. The company believes that this means that the treatment effect of VA is likely to be underestimated. The ERG cannot determine the likely direction, or magnitude, of any inaccuracy in the elicited values as it plausible that the clinicians had been overly optimistic in their estimates of potential benefit.

The company also performed an analysis such that the baseline distribution of health states that patients start in the model accurately reflects the baseline clinical data in the final analysis of the 33 patients included rhLAMAN-10, published in Borgwardt *et al*.[12] The ERG believes that this distribution should be used in the base case rather than a scenario analysis. The ERG notes that in addition to changing the distribution between the walking unassisted, walking with assistance, and wheelchair dependent health states, the final analysis changed a patient's age group from an adolescent to an adult, the reason for this amendment is unknown.

3 Cost-effectiveness results

This section provides the ICERs presented by the company and the results of exploratory analyses undertaken by the ERG.

3.1 The company's revised base case analyses excluding any impact of the proposed MAA

The company's revised base case results are reproduced in Table 1 (for paediatric patients), in Table 2 (for adolescent patients) and in Table 3 (for adult patients). In all base case scenarios, excluding paediatric patients, the cost per QALY gained is in excess of £100,000 which is the threshold published by NICE where the (undiscounted) QALY gain is less 10. The incremental undiscounted QALYs were under [redacted] for all age groups evaluated by the company in its base case.

Table 1: The company's revised base case results - paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	[redacted]	14.56	[redacted]	-	-	-	
VA	[redacted]	16.74	[redacted]	[redacted]	2.18	[redacted]	£88,912

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; VA, velmanase alfa

Table 2: The company's revised base case results - adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	[redacted]	14.35	[redacted]	-	-	-	
VA	[redacted]	16.59	[redacted]	[redacted]	2.24	[redacted]	£126,214

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; VA, velmanase alfa

Table 3: The company's revised base case results - adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	[redacted]	13.92	[redacted]				
VA	[redacted]	16.25	[redacted]	[redacted]	2.33	[redacted]	£185,872

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; VA, velmanase alfa

In addition to the base case analyses, the company ran multiple scenario analyses. The ERG could not recreate the reported answers for the following scenarios: using a discount rate of 1.5% for adult patients; including carer productivity losses (which the ERG believes also included personal and carer

expenditure); and the time horizon of 20 years for adult patients (where reported incremental life years gained was zero) although these do not impact on the decision problem in the opinion of the ERG.

The company also ran two additional scenario analyses that the ERG believes are relevant for inclusion in the ERG's base case, these were:

- Updating the baseline distributions of walking abilities as reported in the final analysis of rhLAMAN-10[12] (as discussed in Section 2.7)
- Allowing patients in the BSC arm to improve health state by adding 10% to the chances of improvement for both VA and BSC as was observed in rhLAMAN-05.[13]

The company ran two further scenario analyses related to 'super-responders', as discussed in Section 2.6. The first changed the number of patients withdrawing after one year from 13.3% to 47.4% in paediatrics and adolescents and from 13.3% to 64.3% in adults; the resulting ICERs were £74,435 in paediatric patients, £108,786 in adolescent patients and £128,790 in adult patients. The second additionally assumed that super-responders would never have disease progression whilst remaining on VA treatment, compared with five years halting of progression in the company's base case; the resulting ICERs were £47,545 in paediatric patients, £77,820 in adolescent patients and £93,241 in adult patients. The ERG notes that there is considerable uncertainty in the duration of any delay in disease progression for super-responders and also that reducing the number of patients assumed to continue on treatment reduces the ICER.

To inform the committee, the ERG has shown the impact of four changes in the company's model that differ between the company's base case and the preferred assumptions of the NICE Appraisal Committee. The first two relate to changes in the assumed utility gain and the duration for which disease progression is halted; the ERG believes that both parameters have considerable uncertainty. The latter two, which relate to changes in the costs associated with home infusions as was the case in earlier submission and the costs of care, are deemed to be appropriate by the ERG. These analyses showing the impact of the four changes are shown in Table 4 to Table 6.

