NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Velmanase alfa for treating alpha-mannosidosis [ID800]

The following documents are made available to the consultees and commentators:

1. **Company re-submission** from Chiesi Ltd

2. **Evidence Review Group report** prepared by ScHARR

3. **Technical engagement response from company**
   - Company response
   - Additional evidence

4. **Technical engagement responses and statements from experts:**
   - Dr Karolina Stepien – clinical expert, nominated by Chiesi Ltd.
   - Sophie Thomas – patient expert, nominated by Mucopolysaccharide Society
   - Dr Duncan Cole – clinical expert, nominated by Chiesi Ltd.
   - Onaissa Jamil – patient expert nominated by Mucopolysaccharide Society

5. **Evidence Review Group critique of response to technical engagement** prepared by ScHARR

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Velmanase alfa for treating alpha-mannosidosis (ID800)

Specification for company submission of evidence

Addendum by Chiesi Limited for reconsideration: 9 March 2022

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Contents

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Executive Summary

This addendum seeks to address the concerns raised by NICE on the plausibility of clinical and cost-effectiveness of velmanase alfa (VA), as summarised in the Final Evaluation Document (FED) dated October 2019 (now withdrawn)[1] and the correspondence with NICE confirming this reconsideration step. Prior to this addendum, Chiesi Limited (Chiesi) presented an original HST submission to NICE in January 2018[2], followed by a resubmission in May 2019.[3]

Since 2019, Chiesi has worked to improve the evidence base for VA and to address the concerns raised with the proposed managed access agreement in collaboration with the MPS Society, Rare Disease Research Partners, and clinical experts who manage patients with alpha-mannosidosis (AM) in England. Key updates relating to this addendum since the resubmission in 2019 include:

- Clarification of the eligible population for VA based on clear stop/start criteria (see Section A)
- New clinical data on the natural history, mortality and cause of death of untreated patients with AM (see Section B)
- New clinical data supporting the effectiveness of VA in new clinical trials and real-world studies (see Section C)
- An updated economic model reflecting new clinical data and updated costs to 2022, including an improved patient access scheme (PAS) (see Section D)
- A proposal for a managed access agreement and updated data collection plan incorporating start/stop criteria and proposed clinical outcomes to be collected and incorporated into future economic analyses (see Section F)

Extensive validation of the previous submissions by UK clinical experts was carried out during 2017-2019; however, our updated analysis and data collection plan will be revalidated via expert interviews prior to the next committee meeting, alongside technical engagement with NICE and NHS England to discuss the feasibility of the updated managed access agreement in clinical practice.

Taken together, the new clinical data, updated modelling results and revised commercial offer strengthen the case for VA having the plausible potential of being cost-effective, while additional data are collected in the SPARKLE registry and AllStripes study to reduce remaining clinical uncertainty. This is especially important in AM, as clinical studies are so challenging due to the very small and heterogenous patient population, for whom there is no other pharmacologic treatment option.

Nature of the condition

AM is an ultra-rare, lysosomal storage disease (LSD) caused by impaired α--mannosidase enzyme activity due to mutations in the *MAN2B1* gene[4]. Reduced activity of α-mannosidase causes intracellular lysosomal accumulation of oligosaccharides, which is toxic to multiple cells and organ systems[4]. AM is an ultra-orphan disease, estimated to affect up to 1 in 500,000 worldwide[5,6]. In England, there are an estimated 25 reported patients with AM, with less than 1 new case of AM expected annually[7].

AM is a chronic, multi-morbid, progressive disease characterised by cognitive impairment and skeletal deformities, resulting in immobility and a reduced quality of life (QoL). As α-mannosidase is present in all cells[8], oligosaccharides can accumulate throughout the body, resulting in various clinical features[4]. As such, AM is highly heterogeneous and clinical features may be strikingly different among patients. Musculoskeletal, central nervous, respiratory and immunological complications lead to cumulative morbidity and early mortality. A recent mortality study of AM patients reported median age of death of [redacted] years (range [redacted] years), with [redacted] % of deaths caused by pneumonia[9]. As well as the burden of recurrent infections, pain and psychological issues, QoL is closely linked to walking ability[10]. Progressive mobility and functional impairment results in severe immobility or wheelchair dependence, which impacts patient independence and activities of daily living (ADL). The impact of this ultra-rare disease on caregivers is underestimated who themselves experience reduced QoL, which worsens over time[10].

Impact of the new technology

There are no pharmacologic, disease-modifying treatments for AM currently available in the UK. Best supportive care (BSC) for AM focuses on relieving symptoms and optimising QoL[11]. Allogeneic haematopoietic stem cell transplant (HSCT) is an option for some younger patients when clinically indicated, but is associated with significant morbidity and mortality[4,5,12]. VA is a recombinant human α-mannosidase enzyme replacement therapy (ERT) administered once weekly by intravenous (IV) infusion indicated for the treatment of non-neurological manifestations in patients with mild-to-moderate AM[13]. As such, VA is considered to be a 'step change' in the management of patients with AM, for whom there is no other licensed treatment option[7].

The efficacy and safety of VA was assessed in the rhLAMAN clinical programme, including a 12-month Phase III randomised placebo-controlled trial (rhLAMAN-05[14]) and an integrated analysis of all studies in patients ≥5 years old (rhLAMAN-10[15,16]) involving 34 patients. New clinical data are available from the Phase II rhLAMAN-08 trial that studied VA in patients <6 years[17] and new real-world data have been collected in the French Etoile-Alpha study[18] and case reports[19,20], with ongoing data collection in the AM Sparkle registry[21] and the AllStripes study[22].

Clinical evidence and expert opinion support the ability of VA to change the natural course of AM by improving patients' ability to walk, decreasing reliance on walking aids, delaying or stabilising disease progression and improving QoL. In rhLAMAN-10, long-term VA treatment (up to 48 months) showed sustained improvements from baseline in serum oligosaccharide and immunoglobin G (IgG) levels, mobility/functional capacity (3-minute stair climb test [3-MSCT]/6-minute walk test [6-MWT]), lung function, QoL, and hearing and cognitive function. In particular, of 10 patients who required walking assistance at baseline, 7 (70%) became assistance independent at last observation[16]. In addition, a post-hoc rhLAMAN-05 responder analysis requested by the European Medicines Agency (EMA) showed 87% of patients treated with VA were responders vs. 30% with placebo (based on response to ≥2 clinically-meaningful domains)[23]. In rhLAMAN-08, treatment for 24 months reduced serum oligosaccharides and improved endurance, hearing, functional

capacity and QoL in patients <6 years[17]. Overall, VA was well tolerated with no safety concerns, including immunogenicity. Treatment with VA was associated with reduced rates of infection, which is likely to reduce the disutility and mortality resulting from severe infections.

Value for money

Updated cost effectiveness analyses compare VA plus BSC vs. BSC alone and incorporate new clinical data, a revised PAS and start/stop criteria. Base-case results in the paediatric, adolescent and adult cohorts show with-PAS incremental cost-effectiveness ratios (ICERs) ranging from £[redacted] to £[redacted] per quality-adjusted life year (QALY). The revised base-case incorporates all of the NICE preferred assumptions from the 2019 submission[3], except an increased on-treatment utility benefit (0.1) and a 5-year delay in disease progression to reflect the long-term improvements from baseline shown by patients treated with VA in the French Etoile Alpha registry study[24]. Scenario analyses determined a wide range of potentially plausible ICERs from £[redacted] to £[redacted] per QALY. As the current cost effectiveness model may not adequately capture the likely treatment effect of VA on pain, minor infections, respiratory function and psychiatric symptoms, these calculations may underestimate the true value of VA for patients with mild-to-moderate AM.

The ultra-rare nature of AM and the low budget impact should be considered alongside the challenges associated with modelling a complex multisystem disease, while additional data are collected to increase the confidence in the longer-term clinical and cost effectiveness of VA to ensure that patients in England can access a life-improving and potentially life-extending treatment.

Impact of the technology beyond direct health benefits

As AM is a multi-morbid lifelong condition, the stabilisation of disease progression associated with VA has potential to offer additional benefits beyond improved health, QoL and direct healthcare costs. The limited evidence available shows that all patients with AM are dependent upon third-party assistance in daily living[10,16,25]. As reported in the UK MPS Society Survey, AM results in a high economic and societal burden on patients, caregivers and other family members, which worsens as the patient's walking ability deteriorates[10]. As described in Section D1, it is anticipated that treatment with VA may result in direct and indirect cost savings to patients, caregivers and wider social/government services, including increased productivity of patients and their caregivers, education benefits and reduced out of pocket expenses.

Section A – Decision problem

Table 1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope presented in the addendum	Rationale for variation from scope
Population	People with alpha-mannosidosis (AM) aged 6 years or older	People with mild-to-moderate AM who are eligible for treatment according to the starting criteria as defined in Section F.	Since 2019 there has been a change to the licensed indication which no longer excludes <6 years – the updated SmPC is included in Appendix A. VA is indicated for enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild-to-moderate AM[13].
Intervention	Velmanase alfa	As per scope	N/A
Comparator(s)	Established clinical management without velmanase alfa (including, where clinically indicated, allogeneic HSCT)	Allogeneic HSCT is not considered as a relevant comparator in this submission	N/A: as justified in previous submission
Outcomes	The outcome measures to be considered include: • mobility and motor function • hearing and language • cognition • lung function • rates of infection • mortality • adverse effects of treatment (including immune response) • health-related quality of life (for patients and carers)	As per scope	N/A
Impact of the technology	• clinical effectiveness • overall magnitude of health	As per scope	N/A

	benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)		
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	As per scope	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service	As per scope with societal costs also included as a sensitivity analysis.	The economic model incorporates estimates of the impact of AM on patient/caregiver expenditure and productivity; however, as no AM specific costs were identified, these have not been included in the base case analysis, and only included in sensitivity analysis.

	• staffing and infrastructure requirements, including training and planning for expertise.		
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will consider any Managed Access Arrangements • Where evidence allows consideration may be given to clinical characteristics (such as, age of onset and severity of disease)	VA is to be used in patients that are eligible according to the starting criteria as defined in Section F. For a patient to start and continue treatment with VA, a series of clinical measurements should be made at baseline and at 12-monthly intervals (serum oligosaccharides, 3-minute stair climb test [3-MSCT], 6-minute walk test [6-MWT], forced vital capacity [FVC], Childhood Health Assessment Questionnaire [CHAQ] disability index, CHAQ pain [Visual Analogue Scale, VAS], EQ-5D-5L and left ventricular ejection fraction [LVEF]).	Only patients with symptomatic AM are eligible for treatment and only patients who respond to treatment are eligible to continue.

Section B – Nature of the condition

1 Disease morbidity

Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Information on the natural disease course of AM were provided in the original submission[2]. New published and unpublished evidence on morbidity and mortality since 2019 are provided in the sections below.

Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

AM is an ultra-rare LSD; globally, its prevalence is estimated between 1 in 500,000 [5] and 1 in 1 million people[6]. An updated systematic literature review is ongoing to further define the epidemiology of AM as there is a scarcity of published evidence reporting incidence/prevalence data.

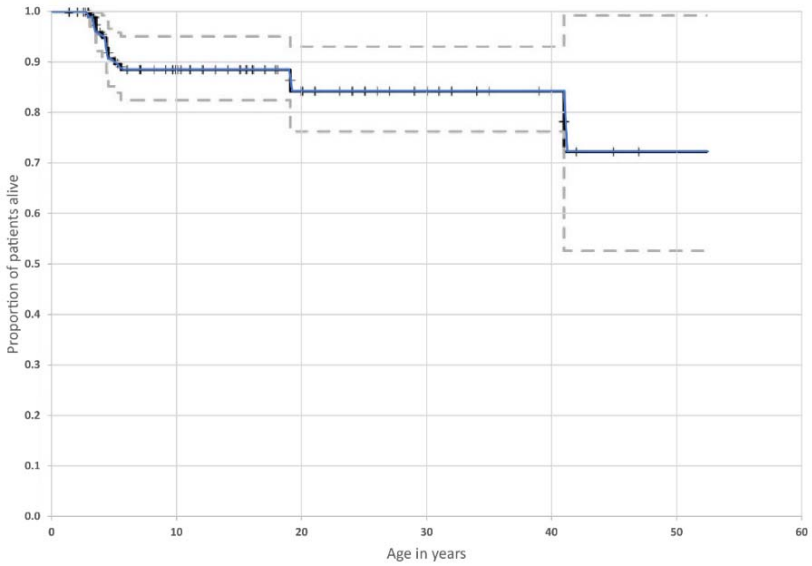
Clinical experts in England estimate there are 25 patients in total diagnosed with AM in England, with less than 1 new case of AM expected annually.

Please provide information about the life expectancy of people with the disease in England and provide the source of data.

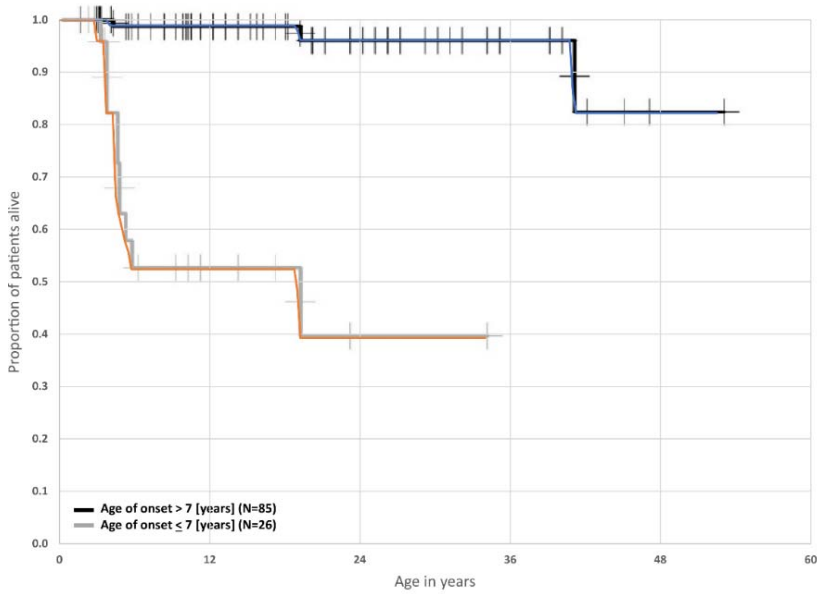
Studies describing the life expectancy of patients with AM are limited; however, survival into adulthood is reported. New epidemiology data are provided by a literature review of 111 patients from 1967 to 2014 that determined the age of disease onset is a predictor of survival[26]. Although follow-up was limited to 2 years, of 111 patients, mean (SD) patient age was 16.12 ± 12.65 years (range: 1.3 to 53.0 years). At the age of 41 years, 72.3% of the 111 patients were alive, and patients with age of symptom onset >7 years survived significantly longer than patients with age of onset ≤7 years (Figure 1). In the 14 patients who died, causes of death were respiratory failure (7/14, 50%), heart failure (1/14, 7.1%), bacterial infection/sepsis (2/14, 14.3%) or not reported (4/14, 28.6%)[26].

Figure 1. Estimated survival distributions for patients with AM (N = 111).

A.



B.



(A) Estimated overall survival distribution for all patients with AM (N = 111). Censored individuals are marked with a "+." Age in years refers to chronological age of patients. (B) Estimated survival distribution for patients with AM with age of onset >7 years (N = 85, blue line) and ≤7 years (N = 26, orange line). Censored individuals are marked with a "+." Log-rank test, P = 0.008. Age in years refers to chronological age of patients.

Source: Adapted from Zielonka et al., [26]

AM mortality study

As data on life expectancy and cause of death are limited in AM, Chiesi commissioned Rare Disease Research Partners (RDRP) to investigate the cause of mortality and age of death[27]. The aim of this retrospective study was to investigate the causes of mortality in patients with AM, using a combined approach of a literature search and clinical data collection via a questionnaire sent to clinicians and patient

organisations. Results were presented as a poster at 2022 WORLD Symposium[28] and have been submitted for publication[9].

A total of [redacted] clinicians and [redacted] LSD patient organisations from [redacted] countries were invited to participate. Data were obtained via a questionnaire completed between April 2021 and May 2021 after obtaining consent. Cause of death and age at death were available for [redacted] patients reported by clinicians or patient organisations. Patients were born from [redacted]; [redacted]% were female. Median age at death was [redacted] years (mean [redacted]; range: [redacted], n=[redacted]). [redacted] occurred during the patient's second decade of life, and [redacted] deaths ([redacted]%) during or after the patients' third decade, including [redacted]%) during their fifth decade and [redacted]%) during their sixth decade. Two female patients reached [redacted] years, the maximum age in the study population.

Cause of death in the [redacted] patients with available data is shown in Table 2. A large proportion of deaths were recorded as pneumonia ([redacted] deaths, [redacted]%) (median age at death, [redacted] years). [redacted] deaths ([redacted]%) were associated with cancer (median age at death, [redacted] years). Other causes of death included [redacted]

Table 2. Conditions reported by clinicians/PO as a cause of death in patients with alpha-mannosidosis (n=15)

Patient	Cause of death	n (%)	Sex	Year of death	Age at death (years)
	[redacted]	[redacted]			
1	[redacted]		[redacted]	[redacted]	[redacted]
2	[redacted]		[redacted]	[redacted]	[redacted]
3	[redacted]		[redacted]	[redacted]	[redacted]
4	[redacted]		[redacted]	[redacted]	[redacted]
5	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]				
6	[redacted]		[redacted]	[redacted]	[redacted]
7	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]			
8	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]			
9	[redacted]		[redacted]	[redacted]	[redacted]
10	[redacted]		[redacted]	[redacted]	[redacted]
11	[redacted]		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]			
12	[redacted]		[redacted]	[redacted]	[redacted]

13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]

F=female; M=male; n/a=not available; PO = patient organisation.
Source: Adapted from Hennerman et al., [9]

2 Impact of AM on quality of life

As an ultra-rare disease, the true QoL burden experienced by patients with AM and their carers is poorly defined. An overview of the effect of AM on patient and carer health-related QoL (HRQoL) was described in the original submission[2], including interim results of a UK MPS Society Survey and clinical expert testimonials describing the QoL impact on 9 patients with AM and their carers. Since then, final results of the UK MPS Society Survey have been published and are included in the sections below [10]. In addition, survey results of two caregivers of adult patients in Italy was published in 2021[29] and caregiver feedback from the rhLAMAN-10 trial was published as a poster in 2021[30].

Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

2.1.1 Patient QoL

In line with QoL data reported in the original submission in the natural history study [25] and the rhLAMAN clinical studies[16], results of the UK MPS Survey showed AM negatively affected multiple aspects of patients' QoL[10]. All studies showed that patients with AM were dependent upon third-party assistance in daily living.

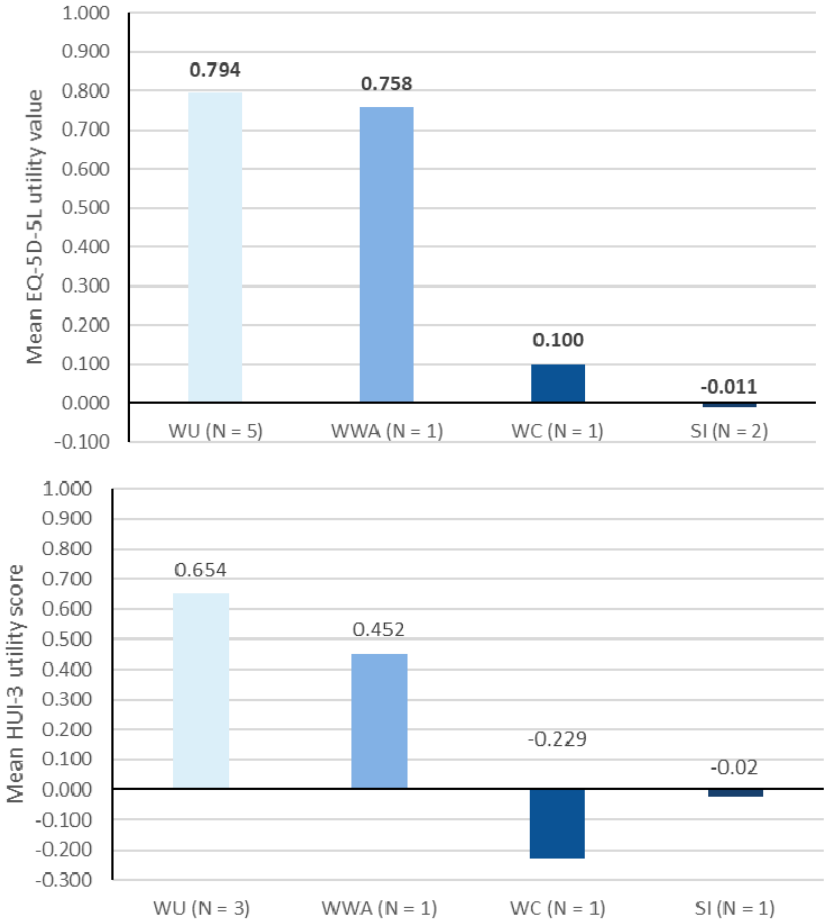
Of the 9 patients included in the UK MPS Survey, the 3 patients who required wheelchair assistance (n=1 wheelchair dependent, n=2 severe immobility) were reported by their carers to be severely disabled and needed support for all aspects of daily life. Where reported, carers commented that these patients had a reduced QoL as a result of immobility, although AM had affected the patients' cognitive function to such an extent that they were not fully aware of their condition.

Nine carers (by proxy) and 3 patients (by self-report) completed patient QoL questionnaires. Based on EQ-5D-5L[1] responses provided by carers, patients' utility ranged from 1.000 to -0.048. When patients were grouped according to their walking ability, there was a reduction in utility with functional impairment: the 'walking unassisted' group had the highest utility and the 'severe immobility' state had the lowest utility (Figure 2). Six complete Health Utility Index (HUI)-3 questionnaires were obtained by proxy, data for the remaining 3 patients were incomplete and scores were unable to be calculated. Analysis of the HUI-3 utility scores for the 6 patients

[1] Including two carer responses to the EQ-5D-Y questionnaires mapped to EQ-5D-5L

showed that HRQoL was again most negatively affected for patients who were wheelchair dependent or severely immobile (Figure 2).

Figure 2. Patient QoL: EQ-5D-5L (n=9) and HUI-3 (n=6) by walking ability



Note: HRQoL of patients as reported by proxy measured using the EQ-5D-5L questionnaire (top) and HUI-3 (bottom) according to walking ability. A score of 1 indicates 'perfect health,' 0 indicates 'death', negative values indicate 'feeling worse than death.' Utility values for 2 patients were mapped from EQ-5D-Y to EQ-5D-5L using the nonparametric crosswalk method.

Abbreviations: HUI-3 = Health Utility Index–3; SI = severe immobility; WC = wheelchair dependent; WU = walking unassisted; WWA = walking with assistance

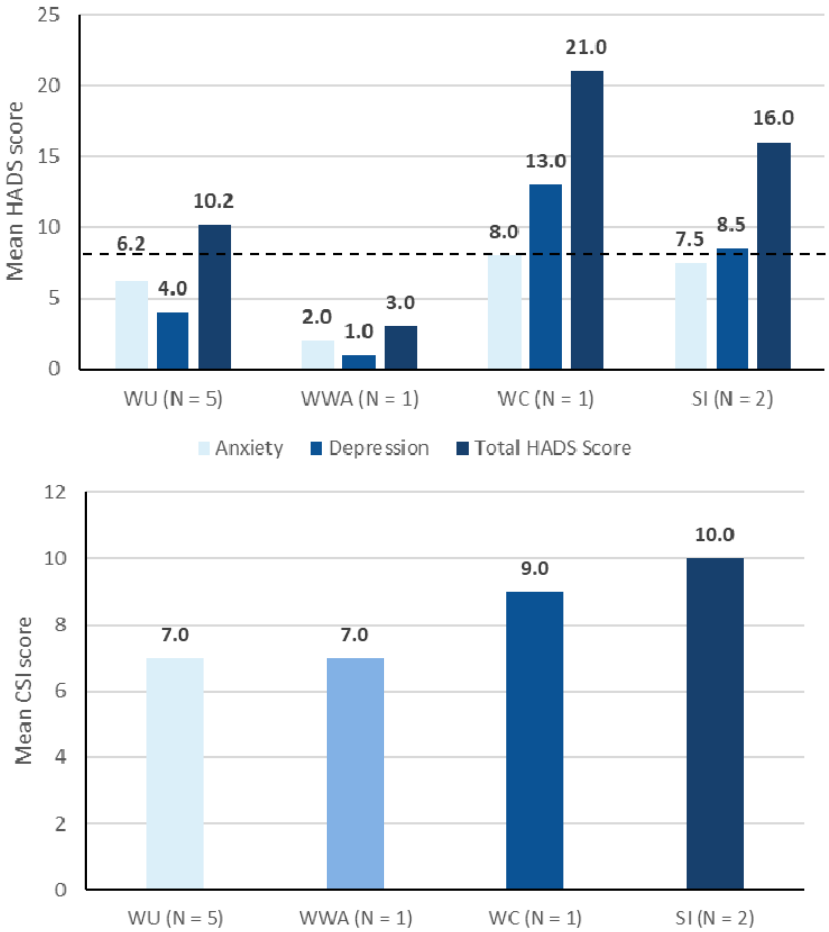
Source: Adapted from Adam, Malone [31]

Compared with proxy conditions, the mean EQ-5D-5L utility values of AM patients who were walking unassisted (0.794) or walking with assistance (0.758) reported in the UK MPS survey were comparable to those reported for patients with moderate rheumatoid arthritis (0.730)[31]. It should be noted that 2 patients in the survey who were walking unassisted presented primarily with mild ataxia-related symptoms. Consequently, the utility values, and self-care and pain/discomfort EQ-5D-5L scores for these patients are likely to underrepresent the level of disability experienced by most patients with AM. In the survey, the utility values of patients who were wheelchair-dependent (0.100) or severely immobile (−0.011) were much lower than those reported for patients with severe rheumatoid arthritis (0.300) [31], and only slightly higher than patients with multiple sclerosis who were bed ridden or completely immobile (−0.049)[32,33].

2.1.2 Carer QoL

Results of the UK MPS Society Survey showed caring for a patient with AM negatively affected the QoL of carers, particularly their mental health. Each carer's level of strain related to care was assessed using the Caregiver Strain Index (CSI) questionnaire. When patients were pooled by walking ability, the average CSI score for carers increased from a mean score of 7 for patients classified as 'walking unassisted' to a mean score of 10 for patients classified with 'severe immobility' (Figure 3). Anxiety and depression in carers were assessed using the Hospital Anxiety and Depression Scale (HADS) questionnaire. Carers reported a mean score for anxiety of 6.2 (minimum = 2, maximum = 10) and a mean score for depression of 5.7 (minimum = 0; maximum = 13). Five carers were reported as borderline abnormal and/or abnormal case of anxiety and/or depression. QoL was most negatively affected for carers of patients who were wheelchair dependent or severely immobile; however, caring for a patient with less severe ambulatory health states was not necessarily associated with decreased carer anxiety or depression (Figure 3) .

Figure 3. Carer QoL: HADS (n=9) and CSI (n=9) by walking ability of patient



Note: QoL of carers measured by walking ability of the patient using the HADS questionnaire (top), CSI questionnaire (bottom)
For HADS, carer scores for anxiety and depression subscales go up to 21 each. 0–7: no case; 8–10: borderline abnormal case; 11–21: abnormal case. For CSI, carer scores go up to 12, with a score of 7 or higher indicating the carer is under a high level of stress related to care provision. The horizontal dotted lines indicate the level at which there is a borderline abnormal case for HADS for each subscale or a high level of stress related to care provision for CSI.

Abbreviations: CSI = Caregiver Strain Index; HADS = Hospital Anxiety and Depression Scale; HRQoL = health-related quality of life; SI = severe immobility; WC = wheelchair dependent; WU = walking unassisted; WWA = walking with assistance

Source: Adapted from Adam, Malone, Lloyd, Lee, Hendriksz, Ramaswami [10]

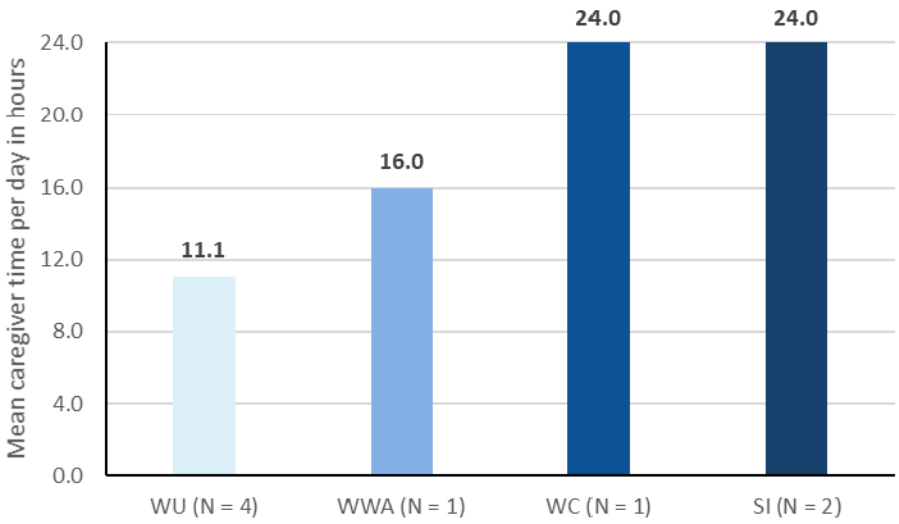
2.1.3 Social functioning and economic burden

Results of the UK MPS Survey showed AM negatively impacted the social integration of patients, affecting comprehension and communication, and their ability to attend school or work [10]. Patients were able to attend mainstream schools, but required specialist learning support. Hearing and cognitive difficulties resulting from AM were reported to negatively affect patient's language and communication skills and learning abilities, resulting in 1 patient attending school a year behind their age group. Of the 5 adult patients surveyed, 2 were employed part-time and 1 was at college 3 days a week; all 3 were described as walking unassisted or walking with assistance. Employment data for the other two adults were missing.

The burden of time spent in hospital and the requirement for regular healthcare appointments also affected patients' QoL. In addition, patients experienced difficulty in making friends and establishing social relationships and were subject to bullying. Carers and families experienced reduced social integration as a result of having a child with AM. Lack of time and tiredness were noted as contributing factors, as was a reduced ability to work due to caring responsibilities. Some carers chose not to socialise or interact with people who did not accept their children with AM.

AM resulted in substantial financial impacts for many carers and their families. The mean time spent caregiving per day was 16.6 hours (range: 4 to 24). The number of hours spent per day caring for the patient increased as the ambulatory health state of the patient deteriorated (Figure 4). As a result, most carers (7/9, 78%) were unable to work full-time, leading to loss of income. In addition, the carers and families of patients with AM incurred personal expenses as a result of disease-related needs such as home adaptations, a larger car, and healthcare-related travel such as hospital visits. Some carers and patients received social support in the form of disability living allowance, personal independence payment and/or carer's allowance.

Figure 4. Caregiver time (n=8) by walking ability



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

Source: Adapted from Adam, Malone, Lloyd, Lee, Hendriksz, Ramaswami [10]

The substantial emotional and financial burden borne by those caring for a family member with AM was also reported in caregiver interviews from Italy, published in 2021 [29]. Interviews were conducted to understand the challenges faced by patients and their caregivers from the first signs of disease, up to and after diagnosis. The survey reported cumulative morbidity resulting from the delayed access to treatment, which necessitated long-term residential care in one patient. Patients and caregivers had to travel frequently and widely, both within Italy and abroad, to receive a diagnosis and care. In one case, the severity of symptoms and physical, emotional, and financial burden required the patient's admission to a residential adult care facility to provide daily management of their disease[29].

Section C – Impact of the new technology

1 Published and unpublished clinical evidence

1.1 Complete list of relevant studies

A summary of all relevant clinical evidence of patients with AM treated with VA is shown in Table 3. Since the original submission in 2018, additional clinical data has been collected, and previously unpublished studies and analyses are now available as published peer-reviewed full-text journal articles. For ease of reference, clinical data that was included in previous submissions has been cross-referenced accordingly, and any new clinical data or publications since the previous submissions are highlighted in bold.

Table 3. List of clinical evidence of patients with AM treated with VA

Study name (acronym)	Study design	Population	Intervention	Comparator	Publication status	Cross-reference to company submission
rhLAMAN-02 (NCT01268358)	Phase I	Patients with AM (aged 5–20 years) N = 10	VA 6.25 U/kg VA 12.5 U/kg VA 25 U/kg VA 50 U/kg VA 100 U/kg	Change from baseline (no active or placebo comparator)	Full-text publication: Borgwardt et al., 2013 [34]	Original submission (Appendix 7)[2]
rhLAMAN-03 (NCT01285700)	Phase IIa	Patients with AM (aged 5–20 years), N = 10	VA 25 U/kg VA 50 U/kg	Change from baseline (no active or placebo comparator)	Full-text publication: Borgwardt et al., 2013 [34]	Original submission, (Appendix 7)[2]
rhLAMAN-04 (NCT01681940)	Phase IIb	Patients with AM (aged 5–20 years), N = 9	VA 1 mg/kg	Change from baseline (no active or placebo comparator)	Abstract: Borgwardt et al., 2014 [35]	Original submission, (Appendix 7) [2]
rhLAMAN-05 (NCT01681953)	Phase III, 12-month core RCT with extension study up to 36 months	25 patients with AM: VA (n=15) • 7 children • 8 adults Placebo (n=10) • 5 children • 5 adults	VA 1 mg/kg	Placebo	**Full-text publication: Borgwardt et al., 2018 [14]**	Original submission, (Section 9 and Appendix 7)[2] **This addendum includes the new publication in Appendix B**
rhLAMAN-10 NCT02478840	Integrated analysis of all patients in rhLAMAN-04, -05 after-trial and CU studies	33 patients with AM: • 19 children • 14 adults	VA 1 mg/kg	Change from baseline (no active or placebo comparator)	**Full-text publications:** • **Efficacy and safety: Lund et al., 2018 [15]** • **HRQoL: Borgwardt et al., 2018 [16]**	Original submission, (Section 9 and Appendix 7)[2]

Study name (acronym)	Study design	Population	Intervention	Comparator	Publication status	Cross-reference to company submission
					• **BOT-2: Phillips et al., 2020** [36] **Abstracts:** • **Infections: Borgwardt et al., 2018** [37] • **Mobility: Lund et al., 2017** [38] • **Caregiver feedback: Lund et al., 2021** [30] • **ADA analysis: Borgwardt et al., 2021** [39]	**This addendum includes the new publications in Appendix B and a summary of new analyses in Section C1.3.1**
Multidomain responder analysis	Post-hoc analysis requested by EMA	33 patients from rhLAMAN-05 and 10	VA 1 mg/kg	rhLAMAN-05: placebo rhLAMAN-10: change from baseline (no active or placebo comparator)	**Full-text publication: Harmatz et al., 2018** [23]	Original submission, (Section 9 and Appendix 7)[2] **This addendum includes new publication in Appendix B**
rhLAMAN-08 (NCT02998879)	**Phase II paediatric study**	**5 patients with AM <6 years**	**VA 1 mg/kg**	**Change from baseline to Month 24 (40 months for 1 patient)**	**Abstract and poster: Guffon et al., 2021**[17] **Unpublished (AIC) CSR:** [40]	**This addendum, Section C 1.3.2 and Appendix E**
Etoile Alpha	**Real-world retrospective registry study (France), conducted as a requirement of**	**16 patients in 3 cohorts:** **7 from rhLAMAN-07** **1 from rhLAMAN-08**	**VA 1 mg/kg**	**Change from baseline (no active or placebo comparator)**	**Unpublished (AIC) CSR: Chiesi** [18]	**This addendum, Section C 1.3.6 and Appendix F**

Study name (acronym)	Study design	Population	Intervention	Comparator	Publication status	Cross-reference to company submission
	conditional market access by HAS	8 patients in nominative ATU				
AM registry (SPARKLE)	Multicentre, post-authorisation noninterventional, prospective cohort study	All patients with AM	Not specified – all patients eligible irrespective of treatment (VA, BSC, HSCT, investigational treatment)	None	Full-text publication Protocol: Hennerman et al., 2020[21] Unpublished (AIC) interim reports: [41,42]	This addendum, Section C 1.3.10
Case reports from rhLAMAN-05	Case report from rhLAMAN-05 (n=2)	2 patients with conducive hearing impairment	VA 1 mg/kg	Change from switch from placebo	Abstract and poster: Lund et al., 2020[43]	This addendum, Section C1.3.11
UK case report	Case report (n=1)	1 UK patient with AM	VA 1 mg/kg	None	Poster: Cole et al., 2021[20]	This addendum, Section C1.3.11
Case report series	Case reports from 3 European centres (n=3, Spain; n=1, Lithuania; Italy, n=1)	5 adult patients	VA 1 mg/kg	None	Full text publication: Garcia-Navarretea et al., 2021 [19]	This addendum, Section C1.3.11

Abbreviations: ADA = anti-drug antibody; AIC = academic in confidence; AM = alpha-mannosidosis; ATU = temporary utilisation authorisation; BOT-2 = Bruininks-Oseretsky test of motor proficiency 2nd edition; BSC = best supportive care; CSR = clinical summary report; CU = compassionate use; EMA = European Medicines Agency; HAS = Haute Autorité de Santé; HRQoL = health-related quality of life; HSCT = haemopoietic stem cell transplant; NPAF = new product assessment form; QoL = quality of life; RCT = randomised clinical trial; VA = velmanase alfa

1.2 Summary of methodology of relevant new studies

The methodology of the new studies not described in previous submissions are described in Table 4 to Table 6. Quality assessments of these studies are included in Appendix C.