Table 4: Impact of changes from the Appraisal Committee's preferred assumptions and in incorporating costs for home infusions – paediatric patients

	Incremental (VA- BSC)		
	Costs	**QALYs**	**ICER**
Company's base case	[redacted]	[redacted]	£88,912
1) Changing utility gain to 0.05	[redacted]	[redacted]	£139,687
2) Assuming halt in disease progression for 1 year in responders to VA	[redacted]	[redacted]	£127,478
3) Removing the costs of home infusions	[redacted]	[redacted]	£76,947
4) Using the company's original cost of care	[redacted]	[redacted]	£128,034
5) Combining 1), 2), 3) and 4)	[redacted]	[redacted]	£199,685

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

Table 5: Impact of changes from the Appraisal Committee's preferred assumptions and in incorporating costs for home infusions – adolescent patients

	Incremental (VA- BSC)		
	Costs	**QALYs**	**ICER**
Company's base case	[redacted]	[redacted]	£126,214
1) Changing utility gain to 0.05	[redacted]	[redacted]	£195,981
2) Assuming halt in disease progression for 1 year in responders to VA	[redacted]	[redacted]	£170,484
3) Removing the costs of home infusions	[redacted]	[redacted]	£114,496
4) Using the company's original cost of care	[redacted]	[redacted]	£178,440
5) Combining 1), 2), 3) and 4)	[redacted]	[redacted]	£271,118

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

Table 6: Impact of changes from the Appraisal Committee's preferred assumptions and in incorporating costs for home infusions – adult patients

	Incremental (VA- BSC)		
	Costs	**QALYs**	**ICER**
Company's base case	[redacted]	[redacted]	£185,872
1) Changing utility gain to 0.05	[redacted]	[redacted]	£209,929
2) Assuming halt in disease progression for 1 year in responders to VA	[redacted]	[redacted]	£269,215
3) Removing the costs of home infusions	[redacted]	[redacted]	£170,481
4) Using the company's original cost of care	[redacted]	[redacted]	£191,978
5) Combining 1), 2), 3) and 4)	[redacted]	[redacted]	£294,131

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

3.2 Exploratory results run by the ERG

3.2.1 Methods

The ERG believed that using the baseline distribution from the final rhLAMAN-10 analysis and allowing patients on BSC to improve, as was observed in rhLAMAN-05[13], both described in Section 3.1, were appropriate amendments to the company's base case. Results were generated incorporating these changes.

Having changed the baseline distributions of walking ability and allowing those on BSC treatment to improve, the ERG used the company's model to perform exploratory analyses changing the duration at which it was assumed that disease was halted for responders to VA and changing the utility associated with VA treatment. These analyses were conducted due to the large uncertainty in the company's assumptions in the base case relating to the utility gain whilst on VA treatment (0.254 for paediatric and adolescent patients and 0.10 for adult patients) and the duration of halting disease progression (5 years for patients responding and remaining on VA treatment). In the ERG's exploratory analyses, the duration that disease progression was assumed halted in responders to VA treatment ranged from 1 year, which is associated with initial response to treatment to the five years assumed in the company's base case. These analyses were performed assuming the 0.10 utility increase associated with VA treatment preferred by the company prior to technical engagement, and the 0.05 value preferred by the Appraisal Committee in the FED for adult patients, and also at the 0.254 value preferred by the company for paediatric and adolescent patients.

The ERG ran one additional set of scenario analyses that used the observed EQ-5D-5L increases shown in rhLAMAN-10, which were increases of 0.08 for paediatric and adolescent patients, and 0.03 for adult patients, including the updated distributions for walking ability, allowed patients on BSC to improve, and varied the duration of time for which it was assumed that disease progression would be halted for ranging from 1, to 5 years. The ERG notes that if any patient had also improved in walking ability state, then the 0.08 and 0.03 increases which are assumed independent of walking ability would be over-estimated.

3.2.2 Results

3.2.2.1 Changing the baseline distribution for walking health states and allowing patients to improve on BSC treatment

It is seen that when the new baseline distributions for walking health state are used and it is assumed that patients can improve on BSC treatment, the ICERs increase (Table **7** to Table 9) compared with the company's base case.