Table 4. Summary of methodology: rhLAMAN-08

Study name	rhLAMAN-08 (NCT02998879)
Objective	To evaluate safety and efficacy of VA in paediatric AM patients aged less than 6 years. The primary objectives of the study were to evaluate safety and tolerability of VA and detect anti-VA immunoglobulin G antibodies (ADA).
Location	Seven sites in the following countries: Denmark (1), France (1), Germany (2), Italy (2) and Austria (1)
Design	Open-label Phase II study. The study consisted of a screening and baseline visit followed by a treatment phase. The study treatment was administered for 24 months (40 months only for one patient enrolled in France). Evaluation visits occurred at Month 6, Month 12, Month 18 and Month 24 (a further evaluation visit at Month 40 occurred for the patient enrolled in France). Safety was assessed in terms of physical examination findings (assessed at baseline and evaluation visits), vital signs (at baseline, at first dose visit, subsequent dose visits and evaluation visits), AEs, routine clinical laboratory evaluations (assessed at baseline and every 8 weeks post-treatment) including haematology, blood chemistry and urinalysis, and IgG immunogenicity monitoring (at baseline and evaluation visits). AEs and serious AEs were assessed at the baseline visit, all dose visits and in connection with dosing during the evaluation visits. Additional safety assessments included electrocardiograms (assessed at baseline, first dose, and certain evaluation visits), echocardiograms (at baseline and certain evaluation visits), growth velocity (at baseline, certain dose visits and all evaluation visits).
Duration of study	24 months (up to 40 months in 1 patient)
Patient population	Paediatric patients below 6 years of age with alpha-mannosidosis
Sample size	5
Inclusion criteria	Included patients had to have a confirmed diagnosis of AM as defined by alpha-mannosidase activity in leukocytes or fibroblasts < 10% of normal activity (historical data) and be aged < 6 years at the time of screening. The custodial parent(s) of the patient had to provide signed informed consent.
Exclusion criteria	Patients were excluded from the study if they did not meet the specific inclusion criteria or if any of the following criteria applied: • Patient's diagnosis could not be confirmed by alpha-mannosidase activity < 10% of normal activity; • Presence of known chromosomal abnormality and syndromes affecting psychomotor development, other than alpha-mannosidosis; • History of BMT; • Presence of known clinically significant (CS) cardiovascular, hepatic, pulmonary, or renal disease or other medical conditions that, in the opinion of the Investigator, would preclude participation in the study; • Any other medical condition or serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the study; • Planned major surgery that, in the opinion of the Investigator, would preclude participation in the study; • Participation in other interventional trials with VA

Intervention(s) (n =) and comparator(s) (n =)	VA 1mg/kg once-weekly (N=5)
Baseline differences	Four patients were white; race was not recorded for 1 patient. Patients ranged in age from 3.7 to 5.9 years with mean age of 4.52 years. Three patients were male (60.0%) and 2 patients were female (40.0%). All patients completed the study.
Follow up	All patients completed the study. Four patients received treatment for 24 months and 1 patient received treatment for 40 months.
Statistical tests	Due to the small sample size (5 patients), data were presented as per data listings. Only when specified, summary statistics were reported. No hypotheses were tested, and no p-values were computed.
Primary outcomes (including scoring methods and timings of assessments)	Primary objectives of the study were to evaluate safety and tolerability of VA and detect anti-VA immunoglobulin G antibodies (ADA). Safety was assessed in terms of physical examination findings (assessed at baseline and evaluation visits), vital signs (at baseline, at first dose visit, subsequent dose visits and evaluation visits), AEs, routine clinical laboratory evaluations (assessed at baseline and every 8 weeks post-treatment) including haematology, blood chemistry and urinalysis, and IgG immunogenicity monitoring (at baseline and evaluation visits). AEs and serious AEs were assessed at the baseline visit, all dose visits and in connection with dosing during the evaluation visits. Additional safety assessments included electrocardiograms (assessed at baseline, first dose, and certain evaluation visits), echocardiograms (at baseline and certain evaluation visits), growth velocity (at baseline, certain dose visits and all evaluation visits).
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints assessed at baseline and the evaluation visits: change from baseline to Month 24 (40 months in 1 patient) for: • Serum oligosaccharides • CSF biomarkers: – Tau protein – Neurofilament protein light (NFL) – Glial fibrillary acidic protein (GFAP) – Oligosaccharides • Functional capacity: – Peabody Developmental Motor Scale – 2nd edition scores – Mullen Scales of Early Learning scores – BOT-2, when applicable by age (from 4 years) or as per the judgement of the investigator • Endurance: – 3-MSCT, 6-MWT in paediatric patients from 4 years of age, or when applicable according to the judgment of the investigator – 2-MWT in paediatric patients below 4 years of age, or when applicable according to the judgment of the investigator • Hearing evaluation: – Otoacoustic emissions testing – Automatic auditory brainstem response audiometry • Immunological profile, when applicable, as per the judgement of the investigator: – Serum immunoglobulin IgG, IgA, IgM; – In vitro synthesis of IgG; – In vitro proliferative response to anti-cluster of differentiation (CD)3, interleukin (IL)-2, phytohaemagglutinin (PHA), anti-CD3+ anti-CD28;

	– Immunophenotype: CD3/CD4/CD8 for T-lymphocytes; CD19/CD20 for B-lymphocytes; • Assessment of QoL via questionnaire to patient's parents as per Pediatric Evaluation of Disability Inventory (PEDI); • Assessment of mannose-rich oligosaccharides in brain tissue, as measured by MRS visual score • MRI (in white matter, grey matter and centrum semiovale), and diffusion-MRI of the brain, when feasible, as per the judgment of the Investigator. • Pharmacokinetics

Source: rhLAMAN-08 CSR; Chiesi data on file, 2021 [40]

Abbreviations: 2-MWT = 2-minute walk test; 3-MSCT = 3-minute stair climb test; 6-MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; AM = alpha-mannosidosis; BMT = bone marrow transplantation; BOT-2 = Bruininks-Oseretsky test of motor proficiency 2nd edition; CSF = cerebrospinal fluid; ICF = informed consent form; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PK = pharmacokinetic; QoL = quality of life; VA = velmanase alfa

Table 5. Summary of methodology: Etoile-Alpha

Study name	Etoile Alpha
Objective	To evaluate the long-term efficacy and safety of VA in patients with AM in France previously included in studies rhLAMAN-07 or -08, or currently treated under ATU conditions
Location	Six centres in France
Design	A multicentre, non-comparative, retrospective observational study (retrospective registry) of patients receiving or having received treatment with VA in France was conducted through June of 2020.
Duration of study	Patients' retrospective data was assessed from the first available data collected in the patient's medical record until June 2020. Data were collected at diagnosis, baseline and several yearly timepoints thereafter. Due to the small sample size, any available data from the small number of patients were reported, resulting in the visits (i.e., assessment timepoints) being different for most patients. Having assessment variables at different timepoints did not allow for a comparative (or integrated) analysis of efficacy in a global manner, therefore, the presented results were adjusted so as to include the results at baseline or the nearest value to the baseline, and the last value recorded, which could be any timepoint from month 6, to month 18, or 24, or 30, or 33, or 54.
Patient population	Patients with AM from the following 3 cohorts: • 7 patients from the previously completed clinical trial rhLAMAN-07 • 1 patient from the previously completed clinical trial rhLAMAN-08 • 8 patients in nominative ATU
Sample size	16
Inclusion criteria	To be eligible for enrolment in the retrospective registry, patients must have fulfilled both of the following inclusion criteria: • Every patient receiving or having received VA therapy in France as part of VA development or clinical use (nominative ATU) • Evidence of a signed informed and non-opposition letter indicating that the patient (or parents or a legally acceptable representative according to local regulation)
Exclusion criteria	Not meeting inclusion criteria
Intervention(s) and comparator(s)	VA 1mg/kg once-weekly (N =16)

Baseline differences	[redacted] females and [redacted] males Mean age in study: [redacted] years Mean age at the time of diagnosis: [redacted] Mean age when VA first administered: [redacted] years old. Mean duration of treatment: [redacted] months
Follow up	As this was a retrospective chart review, there were no patients treated prospectively, hence patient removal information is not applicable in this study. Data from all included patients was used in the data analysis
Statistical tests	Categorical variables are described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation. A missing value was not replaced. Analysis considered data collected at available observational point, according to clinical practice and clinical judgment. In order to summarize data by time point (e.g., one year after baseline, two years after baseline, etc.), the nearest available evaluation/measurement is considered (acceptable range). For exploratory purposes, an intraclass correlation coefficient (ICC) was calculated for each category of numerical variables: biochemical, functional, respiratory, cognitive and audiometric, neurological, quality of life and BOT-2 test to determine the contribution of variance from amongst patients versus across different clinical and laboratory measurements. No inferential statistics was performed due to the small sample size and the quantity of missing data, in which case generated P-values do not represent the precision of estimates.
Primary outcomes (including scoring methods and timings of assessments)	Data was collected at diagnosis, baseline and several yearly timepoints thereafter. • Biochemical variables: – Assessment of changes in levels of serum oligosaccharides (µmol/L), of changes in brain biomarkers and in serum immunoglobulin class IgG concentrations • Functional variables: – Assessment of changes in 3-MSCT, 6-MWT and 2-MWT • Respiratory variables: – Assessment of changes in pulmonary exploration tests: FVC (L and %), FEV1 (L) and PEF (L/s) • Complementary variables: – Urinary oligosaccharides (µmol/L), BOT-2 test, WISC test • Cognitive and audiometric variables: – Assessment of changes in the cognitive test Leiter-R (total score and score per area) – Assessment of changes in the PTA test – Imaging and spectroscopy: • Assessment of changes in neurological and structural functions by MRI and MRS • QoL: If QoL data available, QoL assessed through two questionnaires: CHAQ and EQ-5D-5L – CHAQ-DI disability index and assessment, quantified from 0 (lack of affection) to 3 (very severe affection) – CHAQ-VAS score pain related to the level of pain collected by an EVA graduated from 0 to 100 then transformed in a score from 0 to 3 – CHAQ general state VAS: general state quantified from 0 to 3 – For the 3 scores, a rise of the score will be related to a worsening in terms of disability, pain, or general state

	– EQ-5D-5L associated to patient state (mobility, autonomy, maintenance of usual activities, pain, discomfort, anxiety, and depression) • Safety variables of interest – AEs, SAEs – Reason for a possible stop of LAMZEDE – Infusion related reactions – Immunogenicity: Presence of anti-velmanase-alfa IgG antibodies

Source: Etoile Alpha CSR; Chiesi data on file, 2020 [18]

Abbreviations: 2-MWT = 2-minute walk test; 3-MSCT = 3-minute stair climb test, 6-MWT = 6-minute walk test; ATU = temporary utilisation authorisation; BOT-2 = Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ = Childhood Health Assessment Questionnaire; CHAQ-DI = Childhood Health Assessment Questionnaire Disability Index; FVC = forced vital capacity; IgG = immunoglobulin G; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PEF = peak expiratory flow; PTA = pure tone audiometry; SmPC = summary of product characteristics; QoL = quality of life; VA = velmanase alfa; VAS = visual analogue scale; WISC = Wechsler Intelligence Scale for Children

Table 6. Summary of methodology: SPARKLE

Study name	**The AM Registry (SPARKLE)**
Objective	Primary objective is to assess the long-term effectiveness and safety of treatment with VA under conditions of routine clinical care. Secondary objective is to characterise the AM population, including clinical manifestation, progression and natural history.
Location	The study is expected to involve approximately 40 centres in the EU, with additional sites added, as required. At the time of the 2nd interim report (Feb 2022), 21 sites in 15 countries have enrolled patients (Austria, Belgium, The Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Lithuania, The Netherlands, Romania, Spain, Slovakia and Sweden). The final list of countries and sites will depend on the VA authorisation and capability of the site to administer the treatment. Further enrollment is planned, with 12 patients at 10 sites in the UK, and 3 patients at 2 sites in Ireland.
Design	A multi-centre, multi-country, non-interventional, prospective cohort, in patients with AM. Enrolment will occur during an indefinite timeframe, with a duration of the observation period for each patient of 15 years. Patients with AM receiving and not receiving treatment with VA are/will be enrolled. The study population will be characterised by distinct clinical features and/or a short follow-up duration. This does not permit the definition of a control group and a direct, formally determined a-priori between-group comparison, allowing for descriptive, explorative between-groups comparison only. The registry is conducted under conditions of routine clinical care, without mandatory diagnostic procedures and assessments that can be considered to be outside of routine clinical care. Data collection coincides with routine care visits only according to the judgement of the treating physician. Data collection including retrospective data is allowed.
Duration of study	Observation period for each patient included is 15 years
Patient population	The study includes patients in the EU with AM, whether or not they are receiving treatment with VA.
Sample size	Currently, 40 patients have been enrolled with recruitment ongoing.
Inclusion criteria	Patients must meet all of the following inclusion criteria to be eligible for enrolment: • Evidence of a personally signed and dated informed consent form indicating that the patient (or parents or a legally acceptable representative according to

	local regulation) has been informed of all pertinent aspects of the registry and confirms the willingness to participate in the present observational study and to permit the Investigator to enter assessment data recorded prior to Registry entry if available in the patient's medical records • Diagnosis of AM (based on historical or current diagnosis)
Exclusion criteria	There are no exclusion criteria for the registry. Moreover, patients participating in other clinical trials of any placebo, drug or biological substance conducted under the provisions of a protocol will not be prevented from participating in the registry at the discretion of the investigator.
Intervention(s) (n =) and comparator(s) (n =)	Interim data (N=40): 16 treated with VA, 24 untreated with VA.
Baseline differences	At the time of the interim report, 40 patients were enrolled in the Sparkle study. Participants were 72.5% male (29 male, 11 female). Mean age was 19.55 years (range, 3-51 years), with 18 patients under 18 years and 22 patients aged 18 years or over.
Follow-up	If applicable in accordance with routine clinical practice, the following schedule of assessments is recommended: • Registry Inclusion Visit, at the time of enrolment into the registry with the signature of the informed consent • Registry baseline visit, corresponding to the time in which the observational period will start • Six-month and yearly follow-up visits for all patients included in the registry • Unscheduled follow-up visits, such as but not limited to, 3 months after VA treatment start, or whenever deemed appropriate according to treating physician's judgement for patients who start the VA treatment within 1 year prior to registry participation As patients can start VA treatment at any time during their participation in the registry, if applicable in accordance with routine clinical practice, a repeat baseline visit is recommended before VA administration, and unscheduled visits are recommended as detailed in the setting of patients starting VA treatment within 1 year prior to inclusion in the registry. On the other hand, patients can also terminate the VA treatment at any time during their participation in the registry and still be allowed to complete the 15-year follow-up period.
Statistical tests	All effectiveness variables will be summarised by means of descriptive statistics or frequency distribution, as appropriate. All variables (actual values and change from baseline, if applicable) will be presented by timepoint. In addition, mean and individual profiles by time will be produced. The proportion of responders (i.e., naïve patients able to perform the functional tests who achieve a GTR after 3 years of VA treatment) and the corresponding exact (Clopper-Pearson) Two-sided 95% CI will be presented. Effects of baseline characteristics will be evaluated by means of regression/ logistic models including the following as covariates: • Age subgroup (<18 years, ≥18 years) • Gender (male, female) • Genotype by subcellular localisation of the protein (Genotype Group 1, Genotype Group 2, Genotype Group 3, as defined by Borgwardt et al., 2015) • Baseline residual enzymatic activity (<10 nmol/h/mg, 10 to <15 nmol/h/mg, ≥15 nmol/h/mg) • Baseline CHAQ Disability Index (0|-|1, 1-|2, 2-|3) Comparison with the control group will be done descriptively, provided that a minimum number of non-treated patients with adequate data are enrolled.

Primary outcomes (including scoring methods and timings of assessments)	Primary endpoints: • Estimate the GTR rate as percentage of patients qualified as responders by aggregately assessing multiple endpoints under three GTR domains: pharmacodynamic, functional and QoL domain. The endpoints under each domain are as follows: – GTR-Pharmacodynamic Domain: Serum oligosaccharides (µmol/L) – GTR-Functional Domain: 3-MSCT (step/minute), 6-MWT (m), FVC (% of predicted) – GTR-QoL Domain: CHAQ Visual Analogue Scale-Pain and CHAQ-Disability Index. • Rate of AEs including non-serious and SAEs, non-serious and serious ADRs, AEs leading to treatment discontinuation and AEs leading to death at any time they become available • ADA, IRRs and hypersensitivity (as identified risks)
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints: The following endpoints would be evaluated to characterise the AM population, including clinical manifestation, progression and natural history: • Oligosaccharides in serum (µmol/L) • Endurance based on 3-MSCT (step/minute), 6-MWT (m) and 2-MWT (m) assessment • Respiratory function through FVC (as litre and as % of predicted) • Hearing function with PTA • Rate and length of infections (requiring antibiotics or not) • Rate of psychotic events • Immunological status as per serum IgG, IgA and IgM • QoL assessed by the EQ-5D-5L, Zarit Burden Interview, CHAQ and behaviour checklists (pre-scholar, scholar, adult and older adult) The following were also monitored as part of secondary endpoints: • Acute renal failure, loss of consciousness and medication errors (as potential risks) • Vital signs: SBP, DBP and pulse rate • ECG • Laboratory tests (haematology and chemistry) • Physical examination • Additionally, the following variables (not part of efficacy or safety assessments) will be presented: • Height, weight, body mass index and rate of growth • Hearing test (PTA) • Concomitant procedures and medications

Sources: SPARKLE Interim Reports: Chiesi data on file, 2021[18] and 2022[42]; Hennerman et al., 2020 [21]

Abbreviations: 2-MWT = 2-minute walk test; 3-MSCT = 3-minute stair climb test, 6-MWT = 6-minute walk test; ADA = anti-drug antibody; ADR = adverse drug reaction; AE = adverse event; AM = alpha-mannosidosis; CHAQ = Childhood Health Assessment Questionnaire; CI = confidence interval; DBP = diastolic blood pressure, ECG = electrocardiogram; EU = European Union; FVC = forced vital capacity; GTR = global treatment response; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IRR = infusion related reaction; QoL = quality of life; SAE = serious adverse event; SBP = systolic blood pressure, VA = velmanase alfa

1.3 Results of relevant new clinical evidence

Results of new analyses from rhLAMAN-05/-10 not included in previous submissions are described in Section 1.3.1 below. Results of the new clinical studies (rhLAMAN-08, Etoile Alpha and SPARKLE) are described in Sections 1.3.2 to 1.3.10, as well as new supporting evidence from published case reports in Section 1.3.11.

1.3.1 rhLAMAN-05 and -10: additional analyses

Since the original submission in 2018[2], results of rhLAMAN-05[14], rhLAMAN-10[15,16,36] and the multidomain responder analysis requested by the EMA[23] have been published as full-text peer-reviewed articles, and are included in Appendix B for completeness.

New analyses of rhLAMAN-05/10 not included in previous submissions are summarised below:

rhLAMAN-10: infections

In rhLAMAN-10, levels of serum IgG (a surrogate marker of humoral immunity) were measured for patients in the rhLAMAN-05 trial, and those who continued into rhLAMAN-10. In addition, a questionnaire on the disease burden of infections was administered to caregivers of patients in the rhLAMAN-10 trial. Results were presented as a conference poster by Borgwardt et al., 2018[37].

In rhLAMAN-05, treatment with VA showed improvement in serum IgG levels versus placebo and, in some cases, reverted hypogammaglobulinaemia, which in turn might decrease the infection rate and the use of antibiotics in patients with AM[37]. Of the 25 patients enrolled in rhLAMAN-05, 5 patients (4 paediatric and 1 adult) in the VA arm and 4 patients (1 paediatric and 3 adults) in the placebo arm had hypogammaglobulinaemia at treatment initiation. At last observation (LO) in rhLAMAN-10, all 5 patients in the VA arm had reverted to normal immunological patterns or improved, while no improvement was observed in the placebo arm. Of the patients in the placebo arm who switched to VA treatment under compassionate use and were evaluated after 12 months of treatment in the integrated analysis, all4 patients reverted to normal IgG status or improved IgG levels by LO. Considering only events after 1 month of treatment (assuming VA to be effective at 1 month), the rate of infection per infected patient was 1.5 with placebo vs. 0 with VA[37].

For the infection burden questionnaire in rhLAMAN-10, a total of 21 of 32 caregivers reported frequent infections as an important morbidity of AM that impacted patients' social interactions and quality of life in the pre-treatment period. In the post-treatment period, 22 of 32 caregivers reported fewer or no infections, although the exact number of infections post-treatment was not collected[37].

rhLAMAN-10 immunogenicity

In the rhLAMAN studies, a conservative approach was taken when considering patients as ADA-positive. The rhLAMAN-10 analysis included patients who were ADA-positive at any time, including pre-treatment, and a relatively low threshold of 1.4 U/mL (the lower limit of detection for the assay) was used to determine ADA status.

Using this definition, 10 patients (30.3%) were ADA-positive at some point during the study, and 23 patients (69.7%) were ADA-negative at all timepoints. Two patients had ADA measurements ≥1.4 U/mL before receiving active treatment, but once on active treatment all values were <1.4 U/mL. Therefore, only 8 patients had ADA-positive values at any time under treatment, of whom 6 had at least two tests ≥1.4. Of the 8 patients, 6 had values that fluctuated around the cut-off value of 1.4

U/mL. The remaining 2 patients had more elevated levels (maximum values of 1012 U/ml and 440 U/ml, respectively), and both experienced IRRs.

An analysis of efficacy endpoints by ADA status is described in detail in Appendix D and was published in Borgwardt et al., 2021[39]. Results showed that there was no effect of the presence of ADAs on the primary efficacy endpoints of serum oligosaccharides and 3-MSCT, or on the 6-MWT, CSF oligosaccharides or serum IgG.

rhLAMAN-10: caregiver feedback

Caregiver feedback was used in rhLAMAN-10 to assess the burden of AM through changes in social and leisure skills pre-VA and post-VA treatment and was presented as a conference poster by Lund et al., 2021[30].

Pre-treatment, 75.8% (25/33) of caregivers reported that frequent infections are an important clinical problem of AM that impacted patients' social interactions and QoL. Most patients experienced pre-treatment joint pain (51.5% [17/33]), walking difficulty (72.7% [24/33]), dexterity problems (60.6% [20/33]), and mental delay (90.9% [30/33]). The impact on patients' independence in ADL was important, for example, when eating alone because of an inability to hold cutlery properly or difficulty opening a bottle.

During the post-VA treatment period, 88.0% (22/25) of caregivers reported a reduction in patient infections. Caregivers also reported greater patient independence, measured by improved dexterity (55.0% [11/ 20]), reduced joint pain (58.8% [10/17]), and improved walking ability (66.7% [16/24]). Additionally, 66.7% (20/30) of caregivers noticed an improvement in mental delay, which included reports of increased empathy, ability to understand their surrounding environment, or improved vocabulary.

In conclusion, caregiver feedback revealed some patient status differences between pre-VA-treatment and post-VA treatment that regular trial endpoints did not capture. Each small improvement in independence and social life can markedly impact an individual's QoL, and VA treatment may elicit this additional benefit for patients with AM.

1.3.2 rhLAMAN-08: efficacy results

A summary of the key efficacy results of rhLAMAN-08 are included here, which was also published as a conference poster in 2021 by Guffon et al [17]. Efficacy, safety and HRQoL results are included below, with additional efficacy endpoints in Appendix E. No primary efficacy analysis was defined in this trial; efficacy outcomes were analysed as secondary endpoints. The results of efficacy endpoints that have aggregated data reported for all 5 patients are summarised in this section; results with listed at the individual patient level for each patient and additional endpoints are included in Appendix E.

Patient disposition and baseline characteristics

Six patients were screened in the rhLAMAN-08 trial. There was 1 screening failure due to numerous ventricular extrasystoles. All 5 enrolled patients received VA and completed the 6-, 12-, 18-and 24-month evaluation visits; patient #2501 completed the 40 months evaluation visit. No patients withdrew from the rhLAMAN-08 trial. Key baseline patient characteristics in rhLAMAN-08 are summarised in Table 7.

Table 7. Baseline characteristics of rhLAMAN-08

Characteristic	Overall (N=5)
Age, years	
Mean (SD)	4.52 (0.84)
Median (range)	4.30 (3.7–5.9)
Female, n (%)	2 (40.0)
Male, n (%)	3 (60.0)
Race, n (%) White Asian Black Other Missing	 4 (100.0) - - - 1
Weight, kg	
Mean (SD)	18.88 (2.47)
Height, cm	
Mean (SD)	104.16 (5.40)
Head circumference, cm Mean (SD)	 51.80 (3.73)
BMI, kg/m^2	
Mean (SD)	17.35 (1.09)

Abbreviations: BMI = body mass index; SD = standard deviation

Source: Chiesi [40]; Guffon [17]

rhLAMAN-08 results: serum oligosaccharides

At 24 months, there was a decrease in serum oligosaccharides compared to baseline: 5 patients for GlcNac(Man)2; 4 patients for GlcNac(Man)3 (the 5th patient had concentrations below lower limit of quantification [LLOQ]); and 1 patient for GlcNac(Man)4 (the other 4 patients had concentrations below LLOQ). The mean decrease from baseline after 24 months was [redacted] % (range: [redacted] % to [redacted] %) for the 5 patients for GlcNac(Man)2. The mean decrease was [redacted] % (range: [redacted] % to [redacted] %) for 4 patients for GlcNac(Man)3, and was [redacted] % for 1 patient for GlcNac(Man)4. Table 8 summarises results based on aggregated data for all patients whose serum oligosaccharides concentrations were not below LLOQ.

At the 40 months evaluation visit performed only for 1 patient (Patient #2501), the decrease from baseline was [redacted] % for GlcNac(Man)2 and [redacted] % for GlcNac(Man)3, with serum concentration of GlcNac(Man)4 below LLOQ.

A decrease in serum concentration of GlcNac(Man)2 compared to baseline was observed at all visits (i.e., at 6, 12, 18 months visits) until 24 months. Serum concentrations of GlcNac(Man)3 were below LLOQ for all patients except 1 at the 18-month visit. A decrease in serum concentrations of GlcNac(Man)3 compared to baseline was observed at the other visits until 24 months. Serum concentrations of GlcNac(Man)4 were below LLOQ for all patients at the 18 months visit. A decrease in serum concentrations of GlcNac(Man)3 compared to baseline was observed at the other visits until 24 months. Serum concentrations of GlcNac(Man)5 and GlcNac(Man)6 were below LLOQ for all patients at all visits.

Table 8. rhLAMAN-08: Change from baseline in serum oligosaccharides

			Serum GlcNac(Man)2	Serum GlcNac(Man)3	Serum GlcNac(Man)4
Baseline Visit	Actual values (µmol/L)	n	[redacted]	[redacted]	[redacted]
		Mean (SD)	[redacted]	[redacted]	[redacted]
		Median (Min ; Max)	[redacted]	[redacted]	[redacted]
		IQR	[redacted]	[redacted]	[redacted]
24 months evaluation visit	Actual values (µmol/L)	n	[redacted]	[redacted]	[redacted]
		Mean (SD)	[redacted]	[redacted]	[redacted]
		Median (Min ; Max)	[redacted]	[redacted]	[redacted]
		IQR	[redacted]	[redacted]	[redacted]
	Change from baseline	n	[redacted]	[redacted]	[redacted]
		Mean (SD), µmol/L	[redacted]	[redacted]	[redacted]
		Mean (SD), %	[redacted]	[redacted]	[redacted]
		Median (IQR), µmol/L	[redacted]	[redacted]	[redacted]
		Median (IQR), %	[redacted]	[redacted]	[redacted]

Abbreviations: IQR = interquartile range; max = maximum; min = minimum; SD = standard deviation

[a] Actual serum concentration – data available for only one patient

[b] Actual change/percent change from baseline for the patient

Source: Chiesi [40]

rhLAMAN-08: 6-MWT

The 6-MWT was administered to all 5 patients, with results obtained from 4 patients; lack of motivation was noted for one patient, at the baseline assessment, and the 6-, 18- and 24-month visits. Results were obtained from all 5 patients at the 12 months visit. Based on the available data, the mean (SD) and median (Q1, Q3) 6-MWT at baseline were [redacted] metres and [redacted] metres, respectively. At 6 months, 12 months, 18 months and 24 months, mean (SD) 6-MWT were [redacted] metres, respectively. The corresponding median (Q1, Q3) total distances were [redacted] metres, respectively.

At 24 months, an improvement from baseline (i.e., increase in the total distance walked in 6 minutes) was noted for 3 patients ranging from [redacted] (2 patients assessed at 24 months, and 1 patient at an unscheduled visit approximately 26 months after baseline). One patient (Patient #2501), evaluated at both 24 and 40 months, had a decrease from baseline of [redacted]% at 24 months, but an increase from baseline of [redacted]% at 40 months. Results are shown in Figure 5.

Figure 5. rhLAMAN-08: results of the 6-MWT (n=5)

Source: Chiesi [40]

rhLAMAN-08: 3-MSCT

The 3-MSCT was administered to all 5 patients. Results were obtained from 4 patients, and lack of motivation was noted for 1 patient, at baseline and the 6 months and 12 months. Based on available data, the mean (SD) and median (Q1, Q3) total steps climbed in 3 minutes at baseline were steps and steps, respectively. At 6 months, 12 months, 18 months and 24 months, mean (SD) 3-MSCT were steps, respectively. The corresponding median (IQR) 3-MSCT were steps, respectively.

At 24 months, an improvement from baseline (i.e., increase in the number of steps climbed in 3 mins) was noted for 2 patients ranging from % (1 patient assessed at 24 months and another at an unscheduled visit at approximately 26 months), and decreases from baseline (of %) were noted for 2 patients. One patient evaluated at both 24 and 40 months had a decrease from baseline of % at 24 months, but an increase from baseline of % at 40 months. Results of the 3-MSCT are shown in Figure 6.

Figure 6. rhLAMAN-08: results of the 3-MSCT (n=5)

Source: Chiesi [40]

rhLAMAN-08: immunological profile

Change from baseline in serum concentrations of IgG, IgA and IgM were analysed; the results are summarised in Table 9. At baseline, the mean (SD) concentrations for serum IgG, IgA and IgM were g/L, respectively and median (Q1, Q3) concentrations for serum IgG, IgA and IgM were g/L, respectively.

An increase in serum IgG concentration compared to baseline was observed at all evaluation visits until 24 months of treatment, with the greatest increase observed at the 6-month evaluation visit. An increase in serum IgA concentration compared to baseline was observed at all evaluation visits until 24 months of treatment, with the greatest increase at the 6-month evaluation visit. A decrease in serum IgM concentrations compared to baseline was noted at all evaluation visits until the 18-month evaluation visit when mean (SD) and median (Q1, Q3) concentrations were g/L, respectively; mean (mean percent) and median (median percent) decreases from baseline were g/L %) and g/L % respectively.

No trends were noted for change from baseline for other immunological parameters assessed, or for parameters related to in vitro synthesis of IgG.

Table 9. rhLAMAN-08: change from baseline in serum Ig concentrations

			Serum IgG	Serum IgA	Serum IgM
Baseline visit	Actual values (µmol/L)	n			
		Mean (SD)			
		Median (Min ; Max)			
		IQR			
24-month evaluation	Actual values (µmol/L)	n			
		Mean (SD)			

			Serum IgG	Serum IgA	Serum IgM
visit		Median (Min ; Max)	[redacted]	[redacted]	[redacted]
		IQR	[redacted]	[redacted]	[redacted]
	Change from baseline	n	[redacted]	[redacted]	[redacted]
		Mean (SD), µmol/L	[redacted]	[redacted]	[redacted]
		Mean (SD), %	[redacted]	[redacted]	[redacted]
		Median (IQR), µmol/L	[redacted]	[redacted]	[redacted]
		Median (IQR), %	[redacted]	[redacted]	[redacted]

Abbreviations: IgA = immunoglobin A; IgG = immunoglobin G; IgM = immunoglobin M; IQR = interquartile range; max = maximum; min = minimum; SD = standard deviation

Source: Chiesi [40]

rhLAMAN-08: additional endpoints

Results of additional endpoints are shown in Appendix E and were published in Guffon, 2021 [17]. Results showed slight but initial improvements of hearing function in children aged <6 years, suggesting that hearing functionality could benefit from initiation of treatment at an early age [44]. For the automatic auditory brainstem response (A-ABR) audiometry test, for 1 patient, hearing was assessed as abnormal at baseline and normal at subsequent assessments. Treatment with VA also showed improvement in functional capacity, as assessed by the Peabody Developmental Motor Scale – 2nd edition (PDMS-2), and the Mullen Scales of Early Learning (MSEL).

1.3.3 rhLAMAN-08: QoL results

rhLAMAN-08 showed improvement from baseline in HRQoL, as measured using the PEDI questionnaire, for all 5 trial patients with long-term VA treatment. [redacted]

1.3.4 rhLAMAN-08: safety and tolerability in paediatric patients

The primary endpoints of rhLAMAN-08 were safety and tolerability (as per AEs including IRRs, vital signs and clinical laboratory parameters), and detection of ADAs. Safety data were presented as a conference abstract in 2021[17] and are being submitted for publication.

The mean (SD) duration of exposure was [redacted] weeks with a median exposure of 108.3 (range, 105.4, 169.6) weeks, and actual exposure ranging from [redacted] weeks. One patient enrolled in France received VA for 40 months, while other patients received VA for 24 months[17].

All patients experienced TEAEs (184 events), including serious TEAEs (15 events). The majority of TEAEs were mild/moderate in intensity; only 1 event was severe in intensity and serious. Four (80.0%) patients experienced adverse drug reactions (ADR) (16 events) of which 2 events were serious, 3 (60.0%) patients experienced IRRs (15 events) of which 2 events were serious, and 3 (60.0%) patients experienced TEAEs within 2 hours of the start of VA infusion (15 events), of which 2 events were serious. There were no TEAEs leading to discontinuation of study treatment and no deaths were reported during the study. The summary of AEs experienced by trial patients is presented in Table 10 [17].

The most frequently reported TEAEs (in ≥40.0% of patients by preferred term, PT) included vomiting (11 events in 5 [100%] patients), pyrexia (20 events in 4 [80%] patients, cough (10 events in 4 [80%] patients. A total of 15 serious TEAEs were reported in 5 [100%] patients. Serious TEAEs were most frequently reported (in ≥40% of patients by system organ class, SOC) from the SOCs Infections and Infestations (4 events in 2 [40%] patients), Gastrointestinal Disorders (2 events in 2 [40%] patients) and Respiratory, Thoracic and Mediastinal Disorders (2 events in 2 [40%] patients). No PT was reported for >1 patient during the study for serious TEAEs.

Other frequently occurring TEAEs are listed in Table 11. In terms of AEs concerning vital signs, no TEAEs relating to changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) or respiratory rate were reported for any patient during the study. There were no meaningful safety signals arising from physical examination, electrocardiograms (ECG) or echocardiograms. For one patient, clinically significant findings on examination of the skin were reported as a sign of the moderate, serious TEAE (PT: Henoch Schönlein purpura), which resolved after treatment, and was judged as not related to study treatment or to infusion.

Two patients experienced a total of 12 IRRs during the trial. Two moderate IRRs (PTs: chills and hyperthermia), experienced by the same patient (Patient #2501), were assessed as serious; the events resulted in overnight hospitalisation and reduction in the dose of study treatment. The dose of study treatment was reduced for only one other patient due to a moderate event (PT: urticaria). All events of IRRs were manageable with no event leading to discontinuation of study treatment. All IRRs were assessed as ADRs. The outcomes of all IRRs were reported as recovered/resolved. The most frequently reported PT was urticaria (5 events), followed by chills (3 events), anal pruritus (3 events), hyperthermia (2 events) and cyanosis (2 events). One patient (Patient #2501) experienced approximately 50% (7 events) of the reported IRRs (PTs: chills [3 events], hyperthermia [2 events] and cyanosis [2 events]). Patient #2771 experienced 5 events of urticaria, and Patient #3801 experienced 3 events of anal pruritus.

All patients were negative for ADAs at baseline and 4 patients developed ADAs during the trial. Of these 4 patients, only 1 patient developed clinically relevant high concentration of ADAs (maximum concentration:174 U/mL), and 3 patients developed neutralising/inhibitory antibodies.

Table 10. rhLAMAN-08: summary of AEs

AE	Overall (N=5)	
	n (%) of patients	Number of events
Pre-treatment AEs	4 (80.0)	10
TEAEs	5 (100.0)	184
Serious TEAEs	5 (100.0)	15
Severe TEAEs	1 (20.0)	1
ADRs	4 (80.0)	16
IRRs	2 (40.0)	12
TEAEs leading to discontinuation of study treatment	0 (0.0)	0
TEAEs leading to death	0 (0.0)	0

Abbreviations: ADR = adverse drug reaction; AE = adverse event; IRR = infusion-related reaction; TEAE = treatment-emergent adverse event; VA = velmanase alfa

Source: Guffon [17]; Chiesi [40]

Table 11. rhLAMAN-08: TEAEs in ≥40.0% of patients

AE	N=5	
	n (%)	Events
Infections and infestations		
Otitis media	4 (80.0)	9
Nasopharyngitis	3 (60.0)	10
Rhinitis	3 (60.0)	10
Conjunctivitis	2 (40.0)	4
Ear infection	2 (40.0)	5
Gastroenteritis	2 (40.0)	6
Tonsillitis	2 (40.0)	2
Upper respiratory tract infection	2 (40.0)	5
Gastrointestinal disorders		
Vomiting	5 (100.0)	11
Diarrhoea	3 (60.0)	4
Dental caries	2 (40.0)	2
General disorders and administration site conditions		
Pyrexia	4 (80.0)	20
Respiratory, thoracic and mediastinal disorders		
Cough	4 (80.0)	10
Oropharyngeal pain	2 (40.0)	2
Injury, poisoning and procedural complications		
Fall	2 (40.0)	2
Ligament sprain	2 (40.0)	2
Skin and subcutaneous tissue disorders		
Swelling face	2 (40.0)	2

Abbreviation: AE = adverse event

Source: Guffon [17]; Chiesi [40]

1.3.5 rhLAMAN-08: conclusions

rhLAMAN-08 showed long-term treatment with VA for 24 months (40 months for 1 patient) was well tolerated and efficacious in the reduction of serum oligosaccharides and increasing IgG levels from baseline in patients with AM <6 years of age.

- After 24 months of treatment, serum oligosaccharides concentrations decreased compared to baseline for 5 patients for GlcNac(Man)2 (of [redacted] %), 4 patients for GlcNac(Man)3 (of [redacted] %) and 1 patient for GlcNac(Man)4 (of [redacted]%).
- After 24 months, there was an increase vs. baseline in serum IgG concentrations for 5 patients (of [redacted] %). An increase in serum IgA concentrations was noted for 4 patients (of [redacted] %), and a decrease for 1 patient (of [redacted]%). There was a decrease in serum IgM concentrations for 4 patients (of [redacted] %) and an increase of [redacted]% for 1 patient.

Treatment with VA showed improvement in endurance from baseline, as assessed by the 6-MWT and 3-MSCT.

- Improvements vs. baseline were observed in the 6-MWT for 3 patients (from [redacted]%) after 24 months of treatment. The patient who received treatment for 40 months had a decrease (-[redacted]%) from baseline at 24 months, but an increase from baseline after 40 months (+[redacted]%).
- Improvements vs. baseline were also observed in the 3-MSCT for 2 patients (of [redacted] %) after 24 months of treatment. One patient had a small decrease (- [redacted]%) from baseline. The patient who received treatment for 40 months had a decrease from baseline (- [redacted]%) at 24 months, but an increase from baseline after 40 months (+ [redacted]%).

In rhLAMAN-08, the lack of accumulation of VA at steady state and the safety/efficacy results confirmed that the dose of 1 mg/kg is appropriate in patients younger than 6 years.

Overall, treatment with VA was well tolerated with the majority of TEAEs being mild/moderate in intensity. No TEAEs resulted in treatment discontinuation during the 24-month treatment duration (40 months for 1 patient), suggesting long-term tolerability of VA in patients with AM <6 years:

- The most frequently reported TEAEs were vomiting (100.0% of patients), pyrexia (80.0%), cough (80.0%), otitis media (80.0%), nasopharyngitis (60.0%), rhinitis (60.0%) and diarrhoea (60.0%).
- For serious TEAEs, no PT was reported for >1 patient. The majority of events were moderate in intensity with only 1 event of severe intensity (PT: concussion). Patients received appropriate treatment and the outcome of all events was recovered/resolved.
- Twelve events of IRRs were experienced by 2 patients, of which 2 events were assessed as serious. All IRRs were of mild/moderate intensity. All events were manageable with outcome reported as recovered/resolved.
- All patients were negative for ADAs at baseline and 4 patients developed ADAs during the trial. Of these 4 patients, only 1 patient developed clinically relevant high concentration of ADAs (maximum concentration: 174 U/mL).