Table 7: Impact of the new baseline distributions for walking ability and allowing for improvement for patients on BSC – paediatric patients

Description	Incremental (VA- BSC)		ICER
	Costs	QALYs	
Company's base case	[redacted]	[redacted]	£88,912
1) New baseline distributions for walking ability	[redacted]	[redacted]	£95,107
2) Increase of improvement of 10% for VA and BSC	[redacted]	[redacted]	£92,290
3) Combining 1) and 2)	[redacted]	[redacted]	£96,496

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

Table 8: Impact of the new baseline distributions for walking ability and allowing for improvement for patients on BSC – adolescent patients

Description	Incremental (VA- BSC)		ICER
	Costs	QALYs	
Company's base case	[redacted]	[redacted]	£126,214
1) New baseline distributions for walking ability	[redacted]	[redacted]	£130,413
2) Increase of improvement of 10% for VA and BSC	[redacted]	[redacted]	£130,521
3) Combining 1) and 2)	[redacted]	[redacted]	£132,852

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

Table 9: Impact of the new baseline distributions for walking ability and allowing for improvement for patients on BSC – adult patients

Description	Incremental (VA- BSC)		ICER
	Costs	QALYs	
Company's base case	[redacted]	[redacted]	£185,872
1) New baseline distributions for walking ability	[redacted]	[redacted]	£196,719
2) Increase of improvement of 10% for VA and BSC	[redacted]	[redacted]	£194,824
3) Combining 1) and 2)	[redacted]	[redacted]	£203,104

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

3.2.2.2 Varying the assumed utility gain associated with VA treatment and the duration for which disease progression is halted by VA treatment

These analyses build on those reported in 3.2.2.2. The results are contained in Table 10 for a paediatric population, Table 11 for an adolescent population, and Table 12 for an adult population. The incremental undiscounted QALYs were under [redacted] for all scenarios evaluated by the ERG in these tables.

Table 10: ERG exploratory results for a paediatric population varying the utility increase associated with VA treatment and the duration for which disease progression is halted

Description	Assuming an increased utility of 0.05 related to VA treatment			Assuming an increased utility of 0.10 related to VA treatment			Assuming an increased utility of 0.254 related to VA treatment		
	Incremental			Incremental					
DOHDP (years)	Costs (£)	QALYs	ICER (£ / QALY gained	Costs (£)	QALYs	ICER (£ / QALY gained	Costs (£)	QALYs	ICER (£ / QALY gained
1	[redacted]	[redacted]	£241,969	[redacted]	[redacted]	£202,809	[redacted]	[redacted]	£135,345
2	[redacted]	[redacted]	£209,460	[redacted]	[redacted]	£178,119	[redacted]	[redacted]	£121,927
3	[redacted]	[redacted]	£185,748	[redacted]	[redacted]	£159,651	[redacted]	[redacted]	£111,430
4	[redacted]	[redacted]	£167,995	[redacted]	[redacted]	£145,563	[redacted]	[redacted]	£103,143
5	[redacted]	[redacted]	£154,331	[redacted]	[redacted]	£134,564	[redacted]	[redacted]	£96,496

Abbreviations: BSC, best supportive care; DOHDP, duration of halting disease progression; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

Table 11: ERG exploratory results for an adolescent population varying the utility increase associated with VA treatment and the duration for which disease progression is halted

Description	Assuming an increased utility of 0.05 related to VA treatment			Assuming an increased utility of 0.10 related to VA treatment			Assuming an increased utility of 0.254 related to VA treatment		
	Incremental			Incremental					
DOHDP (years)	Costs (£)	QALYs	ICER (£ / QALY gained	Costs (£)	QALYs	ICER (£ / QALY gained	Costs (£)	QALYs	ICER (£ / QALY gained
1	[redacted]	[redacted]	£307,557	[redacted]	[redacted]	£260,395	[redacted]	[redacted]	£176,862
2	[redacted]	[redacted]	£271,180	[redacted]	[redacted]	£232,577	[redacted]	[redacted]	£161,685
3	[redacted]	[redacted]	£244,513	[redacted]	[redacted]	£211,717	[redacted]	[redacted]	£149,822
4	[redacted]	[redacted]	£224,375	[redacted]	[redacted]	£195,696	[redacted]	[redacted]	£140,417
5	[redacted]	[redacted]	£208,782	[redacted]	[redacted]	£183,129	[redacted]	[redacted]	£132,852