1.3.6 Etoile Alpha: efficacy results

Etoile Alpha was a retrospective French registry study conducted in 16 patients receiving VA in France up to June 2020, as a requirement of conditional market access and data collection by the *Haute Autorité de Santé* of France (HAS)[18]. Results have been submitted for publication so are marked as academic in confidence (AIC). Key efficacy results, HRQoL and safety are included here, with patient case reports in Section 1.3.11 and additional efficacy endpoints in Appendix F.

Patient disposition for Etoile Alpha study

The study included a total of [redacted]) who received VA. Data were collected retrospectively.

The study included [redacted] patients ([redacted] female and [redacted] male) with an average age of [redacted] years. The average age at the time of diagnosis was [redacted] years; excluding the [redacted] outliers aged [redacted] and [redacted] years at the time of diagnosis, the average age at diagnosis was [redacted] years. The average age when VA was first administered to the patients was [redacted] years. Finally, the average duration of treatment with VA was [redacted] months. Patient demographics are summarised in Table 12.

Table 12. Patient demographics of Etoile Alpha study

Patient	Age (years)	Female	Male	Date VA initiated	Age at time of diagnosis (years)	Age at VA exposure (years)	Duration of VA use (months)
0101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0102	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0105	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0106	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0107	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0110	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0111	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0201	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0301	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0401	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0402	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Chiesi [18]

Efficacy results: Intraclass correlation coefficient analysis

Disease stabilisation or improvement, absence of respiratory infections, and digression of patient's overall health status were considered the most clinically meaningful measures of treatment effectiveness, considering the small sample size and the nature of the disease rendering precise estimation of specific disease factors due to comorbidities.

An intraclass correlation coefficient (ICC) analysis for each category (biochemical oligosaccharides, brain biomarkers concentration, functional, respiratory, cognitive, audiometric, neurological, quality of life and BOT-2 test) was calculated to determine the extent of uniformity and the consistency of effect across patients for each category. A low ICC, close to 0, indicates that the treatment effects across patients for the same category are not similar. According to clinical KOLs, an ICC between 0.75 and 0.9 is considered as a good ICC, while an ICC greater

than 0.90 indicates excellent reliability. A high ICC close to 1 indicates high similarity between values from the same group. The ICC values were calculated on the mean percentage change for each efficacy variable from baseline until the last assessment, and are presented in Table 13.

[redacted]

Table 13. Etoile-Alpha: ICC results across different categories (N=16)

Variable	ICC	P-value	CI
Biochemical variables - oligosaccharides	[redacted]	[redacted]	[redacted]
Biochemical variables – CSF	[redacted]	[redacted]	[redacted]
Respiratory variables	[redacted]	[redacted]	[redacted]
Functional variables	[redacted]	[redacted]	[redacted]
Audiometric variables	[redacted]	[redacted]	[redacted]
Cognitive and IQ variables	[redacted]	[redacted]	[redacted]
Cognitive, memory and visualisation variables	[redacted]	[redacted]	[redacted]
Neurological variables	[redacted]	[redacted]	[redacted]
Quality of life	[redacted]	[redacted]	[redacted]
BOT-2	[redacted]	[redacted]	[redacted]

Source: Chiesi [18]

Abbreviations: BOT-2 = Bruininks-Oseretsky test of motor proficiency 2nd edition; CI = confidence interval; CSF = cerebrospinal fluid; ICC = intraclass correlation coefficient

Laboratory variables

Results of changes in important biochemical parameters are presented in Table 14. Overall, there was an average decrease in serum oligosaccharides (-[redacted]%) and urinary oligosaccharides (-[redacted]%). [redacted]

Table 14. Etoile Alpha: laboratory changes over time

Patient	% change in Serum oligosaccharide from baseline to last month of evaluation	% change in urinary oligosaccharide from baseline to last month of evaluation	% change in CSF oligosaccharide from baseline to last month of evaluation	% change in CSF NFL from baseline to last month of evaluation	% change in CSF Tau from baseline to last month of evaluation	% change in CSF GFA from baseline to last month of evaluation	Serum IgG BASELINE (g/L)	Serum IgG last month of evaluation (g/L)
0101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0102	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0105	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0106	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0107	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0110	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0111	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0401	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Chiesi [18]

Abbreviations: CSF = cerebrospinal fluid; IgG = immunoglobin G

Figure 7. ICC Scatterplot and boxplot for oligosaccharides

X-axis legend: 1 = S-Oligosaccharides; 2 = U-Oligosaccharides
Source: Chiesi [18]

Figure 7 shows patient data observed for serum and urinary oligosaccharides. During VA treatment, U- and S-oligosaccharide outcomes were [redacted] vs. baseline. Due to the quantity of missing data, the ICC results and the corresponding P value must be interpreted with caution.

For CSF biochemical variables (Figure 8), [redacted].

Figure 8. ICC Scatterplot and boxplot for CSF biochemistry

X-axis legend: 1 = CSF Oligosaccharides; 2 = CSF NPL; 3 = CSF Tau; 4 = CSF GFA
Source: Chiesi [18]
Abbreviation: CSF = cerebrospinal fluid

Serum IgG concentrations [redacted] during treatment with VA, as seen in Figure 9.

Figure 9. ICC, scatterplot and boxplot for biochemical tests: serum IgG

Source: Chiesi [18]

Abbreviation: CSF = cerebrospinal fluid

Functional variables

Results of 3-MSCT and 6-MWT are presented in Table 15.

Table 15. Walking test results over time

Patient	3-MSCT (mean absolute value) BASELINE (m)	3-MSCT (mean absolute value) last available month (m)		6-MWT (mean absolute value) BASELINE (m)	6-MWT (mean absolute value) last available month (m)
0101	[redacted]	[redacted]		[redacted]	[redacted]
0102	[redacted]	[redacted]		[redacted]	[redacted]
0104	[redacted]	[redacted]		[redacted]	[redacted]
0105	[redacted]	[redacted]		[redacted]	[redacted]
0106	[redacted]	[redacted]		[redacted]	[redacted]
0107	[redacted]	[redacted]		[redacted]	[redacted]
0108	[redacted]	[redacted]		[redacted]	[redacted]
0109	[redacted]	[redacted]		[redacted]	[redacted]
0110	[redacted]	[redacted]		[redacted]	[redacted]
0111	[redacted]	[redacted]		[redacted]	[redacted]
0112	[redacted]	[redacted]		[redacted]	[redacted]
0201	[redacted]	[redacted]		[redacted]	[redacted]
0301	[redacted]	[redacted]		[redacted]	[redacted]
Average	[redacted]	[redacted]		[redacted]	[redacted]
Median	[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: 3-MSCT = 3 minute stair climb test; 6-MWT = 6 minute walk test

Source: Chiesi [18]

As seen in Figure 10, most of the values are [redacted].

Figure 10. ICC, scatterplot and boxplot: 3-MSCT and 6-MWT efficacy criteria

X-axis legend: 1 = 3-MSCT; 2 = 6-MWT

Source: Chiesi [18]

Abbreviations: 3-MSCT = 3 minute stair climb test; 6-MWT = 6 minute walk test

Respiratory variables

The average FVC, PEF and the FEV_1 at baseline were [redacted], respectively, vs. [redacted] in the last month of evaluation. [redacted] (Table 16).

Table 16. Respiratory function test results over time

Patient	FVC Baseline	PEF Baseline	FEV_1 Baseline	FVC Last available month	PEF Last available month	FEV_1 Last available month
0101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0102	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0105	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0106	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0107	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0110	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0111	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0301	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FEV_1 = forced expiratory volume; FVC = forced vital capacity; PEF = peak expiratory flow

Source: Chiesi [18]

With an ICC of [redacted], the values were [redacted], as seen in Figure 11. [redacted].

Figure 11. ICC, scatterplot and boxplot for respiratory function tests

X-axis legend: 1 = FVC; 2 = FEV_1; 3 = PEF

Source: Chiesi [18]

Abbreviations: FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow

Etoile-Alpha: additional endpoints

Results of additional endpoints are included in Appendix F, including neurological, audiometry, cognitive, BOT-2 test and left ventricular ejection fraction (LVEF) tests. Outcomes regarding cognitive function were not fully clear due to the large quantity of missing data. But results showed there was an overall [redacted].

1.3.7 Etoile-Alpha: QoL

In Etoile Alpha, QoL was measured using the CHAQ and EQ-5D-5L questionnaires. Baseline data from CHAQ, and most of EQ-5D-5L were not fully available. In general, a conclusion on the improvement of cognitive abilities cannot be determined due to the quantity of missing comparative data from baseline. For interpretation of the results below, Dempster et al.[45] showed that the median CHAQ scores corresponding to mild, mild-to-moderate, and moderate disability were [redacted], respectively, which may be used to interpret the results presented in Table 17.

Table 17. Etoile Alpha: CHAQ and EQ-5D-5L QoL questionnaires (n = 7)

Patient	CHAQ disability index at month 30	EQ-5D-5L index at month 30	EQ-5D-5L % change from baseline at month 30
0101	[redacted]	[redacted]	[redacted]
0102	[redacted]	[redacted]	[redacted]
0103	[redacted]	[redacted]	[redacted]
0105	[redacted]	[redacted]	[redacted]
0106	[redacted]	[redacted]	[redacted]

Patient	CHAQ disability index at month 30	EQ-5D-5L index at month 30	EQ-5D-5L % change from baseline at month 30
0107	[redacted]	[redacted]	[redacted]
0112	[redacted]	[redacted]	[redacted]
Average	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Abbreviation: CHAQ = Childhood Health Assessment Questionnaire

Due to limited availability of QOL data and the widely scattered results, no cluster or global trend could be observed. However, some [redacted] outliers for some classes were noted (2 = CHAQ, evaluation of pain; 3 = CHAQ, evaluation of overall wellbeing; 4 = EQ-5D-5L, mobility; 5 = EQ-5D-5L, self-care; 7 = EQ-5D-5L, pain/discomfort), demonstrating [redacted] in QoL for some patients (Figure 12).

Figure 12. Scatterplot and boxplot for QoL results

X-axis legend: 1 = CHAQ - Disability Index, 2 = CHAQ - Evaluation of pain, 3 = CHAQ - Evaluation of overall well-being, 4 = EQ-5D-5L Mobility, 5 = EQ-5D-5L - Self-care, 6 = EQ-5D-5L - Usual activities, 7 = EQ-5D-5L - Pain/discomfort, 8 = EQ-5D-5L - Anxiety/depression

Abbreviation: CHAQ = Childhood Health Assessment Questionnaire

1.3.8 Etoile Alpha: safety and tolerability

In Etoile Alpha, the average duration of exposure to treatment with VA was [redacted] months. The average age at which the treatment was first initiated was [redacted] years. Overall, treatment with VA was well tolerated; only [redacted] events were reported as serious, with outcomes reported as resolved for both events. [redacted] deaths occurred during the study. Few respiratory infections occurred during the review period; absence of these in a population that is vulnerable to respiratory infection can be interpreted as a sign of treatment effect.

[redacted]

1.3.9 Etoile Alpha: conclusions

Etoile Alpha was conducted in patients receiving VA in France up to June 2020, as a requirement of conditional market access by HAS [18]. In Etoile-Alpha, the ICC, which reflects the uniformity and the consistency of effect across different tests, was calculated for each category of variables (biochemical, functional, respiratory, cognitive and audiometric, neurological, QoL and BOT-2 test). Results showed [redacted].

For oligosaccharides, there was a [redacted] in surrogate markers that support treatment efficacy, with a [redacted] concentrations. No signs of decrease in surrogate markers such as the [redacted].

During the assessment period, [redacted].

In terms of respiratory function, there was an [redacted].

In conclusion, the investigators' opinions on each patient were evaluated in detail and an overall [redacted]. The results of Etoile Alpha were submitted as part of the reassessment by HAS in January 2022. The Transparency Committee considered that the new data available are likely to modify its previous assessment of the service medical rendu (SMR) rating from a "moderate" rating to a "high" rating, resulting in VA gaining reimbursement in France[46].

1.3.10 SPARKLE Registry: Safety and tolerability

The AM Registry, also known as the SPARKLE study, was requested by the EMA in connection with VA's marketing authorisation and RMP. The Sparkle study aims to collect additional information on long-term effectiveness and safety of VA up to 15 years. Furthermore, the study aims to expand the current understanding of AM, by collecting additional data on natural history in patients with AM despite the therapeutic treatment they receive. Study methodology is summarised in Table 6.

The enrolment for participation in the registry will occur during an indefinite timeframe. The duration of the observation period for each patient is 15 years. Interim reports are submitted to the EMA as part of its yearly reassessment process. The information presented here is from the 2nd yearly interim report, with data collection start date of 31 January 2020 and data-lock point (DLP) of 14 Oct 2021[42].

Patient disposition for Sparkle study

At the time of the 2nd interim report, 40 patients were enrolled in the Sparkle study. The first patient was enrolled on 10 December 2019 in Denmark. There are currently 24 active sites in Europe, with 21 sites having patients enrolled, comprising: 4 sites in Italy, 2 sites each in Austria, Germany and Spain, and 1 site each in Belgium, The Czech Republic, Denmark, Finland, France, Hungary, Lithuania, The Netherlands, Romania, Slovakia and Sweden. Further patient enrollment is planned, with 12 patients at 10 sites in the UK, and 3 patients at 2 sites in Ireland.

The key baseline patient characteristics in Sparkle are summarised in Table 18.

Table 18. Baseline characteristics of Sparkle: interim data (n = 40)

	N = 40
Age [years, mean (SD)]	19.55 (11.98)
Age [years, median (min , max)]	19.00 (3.0, 51.00)
Age class, n (%) <18 years ≥18 years	 18 (45.0%) 22 (55.0%)
Gender, n (%) Male Female	 29 (72.5%) 11 (27.5%)

Abbreviations: max = maximum; min = minimum; SD, standard deviation

Source: Chiesi data on file, 2022 [42]

Sparkle Registry: interim safety results

Given the low number of patients enrolled in this study and the short mean follow-up duration, no effectiveness data are yet available; only safety results were included in the interim report. During the reference period, 16 of the 40 enrolled patients received treatment with VA. At the DLP for this report, no patient had completed the long-term observation period of 15 years; all enrolled patients had a follow-up duration of less than 2 years[42].

During the reference period, 2 serious study-emergent AEs were reported in 2 patients (preferred terms, PT: COVID-19 and joint dislocation). Neither were considered treatment-related, were either mild or moderate in intensity and both patients recovered from the events.

A total of 14 study-emergent adverse drug reactions were reported in 2 patients; 1 patient experienced 1 event (PT: night sweats) and 1 patient experienced 13 events (PTs: 3 events each of apathy, hypotonia and pallor, and 1 event each of mild fever, restlessness, tachycardia and hypotension). All events were considered possibly related, were mild in intensity, and none were considered serious. All events were resolved. The above events of hypotension, apathy, hypotonia and pallor were considered infusion-related reactions (IRRs); a total of 10 IRRs in 1 patient. No other IRRs were reported, and no events of ADAs or hypersensitivity were reported.

1.3.11 Supportive evidence: case reports

UK case report of an adult patient treated with VA

The UK MPS Survey reported QoL in a UK adult patient treated with VA as part of rhLAMAN-05 who continued treatment on compassionate use[10]. The patient was 30 years old when VA was initiated, and 34 years old at the time of the survey. Treatment with VA was reported by the patient to improve physical symptoms, causing a reduction in joint pain and rate of ear infections, and a patient-perceived improvement in gait. The health and HRQoL of both the patient and their carers improved. At the time of the survey, the patient was walking with assistance (using supportive footwear) and the EQ-5D-5L utility value for this patient was 0.758 compared with 0.378 for patients who received best supportive care only.

Long-term treatment of the same patient aged 37 years was reported at >5 years post-treatment with VA by Cole et al.[20]. Pre-treatment, the patient exhibited many clinical manifestations of AM; post-treatment, there was stabilisation and some improvement observed, as described in Table 19.

Table 19. Clinical outcomes of long-term VA treatment in an adult UK patient

Domain	Pre-treatment	>5 years post-treatment
Musculoskeletal system	• Significant musculoskeletal pain; especially in ankles with analgesia requirements • Bilateral foot deformities; knee effusions	• Improvement in pain scores and reduction in analgesia requirements • No change in foot deformities, awaiting surgical orthopedic procedure
Immune system	• Frequent ear infections requiring antibiotic treatment, occurring every 3-4 months	• No further ear infections and several years since antibiotics have been required
Cognition and social skills	• Poor attention span, difficulty reading • Significant anxiety around	• Significant subjective improvement reported by family • Able to read books; improved

	ADL, eg. handling money and taking public transport • Difficulty speaking to strangers and answering questions	confidence leading to increases in independence, such as attending community groups • Now volunteers in a charity shop and deals with customer enquiries and money handling
Mobility and coordination	• Timed sit to stand: 15 secs • 6MWT = 340m • Outdoor mobility = 50m	• Timed sit to stand: 5 secs • 6MWT = 500m • Outdoor mobility = unlimited

6MWT = 6-minute walk test; ADL = activities of daily living; VA = velmanase alfa

Source: Cole et al., 2021 [20]

rhLAMAN-05: case reports of patients with hearing impairment

Treatment with VA has the potential to improve conductive hearing impairment and infections in AM, as evidenced from a published case report of 2 patients from the rhLAMAN programme who had hypogammaglobulinaemia and a history of hearing impairment and infections[43].

- Patient 1 was a child who received placebo for 12 months, switched to VA at study conclusion, and reached 15 months of treatment at the time of this evaluation. Patient 1 had a history of medical and surgical ear problems. On placebo, the child experienced 5 episodes of nasopharyngitis and ear discomfort. Post-VA treatment, no events were recorded; improvements were reported PTA bone conduction in the best ear; and PTA air conduction in both ears.
- Patient 2 was an adult who received VA for 27.5 months. Patient 2 had a similar history of medical and surgical ear problems and recurrent infections; PTA bone conduction and PTA air conduction improved in both ears post-VA treatment. After the first 12 months of VA treatment, no infective events were reported.

Patient 1 achieved, and patient 2 approached, a decrease (improvement) of 15 dB HL vs. baseline, the MCID in noise-related hearing impairment. Both patients had normal IgG levels post-treatment.

Etoile Alpha: French case reports of patients treated with VA

Investigator case reports on the [redacted] patients treated with VA in the Etoile Alpha study are summarised in Table 20. According to the investigators, many clinical manifestations of AM observed in patients either improved or stabilised, including balance and coordination, muscular weakness, motor skills, cognitive delay, pain, tiredness, joint abnormalities and respiratory infections[24]. These reports support the plausible potential of VA to improve or stabilise the symptoms of AM in both adults and children with AM, and the benefits of early treatment initiation.