Abbreviations: BSC, best supportive care; DOHDP, duration of halting disease progression; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

Table 12: ERG exploratory results for an adult population

DOHDP	Assuming an increased utility of 0.05 related to VA treatment			Assuming an increased utility of 0.10 related to VA treatment		
	Incremental			Incremental		
Duration (years)	Costs (£)	QALYs	ICER (£ / QALY gained	Costs (£)	QALYs	ICER (£ / QALY gained
1	[redacted]	[redacted]	£343,945	[redacted]	[redacted]	£291,397
2	[redacted]	[redacted]	£301,828	[redacted]	[redacted]	£259,228
3	[redacted]	[redacted]	£271,389	[redacted]	[redacted]	£235,419
4	[redacted]	[redacted]	£248,583	[redacted]	[redacted]	£217,263
5	[redacted]	[redacted]	£231,035	[redacted]	[redacted]	£203,104

Abbreviations: BSC, best supportive care; DOHDP, duration of halting disease progression; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

3.2.2.3 Using the observed EQ-5D-5L utility gains observed in rhLAMAN-10.

These analyses build on those reported in 3.2.2.2 and assume a utility gain of 0.08 for paediatric and adolescent patients and 0.03 for adult patients. The results are contained in Table 13 for paediatric and adolescent populations, and Table 14 for an adult population. The incremental undiscounted QALYs were under [redacted] for all scenarios evaluated by the ERG in these tables.

Table 13: ERG exploratory results for paediatric and adolescent populations assuming an increased utility of 0.08 related to VA treatment

Description	Paediatric population			Adolescent population		
	Incremental			Incremental		
DOHDP (years)	Costs (£)	QALYs	ICER (£ / QALY gained	Costs (£)	QALYs	ICER (£ / QALY gained
1	[redacted]	[redacted]	£216,847	[redacted]	[redacted]	£277,411
2	[redacted]	[redacted]	£189,458	[redacted]	[redacted]	£246,619
3	[redacted]	[redacted]	£169,157	[redacted]	[redacted]	£223,719
4	[redacted]	[redacted]	£153,776	[redacted]	[redacted]	£206,240
5	[redacted]	[redacted]	£141,830	[redacted]	[redacted]	£192,595

Abbreviations: BSC, best supportive care; DOHDP, duration of halting disease progression; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

Table 14: ERG exploratory results for an adult population assuming an increased utility of 0.03 related to VA treatment

Description	Adult population		
	Incremental		
DOHDP (years)	Costs (£)	QALYs	ICER (£ / QALY gained
1	[redacted]	[redacted]	£370,684
2	[redacted]	[redacted]	£323,063
3	[redacted]	[redacted]	£289,056
4	[redacted]	[redacted]	£263,794
5	[redacted]	[redacted]	£244,483

Abbreviations: BSC, best supportive care; DOHDP, duration of halting disease progression; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa

3.3 Additional uncertainties that remain unaddressed

Within previous ERG reports, the ERG highlighted a number of limitations within the modelling; two of which remain. These relate to the potential of the elicitation exercise to overestimate the benefit of VA treatment and the timing of discontinuation of VA treatment.

4 Critique of the proposed Managed Access Agreement

The company's proposed starting and stopping criteria were summarised in Table 14 and Table 15 and critiqued in Section 5 of the ERG report of April 2022.[2] These criteria were derived through KOLs and patient groups, and using minimum clinically important differences from the EMA responder analysis, published in Harmatz et al. 2018.[14]. For each criterion within a domain, there are cut points in change from baseline values that define the improvements or stabilisation required to meet that criterion. In some domains (for example, 6MWT, SPPB, FVC) there are different criteria for those with baseline values ≥2 standard deviations (SD) below the mean for an age-matched measurement and those with baseline values <2SD below the mean. Patients are assessed at 12 months, 24 months and then measured annually thereafter.