Table 20. Etoile Alpha: Investigator remarks for each patient (N=16)

Patient ID	Age, Sex (age diagnosed)	Age at VA initiation (treatment duration)	Remarks before VA	Remarks after VA
0101	[redacted]	[redacted]	[redacted]	[redacted]
0102	[redacted]	[redacted]	[redacted]	[redacted]
0103	[redacted]	[redacted]	[redacted]	[redacted]

0104	[redacted]	[redacted]	[redacted]	[redacted]
0105	[redacted]	[redacted]	[redacted]	[redacted]
0106	[redacted]	[redacted]	[redacted]	[redacted]

0107	[redacted]	[redacted]	[redacted]	[redacted]
0108	[redacted]	[redacted]	[redacted]	[redacted]
0109	[redacted]	[redacted]	[redacted]	[redacted]

			[redacted]	[redacted]
0110	[redacted]	[redacted]	[redacted]	[redacted]
0111	[redacted]	[redacted]	[redacted]	[redacted]
0112	[redacted]	[redacted]	[redacted]	[redacted]

0201	[redacted]	[redacted]	[redacted]	[redacted]
0301	[redacted]	[redacted]	[redacted]	[redacted]
0401	[redacted]	[redacted]	[redacted]	[redacted]
0402	[redacted]	[redacted]	[redacted]	[redacted]

Source: Etoile Alpha CSR, Chiesi data on file [18]

Real-world case series of adult patients treated with VA

A case series of 5 adult patients treated with VA in 3 European centres demonstrates the plausible potential of VA to delay disease progression, retain or improve walking ability and maintain function and school/work attendance over time. This is contrary to what would be expected from the natural course of untreated patients with AM, whose function declines with age[19].

- Patient 1 (male, aged 21 years, Spain): treated continually[2] with VA for over 10 years from childhood to adult life, initially as part of the rhLAMAN programme and continued in the SPARKLE registry. Despite mild progression of sensorineural hearing loss and maturation delay, other AM manifestations remained stable, with no motor progression, bone pain or difficulty in movement. No adverse effects of treatment were observed. The patient completed secondary education and is employed as a stockman.
- Patient 2 (female, aged 20 years, Lithuania): diagnosed at 4 years but could only access VA treatment aged 18 years after reimbursement was approved. Prior to treatment, the patient could walk short distances unassisted until age 17 years, but required a wheelchair at 18 years due to progressive arthropathy and spinal abnormalities. At 6 months after VA initiation, the patient had decreased oligosaccharide levels, better cognitive function and improved physical disability. No adverse reactions were observed. Post-treatment, intellectual disability and speech improved, with improved communication and ability to socialise. She also reported she was physically stronger and could move without a wheelchair with a little assistance.
- Patients 3 and 4 (male and female siblings, aged 28 and 24 years respectively, Spain): treated from childhood for over 7 years as part of rhLAMAN-05/10. Treated continually except for a temporary period of 60-70 days during COVID-19 lockdown. During this time without ERT, both patients showed worsening of gait/mobility and problems with social interaction. Treatment was restarted in June 2020 with progressive improvement in motor symptoms, which returned to previous baseline. Since starting ERT, both patients have not suffered any serious infections or required hospitalization in over 7 years. Moreover, both are still able to walk unaided and are not wheelchair-dependent, contrary to what would be expected from the natural course of patients with AM in their third decade of life.
- Patient 5 (male, 21 years, Italy): diagnosed aged 19 years and treated with VA for 18 months. Administration was home-based for the entire treatment period, with a positive impact on therapy compliance and acceptance. VA treatment was well tolerated, with no serious or non-serious adverse events reported on treatment. Over 18 months of treatment, serum oligosaccharide levels returned to normal ranges and all endurance and pulmonary function

[2] Except for a 1-week suspension owing to COVID-19 infection in 2021

test results remained stable, as did audiometry. Quality of life (EuroQOL) improved from a high baseline score of 70/100 to a score of 80/100 after 18 months. The improvement was especially noticed in the domain “ability to perform usual activities”. On a practical level, this improved quality of life was noticed by the patient and caregiver, who indicated a major improvement in vital energy and self-efficacy, which materialized through finding a job he could deal with all day, as he no longer needs to sleep in the afternoon.

2 Ongoing studies

A summary of ongoing studies supporting the use of VA in patients with AM is shown in Table 21.

If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

VA is currently undergoing an initial assessment with the Scottish Medicines Consortium (SMC) via the ultra-orphan pathway (SMC2466), with publication of the ultra-orphan framework for data collection expected in [redacted].

Table 21. List of ongoing studies with VA

Study name (acronym)	Study design	Population	Intervention	Comparator	Publication status	Estimated completion date
rhLAMAN-07 (NCT01908712)	Open-label, long-term safety trial in France	Patients previously completing rhLAMAN studies (N=10)	VA 1mg/kg	None	Unpublished	March 2023
rhLAMAN-09 (NCT01908725)	Single-centre, open-label, long-term safety trial in Denmark	Patients previously completing rhLAMAN studies (N=5)	VA 1mg/kg	None	Unpublished	March 2023
AM registry (SPARKLE)	Multicentre, post-authorisation noninterventional, prospective cohort study EU (including UK)	All patients with AM	Not specified – all patients eligible irrespective of treatment (VA, BSC, HSCT, investigational treatment)	None	Full text publication Protocol: Hennerman et al., 2020 [21] Unpublished interim reports: [41,42]	15-year follow-up (estimated completion 2035)
Expanded Access Programme (NCT04959240)	Compassionate Use Programme in the US	All eligible patients with AM	VA 1mg/kg	None	N/A	N/A
All Stripes study	Retrospective natural history cohort study in US, Canada and UK	Patients with AM with no prior HSCT	Not specified – all patients eligible irrespective of treatment (except HSCT)	None	Unpublished (AIC) Research plan [22]	Q4 2022

Abbreviations: ADA = anti-drug antibody; AIC = academic in confidence; AM = alpha-mannosidosis; ATU = temporary utilisation authorisation; BOT-2 = Bruininks-Oseretsky test of motor proficiency 2nd edition; BSC = best supportive care; CSR = clinical summary report; CU = compassionate use; EMA = European Medicines Agency; HRQoL = health-related quality of life; HSCT = haemopoietic stem cell transplant; NPAF = new product assessment form; QoL = quality of life; RCT = randomised clinical trial; VA = velmanase alfa

3 Measurement and valuation of health effects

3.1 Updates to QoL data used in cost-effectiveness analysis

The primary utility values used in the base case cost-effectiveness analysis are presented in Table 22. Most of the utilities are the committee's preferred values from 2019: any changes to the utility values in the updated model since the resubmission in 2019[3] are highlighted in bold, with further detail described below.

Table 22. Summary of QoL values for cost-effectiveness analysis

	Utility value	CI	Reference in submission	Justification
Health state utility				
Walking unassisted	0.652	-	rhLAMAN-10[16]	rhLAMAN-10 EQ-5D-5L utility values
Walking with assistance	0.577			
Wheelchair-dependent	0.100		Adam et al, 2019[10]; short-end stage assumed equivalent to severe immobility	Health states not observed in clinical study. MPS Society Survey EQ-5D-5L reported by proxy (n=9) by walking ability
Severe immobility/ short-end stage	-0.011			
VA on-treatment utility increment				
Utility increment while on VA	**0.10**	**-**	**Assumption, UK KOL interviews[7]**	**Disease improvement and delayed progression observed in Etoile Alpha[24]: see below and Section D**
Disutilities				
Severe infection	0.18	-	Drabinski et al, 2001[47]	A published source of EQ-5D values during 6-month follow-up/recovery from sepsis
Major surgery	0.25	-	Elosulfase alfa [ID744] HST, company submission, Table D14, p178[48]	Accepted value by NICE for a related MPS condition (MPS IVA)
Caregiver disutilities				
Walking unassisted	-0.01	-	UK KOL interviews[7] EDSS caregiver disutility[49]	Gani is a published source of caregiver disutility stratified by level of severity in patients with multiple sclerosis using the EDSS instrument. WU, WWA, WC and SI were assumed by clinical expert opinion to have an EDSS level of 2.5, 4.5, 6.5 and 8.5, respectively.
Walking with assistance	-0.02	-		
Wheelchair-dependent	-0.05	-		
Severe immobility/ Short end stage	-0.14	-		

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; KOL = key opinion leader; MPS = mucopolysaccharidosis; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Treatment with VA demonstrated a utility benefit in rhLAMAN-10.[16] However, it is

plausible that the utility gain observed in this trial is underestimated due to the difficulty in assessing QoL. Furthermore, it is possible that some QoL benefits of VA only materialise after longer-term treatment, beyond the latest timepoint in the clinical trial (up to 48 months in rhLAMAN-10). This includes potential benefits of VA treatment that were not possible to incorporate into the cost-utility analysis, due to the heterogeneity and complexity of AM and the pragmatic model design. These additional potential benefits include the impact of VA on minor infections, pain, minor surgeries, psychiatric complications, ventilator dependency, and intra-ambulatory health state improvement/progression (i.e., reducing the number of ambulatory aids required). Similarly, in the Etoile-Alpha study, assessment of QoL were measured using CHAQ and EQ-5D-5L[18]. Due to limited availability of QoL data and the widely scattered results, no cluster or global trend could be observed. However, some positive outliers for some classes were noted which demonstrated excellent improvement in QoL for some patients (Section 4.3.4). For these reasons, an on-treatment utility increment of 0.1 is included in the base-case analysis, and was validated by UK KOL experts[7]. It was assumed that this on-treatment utility increment stopped if a patient discontinued treatment, although this assumption is tested within the scenario analysis (Section D1.3.4).

Disutilities for severe infection, major surgery and caregiver disutility are unchanged from the previous submission; further details are included in Appendix G for completeness.

Scenario analysis – health state utility values

The MPS Society Survey study reported by Adam et al., (2019) reported EQ-5D-5L data by walking ability that were proxy completed by carers[10]. The utility values derived from this study are reported below in Table 23 and are included as a scenario analysis in Section D1.3.4.

Table 23. EQ-5D utilities from UK MPS Survey

Health State	N	EQ-5D-5L	Reference
Walking unassisted	5	0.794	Adam et al., (2019)[10]
Walking with assistance	1	0.758	
Wheelchair	1	0.100	
Severe immobility; short end stage	2	-0.011	

3.1.1 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Table 24. Summary of updates to quality-of-life values for cost-effectiveness analysis

State / variable	Utility value / disutility	Confidence interval	Reference
VA on-treatment increment	**0.10**	**N/A**	**Assumption, UK KOL interviews[7]**
Health state patient disutility – WU	0.348	N/A	rhLAMAN-05[14]
Health state disutility – WWA	0.423	N/A	rhLAMAN-05[14]
Health state disutility – WC	0.900	N/A	Adam et al, (2019)[10]
Health state disutility – SI	1.011	N/A	Adam et al, (2019)[10]
Health state caregiver disutility – WU	0.01	N/A	UK KOL interviews[12] EDSS caregiver disutility[49]
Health state caregiver disutility – WWA	0.02	N/A	
Health state caregiver disutility – WC	0.05	N/A	
Health state caregiver disutility – SI and short-end stage	0.14	N/A	

3.2 Treatment continuation rules

3.2.1 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- *The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).*
- *The robustness and plausibility of the endpoint on which the rule is based.*
- *Whether the 'response' criteria defined in the rule can be reasonably achieved.*
- *The appropriateness and robustness of the time at which response is*

measured.

- *Whether the rule can be incorporated into routine clinical practice.*
- *Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.*
- *Issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

The economic model is aligned with the start/stop criteria presented in Section F.

The model assumes that any treatment monitoring for VA-treated patients is included as part of routine BSC appointments with metabolic specialists/paediatricians, as validated in the UK KOL interviews. VA-treated patients are expected to have at least 2 visits with a metabolic medicine specialist per annum. At a consultation to consider starting treatment with VA, this will include standard biochemical, enzymatic, disability and functional tests that are all performed in clinical practice at routine assessments of patients with AM, and no additional tests are required. For a patient to start and continue treatment with VA, a series of clinical measurements (serum oligosaccharides, 3-MSCT, 6-MWT, FVC, CHAQ disability index, CHAQ pain [VAS], EQ-5D-5L and LVEF) should be made at baseline and at 12-month intervals.

No additional NHS infrastructure is required to ensure the safe and effective use of VA in those centres which are already experienced in the diagnosis and management of LSDs. As is the case for other ERTs, VA will be offered to patients via homecare by the NHS once patients have been stabilised following initiation of treatment in the clinical centre. Homecare administration will be by a trained nurse as is standard practice for the administration of other ERTs in the UK.

Patients can discontinue treatment after one year, due to a 'non-response' based on criteria in the posthoc, multi-domain responder analysis (13.3% of patients are a non-responder, as per the rhLAMAN-05 multi-domain responder analysis)[23]: for detail on the clinical assessments required, see Section F.

In multi-domain responders, it is assumed there is a 5-year delay before disease progression can occur. After the 5-year delay in progression from treatment response, and over the remaining time on treatment, multi-domain responders have a slower rate of disease progression on VA, compared with BSC-treated patients. This rate of progression is dependent on the patient cohort (paediatric, adolescent or adult), and health state they are currently in.

Section D – Value for Money and cost to the NHS and personal social services

1 Updated economic analysis

1.1 Summary of cost-effectiveness evidence for VA

In the original submission, Chiesi developed a de novo economic model to estimate the impact of VA treatment in terms of costs and QALYs in patients with AM. The model incorporated clinical data from 33 patients included in the rhLAMAN-05 RCT, the rhLAMAN-10 integrated analysis and the multi-domain responder analyses[23], which represents a substantial proportion of the diagnosed AM population. The Committee concluded in the evaluation consultation document that *"… the overall model structure was adequate for decision-making"*[50]. The updates to the model presented here reflect new clinical data from the rhLAMAN-08 clinical trial[17], a real-world registry (Etoile Alpha)[18] and case reports[19]. Additional data are being collected to increase the confidence in the longer-term clinical effectiveness of VA in the European-wide SPARKLE registry and the global AllStripes Study.

The analysis compares BSC without VA against VA plus BSC. The base-case analysis is conducted from a NHS/Personal Social Services (PSS) perspective and estimates costs and QALYs over a lifetime time horizon. The structure of the model is unchanged from the previous submission: a cohort Markov design, with 4 primary health states representing different levels of ambulatory status (walking unassisted, walking with assistance, wheelchair dependent, and severe immobility). The model can present 3 different cohorts based on age at treatment initiation with VA: a paediatric cohort (6 to 11 years), an adolescent cohort (12 to 17 years) and an adult cohort (≥18 years). These cohorts correspond to a post-hoc analysis of the rhLAMAN clinical programme by 3 age groups. The starting state distribution for the model is based on the ambulatory status of the rhLAMAN-10 baseline population.

The chronic and progressive nature of AM is modelled via the gradual progression (deterioration) of ambulatory status and functional capacity. Patients move through the health states in sequence unless they die due to background mortality, a severe infection, or major surgery; they may also move directly to the severe immobility health state due to a surgical complication.

The model evaluates patients on VA as being a 'responder' or 'non-responder' after 1 year of treatment, based on the rhLAMAN-5 and rhLAMAN-10 multi-domain responder analysis[23]. Non-responders discontinue treatment, and responders are modelled to remain on treatment with a 10% annual probability of withdrawal, or when they progress to the severe immobility health state.

The primary benefit of VA is to delay the rate of disease progression in responders, but the modelled benefit of VA also includes the ability for disease improvement (the ability for a patient's ambulatory status to improve, and revert to a less severe health state) in the treatment response period, a reduction in the rates, recovery disutility and mortality from severe infections, and a reduction in the recovery disutility, complications and mortality from major surgery. VA is also modelled to have a benefit

by reducing the necessity and complexity of ventilation required by patients in the more severe health states.

In the base-case analysis with the PAS price (presented in Section D1.1), the ICER for VA vs. BSC was £[redacted] in the paediatric cohort, £[redacted] in the adolescent cohort and £[redacted] in the adult cohort. The revised base-case incorporates all of the NICE preferred assumptions from the 2019 submission[3], except an increased on-treatment utility benefit (0.1) and a 5-year delay in disease progression to reflect the long-term improvements from baseline shown by patients treated with VA in the French Etoile Alpha registry study[24]. Scenario analyses determined a range of potentially plausible ICERs from £[redacted] to £[redacted] per QALY.

1.2 Description of updates to the de novo cost-effectiveness analysis not previously reported

A summary of the updated model assumptions is shown in Table 25 below. Any changes from the previous submission and new clinical data to support this change are highlighted in bold.

Table 25. Updated model assumptions

Parameter		Assumption	Source(s)
1	**Disease progression delay**	**In multi-domain responders, there is a 5-year delay before disease progression can occur.**	**UK Clinical Validation Interviews[12]; Etoile Alpha Study[18]**
	Disease progression	After the 5-year delay in progression from treatment response, and over the remaining time on treatment, multi-domain responders have a slower rate of disease progression on VA, compared with BSC-treated patients. This rate of progression is dependent on the patient cohort (paediatric, adolescent or adult) and health state they are currently in.	UK Expert Elicitation Panel[51]; rhLAMAN-10, multi-domain responder analysis[23]; **Etoile Alpha Study[18]**
2	Disease improvement	VA-treated patients will have a reduced dependency on aids/assistance and wheelchair use for walking, compared with BSC-treated patients. The probability of VA to improve patients' ambulation is more likely during the first 2 years of treatment, but may occur in exceptional cases after 3 or more years of treatment. VA-treated patients can only improve by 1 level of functional impairment per year (cycle), for example from WWA to WU:	UK KOL interviews[12]; rhLAMAN-10, CHAQ analysis[16]; **Etoile Alpha Study[18]**
	Years 1 and 2	Following the first 2 years of treatment with VA it is assumed: 20% of patients will transition from WC to WWA 20% of patients will transition from WWA to WU	
	Year 3 onwards	Following ≥3 years of treatment with VA it is assumed: 2.5% of patients will transition from WC to WWA 2.5% of patients will transition from WWA to WU	
3	Ventilation dependency	Treatment with VA will reduce patients' requirements for ventilation compared with BSC alone, in terms of a delay to ventilation, and more simple ventilation requirements once on ventilation, due to an accrued improvement in lung function. The model assumes VA-treated patients spend half the time in ventilation compared with BSC alone.	UK KOL interviews[12]
4	Severe infections	VA-treated patients have a better capacity to respond to/manage severe infections (e.g., better diaphragmatic function, remain more upright, remain more mobile) compared with BSC-treated patients.	UK KOL interviews[12]; rhLAMAN-05, serum IgG analysis[14]; **rhLAMAN-05 infection analysis[37]; Etoile Alpha Study[18]**
	Rate	VA-treated patients have a 50% reduced rate of severe infections compared with BSC-treated patients.	
	Recovery disutility	VA-treated patients have a 50% shorter recovery period after a severe infection compared with BSC-treated patients.	
	Mortality	VA-treated patients have a 50% reduced risk of infection-related mortality compared with BSC-treated patients.	
5	Major surgery	VA-treated patients have a better capacity to respond to/manage major surgery† (e.g., lower risk to anaesthaesia due to improved upper airways and lung function, better ability to regain mobility and manage infections post-surgery) compared with BSC-treated patients.	UK KOL interviews[12]

Parameter		Assumption	Source(s)
	Rate	The rate of major surgeries is assumed to be equivalent in VA-treated patients and BSC-treated patients.	
	Recovery disutility	VA-treated patients have a 50% shorter recovery period after a major surgery compared with BSC-treated patients.	
	Mortality	VA-treated patients have a 50% reduced risk of major surgery-related mortality compared with BSC-treated patients.	
	Complications	VA-treated patients have a 50% reduced risk of post-operative complications leading to a transition to SI compared with BSC-treated patients.	
6	Discontinuation	Patients can discontinue VA treatment via three routes:	UK KOL interviews[12] rhLAMAN-05, multi-domain responder analysis[23]
	Non-response	Discontinuation due to a 'non-response' based on the post hoc, multi-domain response in the first year of treatment (13.3%).	
	Health state	Discontinuation due to patients entering the SI or short-end stage health states.	
	Annual risk	Discontinuation due to an annual risk of withdrawal (10%) due to reasons including IRRs, non-compliance, patient preferences and/or occurrence of other life-limiting conditions (e.g., cancer). This annual risk of discontinuation also accounts for partial/short-term treatment discontinuation (e.g., due to travel, educational studies, ill-health or changes to family/caregiver circumstances preventing treatment) that may occur.	
7	**VA on-treatment utility**	**Improved clinical outcomes for VA-treated patients vs. BSC-treated patients translates into greater HRQoL. A VA on-treatment utility gain of 0.1 is assumed.** **Numerous QoL aspects of AM are incompletely captured in the model structure including minor infections, pain and psychiatric health (see Section D1.3)**	**UK KOL interviews[12]; rhLAMAN-10, CHAQ analysis[16]; Etoile-Alpha study[18]**
8	Caregiver disutility	Caregivers in each health state would suffer from a significant disutility because of caring for patients with multiple and extensive clinical needs (e.g., behavioural, mobility-related, selfcare, activities of daily living)	UK KOL interviews[12] EDSS caregiver disutility[49]
9	Treatment monitoring	Any treatment monitoring for VA-treated patients is included as part of routine BSC appointments with metabolic specialists/paediatricians.	UK KOL interviews[12]
10	Treatment setting	VA administration is assumed to first be completed in an LSD specialist centre (three IV [once weekly] infusions) before administration occurs via homecare (98% of patients) or a local hospital setting (2% of patients). This ratio of homecare to local hospital setting was deemed appropriate to also capture the minority of patients that may revert to hospital briefly for the management of IRRs, before returning to homecare once the IRRs are resolved.	UK KOL interviews[12]

Abbreviations: AM = alpha-mannosidosis; KOL = key opinion leader; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year; PSS = personal social services; UK = United Kingdom; VA = velmanase alfa

1.2.1 Clinical parameters and variables

A summary of the clinical variables used in the updated model is included in Table 26. Any updates from the previous submission are highlighted in bold.

Table 26. Summary of variables applied in the cost-effectiveness model

Variable		Value	Range or 95% CI (distribution)	Source
Age when transition to adult NHS service		16	N/A	UK KOL interviews[12]; National Steering Group for Specialist Children's Services[52]
Paediatric cohort distribution: WU; WWA; WC; SI, %		78%; 22%; 0%; 0%	N/A	rhLAMAN-10, baseline characteristics[15]
Adolescent cohort distribution: WU; WWA; WC; SI, %		73%; 27%; 0%; 0%	N/A	
Adult cohort distribution: WU; WWA; WC; SI, %		62%; 38%; 0%; 0%	N/A	
VA responders, delay in progression, years		**5**	**N/A**	UK Validation Interviews; **Etoile Alpha Study[18]**
Transition probabilities (presented as years in state before progression) – BSC, All cohorts	WU to WWA	11.44	1.70, 23.23	UK Expert Elicitation Panel[51]
	WWA to WC	10.20	2.60, 17.69	
	WC to SI	9.97	2.54, 17.42	
	SI to death	3.02	1.06, 7.43	
Transition probabilities (presented as additional years in state vs. BSC) – VA, Paediatric cohort	WU to WWA	1.54	-0.31, 3.64	UK Expert Elicitation Panel[51]
	WWA to WC	1.35	0.23, 2.59	
	WC to SI	0.58	0.09, 1.68	
	SI to death	0.00	0.00, 0.00	
Transition probabilities (presented as additional years in state vs. BSC) – VA, Adolescent cohort	WU to WWA	2.06	0.23, 2.59	UK Expert Elicitation Panel[51]
	WWA to WC	1.35	0.23, 2.59	
	WC to SI	0.58	0.09, 1.68	
	SI to death	0.00	0.00, 0.00	
Transition probabilities (presented as additional years in state vs. BSC) – VA, Adult cohort	WU to WWA	1.30	0.01, 2.81	UK Expert Elicitation Panel[51] rhLAMAN-10 responder analysis[23]
	WWA to WC	0.96	0.16, 1.85	
	WC to SI	0.42	0.07, 1.20	
	SI to death	0.00	0.00, 0.00	
Year 1 – WC to WWA		20.0%	0.0%, 70.0%	UK KOL interviews[12] Upper range from rhLAMAN-10, CHAQ analysis [16]
Year 2 – WC to WWA		20.0%	0.0%, 70.0%	UK KOL interviews[12]
Year 1 – WWA to WU		20.0%	0.0%, 70.0%	
Year 2 – WWA to WU		20.0%	0.0%, 70.0%	
Year 3+ – WC to WWA		2.5%	0.0%, 5.0%	
Year 3+ – WWA to WU		2.5%	0.0%, 5.0%	

Variable	Value	Range or 95% CI (distribution)	Source
Time-period assessed (years)	1	N/A	rhLAMAN-05 responder analysis[23]
Probability of a 'non-response' from post hoc, multi-domain responder analysis	13.33%	N/A	rhLAMAN-05 responder analysis[23]
Annual risk of withdrawal	10%	N/A	UK KOL interviews[12]
IRR rate	9.1%	N/A	rhLAMAN-10[15]
Proportion male	60.6%	N/A	rhLAMAN-10[15]
Annual probability of progression – from WU health state	19.54%	13.31%, 39.35%	UK Expert Elicitation Panel[51]
Annual probability of progression – from WWA health state	21.19%	15.35%, 39.35%	
Annual probability of progression – from WC health state	49.45%	39.35%, 63.21%	
Annual probability of progression – from SI health state	63.29%	52.85%, 78.02%	
Infection-related mortality – WU	4.50%	0.50%, 10.00%	
Infection-related mortality – WWA	6.25%	2.50%, 15.00%	
Infection-related mortality – WC	12.50%	5.00%, 30.00%	
Infection-related mortality – SI	23.13%	10.00%, 40.00%	
Reduction in rates of severe infections when on VA	50%	N/A	UK KOL interviews[7]
Reduction to infection-related mortality risk when on VA	50%	N/A	
Time in short end-stage state, weeks	4	N/A	
ICU LoS paediatrics, days	6.25	N/A	Paul et al, 2012[53]
ICU LoS adult, days	7.80	N/A	Levy et al, 2012[54]
General care LoS paediatrics, days	2.98	N/A	Paul et al, 2012[53]
General care LoS adult, days	15.00	N/A	Levy et al, 2012[54]
Major surgery			
Annual probability – WU	8.10%	5.0%, 13.0%	UK Expert Elicitation Panel[51]
Annual probability – WWA	13.80%	8.0%, 20.0%	
Annual probability – WC	10.00%	8.0%, 13.0%	
Annual probability – SI	1.50%	1.5%, 1.5%	
Surgery-related mortality risk – WU	5.00%	N/A	UK KOL interviews[12]
Surgery-related mortality risk – WWA	5.00%	N/A	
Surgery-related mortality risk – WC	10.00%	N/A	
Surgery-related mortality risk – SI	10.00%	N/A	
Surgery-related complication risk – WU	10.00%	N/A	
Surgery-related complication risk	10.00%	N/A	

Variable	Value	Range or 95% CI (distribution)	Source
– WWA			
Surgery-related complication risk – WC	20.00%	N/A	
Surgery-related complication risk – SI	20%	N/A	
Reduction in risk of surgery-related mortality when on VA	50%	N/A	
Reduction in risk of surgery-related complications when on VA	50%	N/A	
Severe infection – number of weeks of disutility	26	N/A	Drabinski et al, 2001[47]
Severe infection disutility	0.18	N/A	Drabinski et al, 2001[47]
Reduction in severe infection disutility period on VA (reflecting a shorter recovery period when treated with VA)	50%	N/A	UK KOL interviews[12]
Major surgery – number of weeks of disutility	26	N/A	Elosulfase alfa [ID744] HST, company submission, Table D14, p178[48]
Major surgery disutility	0.25	N/A	Elosulfase alfa [ID744] HST, company submission, Table D14, p178[48]
Reduction in major surgery disutility period on VA (reflecting a shorter recovery period when treated with VA)	50.00%	N/A	UK KOL interviews[12]
VA on-treatment incremental utility benefit	**0.1**	**N/A**	**Assumption, UK KOL interviews[7]**
Health state patient disutility – WU	0.348	N/A	rhLAMAN-05[14]
Health state disutility – WWA	0.423	N/A	rhLAMAN-05[14]
Health state disutility – WC	0.900	N/A	Adam et al, (2019)[10]
Health state disutility – SI	1.011	N/A	Adam et al, (2019)[10]
Health state caregiver disutility – WU	0.01	N/A	UK KOL interviews[12] EDSS caregiver disutility [49]
Health state caregiver disutility – WWA	0.02	N/A	
Health state caregiver disutility – WC	0.05	N/A	
Health state caregiver disutility – SI and short-end stage	0.14	N/A	

Abbreviations: BSC = best supportive care; CI = confidence interval; EDSS = Expanded Disability Status Scale; IRR = infusion-related reaction; KOL = key opinion leader; LoS = length of stay; LSD = lysosomal storage disorder; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SI = severe immobility; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

1.2.2 Resource identification, measurement and valuation

A summary of the cost inputs used in the updated model is included in Table 27. Any updates from the previous submission are highlighted in bold.

Table 27. Costs per treatment/patient associated with the technology in the cost-effectiveness model

Items	Value	Source
Discount rate, costs and QALYs	3.5%	NICE Guide to the methods of technology appraisal[55]
List price of the technology per treatment	£886.61 (excluding VAT) per 10 mg vial. The recommended dose is 1 mg/kg.	Chiesi Limited
PAS discount	[redacted]%	**Chiesi Limited**
Administration cost in hospital, per infusion (once weekly)	**£393**	**NHS Proposed 2020/21 National Tariff Payment System: national prices and prices for blended payments. Vascular access except for renal replacement therapy without CC. Outpatient procedure tariff[56]**
Home care administration cost, per infusion (once weekly)	**£133**	**Calculated from Company Submission, Migalastat for treating Fabry disease, HST4. NICE [57]**
Number of (once weekly) infusions at LSD centre before transfer to home infusion or local hospital setting	3	UK KOL Interviews[12]
Proportion of patients receiving home infusion	98%	
Proportion of patients receiving hospital infusion	2%	

Abbreviations: KOL = key opinion leader; LSD = lysosomal storage disorder

The type and frequency of consultations as part of BSC is unchanged from the previous submission apart from inflated costs to 2020/2021, but is included in Appendix G for completeness.

1.2.3 Miscellaneous costs

All historical costs from the literature have been inflated to 2020/21 cost prices using the PSSRU 2021.[58] Additional costs that have been updated in the model are described below.

Personal social service caregiver costs

The UK MPS Society Survey by Adams et al.[10] provided updated estimates of caregiver time by ambulatory status in patients with AM. This provides an estimate of the health state-wise total annual PSS cost, as shown in Table 28.

Table 28. PSS caregiver costs by health state

	WU	WWA	WC	SI	Source
Proportion of care delivered by professionals	10%	20%	50%	80%	Assumption
Hours of care-giving/day	**11**	**16**	**24**	**24**	**Adam et al, 2019[10]**
Professional carer cost/ hour	**£25.00**				**PSSRU Unit Cost 2021 – Homecare worker per weekday hour[58,59]**
Cost/day	**£24**	**£70**	**£264**	**£422**	**Calculation**
Cost/year	**£8,833.00**	**£25,696**	**£96,360**	**£154,176**	**Calculation**

Abbreviations: PSSRU = Personal Social Services Research Unit; SI = severe immobility; WC = wheelchair dependent; WWA = walking with assistance; WU = walking unassisted

Ventilation costs

UK KOLs indicated that patients with AM typically require ventilatory support as disease severity worsens[7]. Furthermore, the experts suggested that VA may help to reduce the need for ventilatory support, due to the positive effects of treatment on lung function. The KOLs involved in the rhLAMAN clinical trial programme concurred that patients experienced a reduction in the rate of infections, including respiratory infections, following treatment with VA[7], which was reported in an analysis of rhLAMAN-10[37] and evidenced in case reports[19]. This reduction in infections will impact the level of medical intervention a patient may need[7], which could include the use of ventilators in the case of respiratory infections. A summary of ventilation costs is provided in Table 29 and the use of ventilation by health state is presented for BSC and VA in Table 30. The total personal social service costs, combining the costs of caregiving and ventilation, are shown in Table 31 by health state.

Table 29. Ventilation costs

Ventilation type/setting	Annual cost (updated to 2021)	Source
24-hour care ventilation – institutional	£482,190.30	Noyes 2006 [60]
24-hour care ventilation – home	£383,108.16	Noyes 2006 [60]
Overnight ventilation – institutional	£128,226	Noyes 2006 [60]
Overnight ventilation – home	£128,226	Noyes 2006 [60]
Proportion of patients at home	50%	UK KOL interview [12]
Proportion of patients in institution	50%	UK KOL interview [7]

Abbreviations: KOL = key opinion leader; UK = United Kingdom

Table 30. Ventilation resource use and total cost by health state for BSC vs. VA

Treatment	Walking unassisted	Walking with assistance	Wheelchair dependent	Severe immobility	Source
No ventilation					
BSC	100%	100%	80%	0%	UK KOL interviews [12]
VA	100%	100%	90%	50%	
Overnight ventilation only					
BSC	0%	0%	20%	50%	UK KOL interview [7]
VA	0%	0%	10%	25%	
24-hour care ventilation					
BSC	0%	0%	0%	50%	UK KOL interview [7]
VA	0%	0%	0%	25%	
Average total ventilation cost					
BSC	£0	£0	£19,090	£208,751	Calculation
VA	£0	£0	£9,545	£104,375	

Abbreviations: BSC = best supportive care; KOL = key opinion leader; VA = velmanase alfa

The total personal social service costs, combining the costs of caregiving and ventilation, are shown in Table 31 by health state.

Table 31. Total PSS cost (caregiver and ventilation costs) by health state

Health state	Costs, per year	
	VA	BSC
WU	£1,139	£1,139
WWA	£6,833	£6,833
WC	£69,989	£79,534
SI	£201,086	£305,461
WU + SInf	£1,139	£1,139
WWA + SInf	£6,833	£6,833
WC + SInf	£69,989	£79,534
SI + SInf	£201,086	£305,461
SES	£0	£0

Abbreviations: BSC = best supportive care; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair dependent; WWA = walking with assistance; WU = walking unassisted

Personal carer expenditure and productivity loss

A targeted search was conducted to identify papers that reported the social costs and/or personal costs and/or productivity losses for those patients (and carers of patients) with rare, chronic diseases. No studies in a relevant proxy condition were identified. A study by Woolley et al., 2004 [61] estimated that for families caring for a severely disabled child, personal annual expenditure was £5,000 (inflated to £7,042). It was assumed that this cost applies in the 'wheelchair dependent' and 'severe

immobility' health states, and that 50% of the cost applies in the 'walking unassisted' and 'walking with assistance' health states. For the short-end stage state, a publication provided a 3-month end-stage caregiver estimates of £391, which has been scaled and converted into a 4-week cost for short-end stage (£130) [62].

Caregiver productivity loss has been estimated using the human capital method (Table 32). The estimates of caregiver time have been updated using Adam 2019[10], which were assumed to equal the reduction in employment required by a caregiver to provide homecare. This was multiplied by the median UK hourly earnings (£13.86). Due to the 'wheelchair dependent' and 'severe immobility' health states requiring an estimated daily, 24-hour care, it was assumed that no employment is possible at all when caring for a person in these health states. Given that many caregivers are unable to work fulltime and report giving up work as a result of caring for a patient with AM, these may be an underestimate, as further described in Section E.

Table 32. Carer productivity loss by health state

Health state	Hours of caregiving/per day	Total annual productivity loss
WU	1.3	£6,369
WWA	3.9	£19,107
WC	13.8	£26,245
SI	13.8	£26,245
WU + SInf	1.3	£6,369
WWA + SInf	3.9	£19,107
WC + SInf	13.8	£26,245
SI + SInf	13.8	£26,245
SES	13.8	£26,245

Abbreviations: BSC = best supportive care; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair dependent; WWA = walking with assistance; WU = walking unassisted

Sources: Adam et al., 2019 [10]; ONS 2020

1.3 Results of updated economic analysis

1.3.1 Base-case results

The base-case results for VA vs. BSC in the 3 age cohorts are presented below. The settings for the base-case are shown in Table 33. With the PAS price, the ICER for VA vs. BSC was £[redacted] in the paediatric cohort, £[redacted] in the adolescent cohort and £[redacted] in the adult cohort, as shown in Table 1, Table 35 and Table 36. Deterministic results are presented in the base-case, due to linearity in the economic model. Probabilistic Sensitivity Analyses are presented in Section 1.3.4

Table 33. Base-case model settings

Parameter	Setting
Perspective	NHS England and Social Work
Time horizon	Lifetime (100 years)
Population	Paediatric, adolescent and adult populations
Discount rate (costs and outcomes)	3.5%
Health state utility values	rhLAMAN-10 clinical study
Treatment discontinuation	Non-responders after year 1 (13.3%); 10% annual discontinuation rate; patients entering severe immobility health state
Personal/caregiver expenditure	Not included
Caregiver productivity loss	Not included
Caregiver disutility	Included

Abbreviation: NHS = National Health Service

Table 34. Cost-effectiveness results – paediatric cohort

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)
BSC	[redacted]	14.564	[redacted]	-	-	-	
VA	[redacted]	16.740	[redacted]	[redacted]	2.175	[redacted]	[redacted]

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

Table 35. Cost-effectiveness results – adolescent cohort

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)
BSC	[redacted]	14.355	[redacted]	-	-	-	
VA	[redacted]	16.590	[redacted]	[redacted]	2.236	[redacted]	[redacted]

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

Table 36. Cost-effectiveness results – adult cohort

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)
BSC	[redacted]	13.921	[redacted]	-	-	-	
VA	[redacted]	16.248	[redacted]	[redacted]	2.328	[redacted]	[redacted]

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

1.3.2 Clinical outcomes from the model

Clinical outcomes by health state for the base case are shown in Table 37 to Table 39. These values show QALY gains from the mobility health states as more patients are in these states for longer with VA compared with BSC.

Table 37. Clinical benefit of treatment by health state – paediatric cohort

Health state	QALY VA	QALY BSC	Increment	% Absolute increment
WU	[redacted]	[redacted]	[redacted]	[redacted]
WWA	[redacted]	[redacted]	[redacted]	[redacted]
WC	[redacted]	[redacted]	[redacted]	[redacted]
SI	[redacted]	[redacted]	[redacted]	[redacted]
WU + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WWA + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WC + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
SI + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
Short ES	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 38. Clinical benefit of treatment by health state – adolescent cohort

Health state	QALY VA	QALY BSC	Increment	% Absolute Increment
WU	[redacted]	[redacted]	[redacted]	[redacted]
WWA	[redacted]	[redacted]	[redacted]	[redacted]
WC	[redacted]	[redacted]	[redacted]	[redacted]
SI	[redacted]	[redacted]	[redacted]	[redacted]
WU + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WWA + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WC + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
SI + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
Short ES	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 39. Clinical benefit of treatment by health state – adult cohort

Health state	QALY VA	QALY BSC	Increment	% Absolute Increment
WU	[redacted]	[redacted]	[redacted]	[redacted]
WWA	[redacted]	[redacted]	[redacted]	[redacted]
WC	[redacted]	[redacted]	[redacted]	[redacted]

SI	[redacted]	[redacted]	[redacted]	[redacted]
WU + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WWA + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WC + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
SI + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
Short ES	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

The proportion of the cohort in each health state and the mortality for patients on VA and BSC through the time horizon are shown in Table 40 to Table 45. These demonstrate a mortality benefit for patients in the VA arm of the model vs. BSC.