It is unknown whether the starting and stopping criteria would have high sensitivity and specificity in identifying patients based on disease progression status over 5 years whilst on VA treatment. Overall, the ERG expects that application of the start and stop criteria are likely to enhance the efficacy of the treatment in clinical practice compared to simply selecting responders or having no criteria at all. However, without empirical data, the extent to which the selected patients benefit remains unclear.

The ERG also notes the following:

- Since patients only have to respond in four out of five domains, progression in one domain, or in individual components in a domain where one component has been met, is permitted.
- Hamatz et al.,[14] which informed minimum clinically important differences and the responder criteria, only includes the outcomes used in the EMA responder analysis, so it is unclear whether any empirical data were used to define response for the outcomes PPB, SNIP, ejection fraction, infection rate, EQ-5D-5L and visual analogue scale pain, and therefore how robust these criteria are.
- The baseline values are age-matched in the criteria for 6MWT, SPPB and FVC but follow-up values are not; clinical advisors to the ERG previously questioned the appropriateness of not age-matching the FVC values for paediatric patients.
- Beyond two years on treatment, stabilisation of the 6MWT is defined as "*deterioration less than 2% of baseline or last measurement*". The ERG is unclear how this criterion should be applied, but potentially, it could allow for continuous decline year on year at a rate of 2% from the previous measurement, and this may be allowed to continue beyond baseline.
- A cut point of >5% reduction in FVC is used as a stopping criterion. Clinical advice provided previously to the ERG noted that a 5% change could be within the range of normal inter-test variability and performance.

- Discontinuations in the base case model are implemented at 12 months and annually at 10% thereafter, even though the criteria are not the same at 24 months and annually thereafter.

In its TE response the company has proposed stopping criteria which aligns to super-responders, as detailed in Section 2.6. The use of such stopping criteria was shown to decrease the ICER. The ERG has noted the uncertainty inherent in any estimated duration of halted disease progression associated with patients classified as super-responders.

5 Conclusions

The clinical benefits, and therefore the cost-effectiveness of VA treatment remain highly uncertain. The most favourable ICERs reported by the company are £47,545 for paediatric patients, £77,820 for adolescent patients and £93,241 for adult patients but these are predicated on three key assumptions. These assumptions are: (i) that there are utility gains of 0.10 for adult patients and 0.25 for adolescent and paediatric patients that arise due to being on VA treatment in addition to any utility gains associated with being in a better health state, (ii) that 47.4% of paediatric and adolescent patients and 64.3% of adult patients have treatment withdrawn after one year, and (ii) that disease progression is permanently halted for those patients on VA treatment.

Assuming that VA treatment halts disease progression for 5 years, rather than forever, and assuming the withdrawal rates associated with responders, rather than non-responders, increase the ICERs to £88,912 for paediatric patients, £126,214 for adolescent patients and £185,872 for adult patients. These assumptions represent the company's base case.

The least favourable ICERs presented by the ERG are £241,969 for paediatric patients, £307,557 for adolescent patients and £314,716 for adult patients where it is assumed that the utility gain associated with VA treatment is 0.05 (in line with the Appraisal Committee's previously preferred assumption) and that disease progression is only halted for a period of 1 year.

Assuming that the observed utility improvement observed in rhLAMAN-10 was generalisable, the ICERs ranged from £141,830 to £216,847 for paediatric patients dependent on the assumed duration for which disease progression would be halted (between 1 and 5 years). Corresponding values were £192,595 to £277,411 for adolescent patients and £244,483 to £370,684 for adult patients.

The ERG does not believe that compelling evidence has been provided to alter the Appraisal Committee's decision regarding the 0.05 utility gain associated with VA treatment. Similarly, there has been no compelling evidence that treatment with VA would completely halt disease progression in responders for a period of five years. However, both values are associated with considerable uncertainty.

Considering the results of all analyses performed, the ERG believes that the ICER for paediatric patients is likely to be in excess of £150,000 and could be considerably higher. The ICERs for adolescent and adult patients are also believed to be considerably higher than for paediatric patients.

6 References

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