Table 40. Mortality estimates and patient flow for VA – paediatric cohort

Year	WU	WWA	WC	SI	SES	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 41. Mortality estimates and patient flow for VA – adolescent cohort

Year	WU	WWA	WC	SI	SES	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 42. Mortality estimates and patient flow for VA – adult cohort

Year	WU	WWA	WC	SI	SES	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; SES, short end stage; SI, severe immobility; VA, velmanase alfa; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

Table 43. Mortality estimates and patient flow for BSC – paediatric cohort

Year	WU	WWA	WC	SI	SES	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 44. Mortality estimates and patient flow for BSC – adolescent cohort

Year	WU	WWA	WC	SI	SES	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 45. Mortality estimates and patient flow for BSC – adult cohort

Year	WU	WWA	WC	SI	SES	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

1.3.3 Cost outcomes from the model

Costs by health state (excluding drug costs) are summarised in Table 46 to Table 48. The results show that there are greater health state costs for patients receiving VA. Costs for the WU health state are greater for VA, but the delay to more severe health states result in lower health state costs for VA from WWA onwards.

Table 46. Summary of costs by health state – paediatric cohort

Health state	Cost VA, £s	Cost BSC, £s	Increment	% Absolute Increment
WU	[redacted]	[redacted]	[redacted]	[redacted]
WWA	[redacted]	[redacted]	[redacted]	[redacted]
WC	[redacted]	[redacted]	[redacted]	[redacted]
SI	[redacted]	[redacted]	[redacted]	[redacted]
WU + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WWA + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WC + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
SI + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
Short ES	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 47. Summary of costs by health state – adolescent cohort

Health state	Cost VA, £s	Cost BSC, £s	Increment	% Absolute Increment
WU	[redacted]	[redacted]	[redacted]	[redacted]
WWA	[redacted]	[redacted]	[redacted]	[redacted]
WC	[redacted]	[redacted]	[redacted]	[redacted]
SI	[redacted]	[redacted]	[redacted]	[redacted]

WU + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WWA + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WC + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
SI + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
Short ES	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Table 48. Summary of costs by health state – adult cohort

Health state	Cost VA, £s	Cost BSC, £s	Increment	% Absolute Increment
WU	[redacted]	[redacted]	[redacted]	[redacted]
WWA	[redacted]	[redacted]	[redacted]	[redacted]
WC	[redacted]	[redacted]	[redacted]	[redacted]
SI	[redacted]	[redacted]	[redacted]	[redacted]
WU + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WWA + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
WC + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
SI + Sinf	[redacted]	[redacted]	[redacted]	[redacted]
Short ES	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; SES = short-end stage; SI = severe immobility; SInf = severe infection; VA = velmanase alfa; WC = wheelchair; WWA = walking with assistance; WU = walking unassisted

Total costs in the model by cost categories are summarised in Table 49 to Table 51. Results show that the largest component for the overall incremental costs is the cost of VA. Increases in health state costs for VA are offset by savings in PSS costs.

Table 49. Summary of costs by category – paediatric cohort

Health state	Cost VA, £s	Cost BSC, £s	Increment	% Absolute Increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]
PSS cost	[redacted]	[redacted]	[redacted]	[redacted]
Societal cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; PSS = Personal Social Services; VA = velmanase alfa

Table 50. Summary of costs by category – adolescent cohort

Health state	Cost VA, £s	Cost BSC, £s	Increment	% Absolute Increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]

Health state cost	[redacted]	[redacted]	[redacted]	[redacted]
PSS cost	[redacted]	[redacted]	[redacted]	[redacted]
Societal cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; PSS = Personal Social Services; VA = velmanase alfa

Table 51. Summary of costs by category – adult cohort

Health state	Cost VA, £s	Cost BSC, £s	Increment	% Absolute Increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]
PSS cost	[redacted]	[redacted]	[redacted]	[redacted]
Societal cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; PSS = Personal Social Services; VA = velmanase alfa

1.3.4 Updated sensitivity analysis results

Updated results from the univariate sensitivity analyses were plotted in the form of a tornado diagrams to visualise the order and magnitude of the impact of each parameter on the ICER for VA vs. BSC (Figure 13 to Figure 15). All parameters were varied but the figure shows the 10 parameters with the greatest impact. Upper and lower bounds were either taken from reported 95% CIs, or were varied by ±25% around the point estimate for the parameter.

The ICER is most sensitive to variation in the cost of VA, the discontinuation rate, the progression rate, and the proportion of responders who achieve a backwards transition. The impact of these parameters on the ICERs are also demonstrated via scenario analyses in the next section.

In addition to the DSA, extensive scenario analysis testing has been reported to examine alternative assumptions and sources of data for model parameters. The scenarios and their results are detailed in Table 55.

Figure 13. Tornado diagram: paediatric cohort

Figure 14. Tornado diagram: adolescent cohort

Figure 15. Tornado diagram: adult cohort

Probabilistic Sensitivity Analysis: Paediatric cohort

The results of the PSA (based on 1,000 simulations for the paediatric cohort are shown in Table 52 and Figure 16. The cost-effectiveness acceptability curve (CEAC) is shown in Figure 17.

Table 52. Base case PSA results – paediatric cohort

	Total		Incremental		ICER vs BSC (95% CI)
	Costs (95% CI)	QALYs (95% CI)	Costs	QALYs	
BSC	[redacted]	[redacted]	-	-	
VA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life years.

Figure 16. Base case PSA scatterplot of VA vs BSC – paediatric cohort

Abbreviations: BSC, best supportive care; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; VA, velmanase alfa.

Figure 17. Base case PSA CEAC – paediatric cohort

Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; VA, velmanase alfa.

Probabilistic Sensitivity Analysis: Adolescent cohort

The results of the PSA for the adolescent cohort are shown in Table 53 and Figure 18. The CEAC is shown in Figure 19.

Table 53. Base case PSA results – Adolescent cohort

	Total		Incremental		ICER vs BSC (95% CI)
	Costs (95% CI)	QALYs (95% CI)	Costs	QALYs	
BSC	[redacted]	[redacted]	-	-	
VA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life years.

Figure 18. Base case PSA scatterplot of VA vs BSC – adolescent cohort

Abbreviations: BSC, best supportive care; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; VA, velmanase alfa.

Figure 19. Base case PSA CEAC – adolescent cohort

Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; VA, velmanase alfa.

Probabilistic Sensitivity Analysis: adult cohort

The results of the PSA for the adult cohort are shown in Table 54 and Figure 20. The CEAC is shown in Figure 21.

Table 54. Base case PSA results – adult cohort

	Total		Incremental		ICER vs BSC (95% CI)
	Costs (95% CI)	QALYs (95% CI)	Costs	QALYs	
BSC	[redacted]	[redacted]	-	-	
VA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life years.

Figure 20. Base case PSA scatterplot of VA vs BSC – adult cohort

Abbreviations: BSC, best supportive care; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; VA, velmanase alfa.

Figure 21. Base case PSA CEAC – adult cohort

Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; VA, velmanase alfa.

Table 55. Key Scenario Analyses

Scenario	Scenario detail	Paediatric ICER	Adolescent ICER	Adult ICER	Impact of new clinical data on plausibility
Base case	-	[redacted]	[redacted]	[redacted]	
0% discount rate	0% discount rate for costs and benefits	[redacted]	[redacted]	[redacted]	
1.5% discount rate	1.5% discount rate for costs and benefits	[redacted]	[redacted]	[redacted]	
Include personal and caregiver expenditure	Include personal and caregiver expenditure	[redacted]	[redacted]	[redacted]	
Include caregiver productivity loss	Include caregiver productivity losses due to reduced earnings	[redacted]	[redacted]	[redacted]	
Time horizon 50 years	-	[redacted]	[redacted]	[redacted]	
Time horizon 20 years	-	[redacted]	[redacted]	[redacted]	
No annual withdrawal	No treatment discontinuation for responders until they enter the 'wheelchair dependent' health state	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the plausibility of this assumption
No delay in progression in VA responders	No delay in progression in VA responders	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the plausibility of this assumption
Permanent delay in progression in VA responders	A permanent delay in disease progression in VA responders until treatment discontinuation	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the plausibility of this assumption; this is supported by new clinical data in the Etoile Alpha study[18]
Discontinue if wheelchair dependent	Treatment is discontinued upon entering the 'wheelchair dependent' health state	[redacted]	[redacted]	[redacted]	

Scenario	Scenario detail	Paediatric ICER	Adolescent ICER	Adult ICER	Impact of new clinical data on plausibility
No reduction in severe infection probability	No treatment effect for VA in terms of reducing the probability of a severe infection occurring, and in reducing the mortality risk of a severe infection	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the plausibility of this assumption
No reduction in surgery benefit	No treatment effect for VA in terms of reducing the probability of mortality or serious complications arising from a surgical procedure	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the plausibility of this assumption
No homecare administration	No homecare administration, all VA infusions provided in hospital	[redacted]	[redacted]	[redacted]	
Treatment monitoring in addition to BSC	Patients receiving VA require an additional two consultant consultations per annum	[redacted]	[redacted]	[redacted]	
MPS Health State Utilities	MPS Society Survey utility values are used for the health state utility values	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the health state utility values
Exclude carer disutility	Exclude carer disutility	[redacted]	[redacted]	[redacted]	
On-treatment utility = 0.00	On-treatment utility benefit for VA = 0	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the on-treatment utility assumptions, data from Etoile Alpha suggest this scenario is not plausible
On-treatment utility = 0.05	On-treatment utility benefit for VA = 0.05	[redacted]	[redacted]	[redacted]	New data from the MAA will inform the on treatment utility assumptions; data from Etoile Alpha suggest this is a conservative scenario

Abbreviations: ICER = incremental cost-effectiveness ratio; MPS = mucopolysaccharidosis; VA = velmanase alfa

These scenario analyses demonstrated that a conservative base case has been applied for the analyses, and there are scenarios where the ICER was improved when using an alternative source for model inputs, or an alternative assumption. Likewise, the ICER increased in some scenarios, including when a shorter time horizon was applied, when no annual withdrawal on VA for responders was included, when no delay in progression for responders was assumed, and when no on-treatment utility benefit was applied for patients receiving VA.

Validation

Extensive validation of the previous submissions by UK clinical experts was carried out during 2017-2019, including an expert elicitation panel, advisory boards and expert interviews.[2,3] This updated analysis and the data collection plan will be revalidated via expert interviews prior to the next committee meeting, alongside technical engagement with NICE and NHS England to discuss the feasibility of the updated managed access agreement in clinical practice.

1.3.5 Interpretation of economic evidence

In the original submission, Chiesi developed a de novo model to estimate the impact of treatment with VA in terms of costs and QALYs on patients with AM. However, the analysis was based on little published evidence regarding the long-term progression of AM under BSC and the capacity for VA to benefit patients with AM in the long term, due to the extremely ultra-rare nature of the condition. Only 29 people have ever been identified as having AM in the UK according to the UK MPS Society registry[63], and an estimated prevalence in England of 25 patients. Therefore, any economic model developed in AM will be speculative and reliant on expert KOL opinion to design and parameterise. As a result, Chiesi has interacted extensively with expert KOLs through formal expert elicitation and structured interviews to design, validate and parameterise the model as robustly as possible. The model also incorporated clinical data from 33 patients included in rhLAMAN-05, rhLAMAN-10 and multi-domain responder analyses[23], which represents a substantial proportion of the diagnosed AM population. The updates to the model reflect supportive new clinical data from the rhLAMAN-08 clinical trial, real-world studies (Etoile Alpha) and case reports. Additional data are being collected to increase confidence in the longer-term clinical effectiveness of VA in the SPARKLE registry and the AllStripes Study.

In addition to very low patient numbers, model development in AM is extremely challenging when no patient can be perceived as ‘typical’ in reality. Therefore, the model is unlikely to truly capture the expected costs and QALYs for a cohort/average patient. While Chiesi believes the model is verified, robust and informative, it should be used with caution to make definitive comments regarding the cost effectiveness of VA, particularly with respect to willingness-to-pay thresholds. Additionally, there are potentially wider benefits of VA that were not possible to capture in the model. Finally, the ultra-rare nature of this condition and its low budget impact should be considered alongside the cost-effectiveness results, to ensure a very small number of patients with a significant unmet need can access an effective, life-improving and life-extending treatment.

1.3.6 Economic uncertainties that could be resolved by data collection

There are several key parameter uncertainties that have been highlighted via extensive deterministic sensitivity analysis and scenario analyses, which could be resolved by data collection (see Section F, Table 66). These include:

- Utility data:
  - The model results are sensitive to the source used for health state utilities. Both the rhLAMAN-10 utility data [16], and the MPS Society Survey data [10] were limited by a small sample size. Future studies reporting HRQoL in patients receiving VA, in particular those identified as a responder, would be valuable to resolve this uncertainty. Likewise, better understanding the well-being of patients with AM in a broader sense than just HRQoL, through a validated well-being patient-reported outcome instrument, would be of value given the multi-morbid and complex nature of AM. This may capture the impact of the disease, and subsequently the benefit in terms of response to treatment on important well-being domains including dignity, educational achievement, independence, and capability.
- Response data:
  - Data reporting the degree of response achieved by patients receiving VA were limited due to the small sample-size of the rhLAMAN programme. The SPARKLE registry and other future studies reporting patient-relevant clinical responses based on the multi-domain responder analysis criteria will be valuable to resolve this uncertainty. Likewise, a better understanding of what happens to patients who respond, and to those who do not respond, in terms of progression of disease and clinical events and outcomes will be of value to inform critical model uncertainties.
- Progression data:
  - Data reporting the long-term progressive nature of AM were extremely limited, and therefore the model was highly sensitive to changes in the progression rate and delay in progression achieved by patients responding to treatment with VA. Long-term data for patients receiving VA were collected in France in the Etoile Alpha study[18], but supplementing these with data from patients receiving VA, and ideally an indirect treatment comparison with those receiving BSC, would help resolve the uncertainty in these key parameters.
  - Understanding the proportion of patients who achieve a significant improvement in functional capacity (e.g., a backward transition) when a responder to treatment with VA could be collected during a registry of patients who are initiated on treatment with VA, and would reduce the uncertainty in how many patients may achieve a response, and the impact that response has on their functional ability and QoL.
- Personal and caregiver expenditure and productivity losses

  The model requires a number of assumptions to evaluate the personal and caregiver expenditure and productivity losses, and likely significantly underestimates the impact of caregivers and their families. Data reported in Adam 2019 [10] were integrated into the model where possible but were limited due to a small sample size. Data collection efforts to greater understand the financial impact of caring for a person with AM would reduce the uncertainty in the analysis.

2 Cost to the NHS and Personal Social Services

How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

The UK MPS Society Patient Registry have identified 23 living patients with AM aged 6 years and above in England and Wales[63]. In 2017, there were 3 paediatric patients (aged 6–11), 3 adolescent patients (aged 12–17) and 17 adults (aged ≥18).

Given the ultra-rare nature of the condition, estimates of incident rates are variable. The UK MPS Society Patient Registry has reported 28 cases in England and Wales in the last 39 years (0.80 cases in England and Wales per year). Together, European studies estimate 0.17 cases per 100,000 births (130-133), resulting in 1.15 new AM cases per year based on 696,271 live births in England and Wales (6). For pragmatism, we have assumed 1 new AM case per year as a midpoint estimate. The UK MPS Society Patient Registry reports that 71.4%, 14.3% and 14.3% of AM cases in England and Wales were diagnosed when the person was a paediatric, adolescent, and adult, respectively.

Annual mortality probabilities for paediatrics (0.02%), adolescents (1.35%) and adults (2.17%) are taken from the economic model. The budget impact calculations assume that 13.3% of incident patients will discontinue due to being a non-responder, along with all Year 1 prevalent patients, and all patients will have an annual probability of discontinuing of 10%, as assumed in the economic model. The total numbers of patients eligible for treatment are provided in Table 56, with these numbers of patients presented by each age group in Table 57-Table 59.

Describe the expected uptake of the technology and the changes in its demand over the next five years.

Chiesi has estimated market share figures for paediatrics ([redacted]), adolescents ([redacted]) and adults ([redacted]), which are assumed to be constant across the next five years.

The total number of patients/treated patients is presented in Table 56. It is estimated that in Year 1, five patients will be treated with velmanase alfa, increasing to seven patients in Year 5. Full patient numbers by age group, including the number of treated patients, are provided in Table 57-Table 59.

Please note that no 'whole integer' rounding is conducted in the budget impact calculations, meaning that while the calculations are mathematically accurate and account for discontinuation and mortality, results are presented with partial patients treated, and these are carried forward into the treatment cost calculations.

Table 56. Total patient population

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	56.55	57.68	58.81	59.94	61.07
Incident population	1.13	1.12	1.12	1.12	1.12
Total patients	57.68	58.80	59.93	61.06	62.19

Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 57. Paediatric patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	22.62	23.75	24.88	26.01	27.14
Incident population	1.13	1.12	1.12	1.12	1.12
Total patients	23.75	24.87	26.00	27.13	28.26
Mortality	1.00%	1.00%	1.00%	1.00%	1.00%
Net number of patients	23.51	24.62	25.74	26.86	27.98
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation – annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 58. Adolescent patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	11.31	12.44	13.57	14.70	15.83
Incident population	1.13	1.12	1.12	1.12	1.12
Total patients	12.44	13.56	14.69	15.82	16.95
Mortality	1.00%	1.00%	1.00%	1.00%	1.00%
Net number of patients	12.32	13.43	14.54	15.66	16.78
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation – annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 59. Adult patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	22.62	23.75	24.88	26.01	27.14
Incident population	1.13	1.12	1.12	1.12	1.12
Total patients	23.75	24.87	26.00	27.13	28.26
Mortality	1.00%	1.00%	1.00%	1.00%	1.00%
Net number of	23.51	24.62	25.74	26.86	27.98

patients					
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation – annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Chiesi are not aware of any such costs associated with treatment over and above those already incurred in clinical practice and BSC for people with AM.

Describe any estimates of resource savings associated with the use of the technology.

The economic model suggests both health state and PSS cost savings over the lifetime perspective of the analysis. However, it is not believed that VA will result in significant resource savings over years 1–5, following treatment initiation.

Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Chiesi are not aware of any other opportunities.

Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

It is anticipated that significant savings could accrue for welfare, education and local government budgets. Further details are provided in Section E.

What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Budget impact calculations for the total, paediatric, adolescent, and adult cohorts are provided in Table 60–Table 63.

These calculations take into account the increase in treatment cost as weight increases in the paediatric and adolescent cohorts. Administration costs follow the assumptions used in the economic model, with an annual cost of £7,975.33 in the first year (incident population) and £7,210.93 in subsequent years due to the switch to homecare provision.

The total annual budget impact is £[redacted] in Year 1, rising to £[redacted] in Year 5. The total cumulative budget impact over 5 years is £[redacted]

Table 60. Budget impact – total cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 61. Budget impact – paediatric cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 62. Budget impact – adolescent cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Annual budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 63. Budget impact – adult cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A scenario has been provided where no discontinuation or mortality are assumed in the budget impact analysis, to provide an 'upper bound' estimate of budget impact.

Table 64. Total population assuming no discontinuation or mortality

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	56.55	57.68	58.81	59.94	61.07
Incident population	1.13	1.12	1.12	1.12	1.12
Total patients	57.68	58.80	59.93	61.06	62.19
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 65. Budget impact assuming no discontinuation or mortality in the total cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In this scenario, the total annual budget impact is £[redacted] in Year 1, rising to £[redacted] in Year 5. The total cumulative budget impact over 5 years is £[redacted].

Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

We believe the figures to be robust and are based on direct estimates of the number of patients with AM from the UK MPS Society Patient Registry. The estimates of mortality and discontinuation are taken directly from the economic model, which has been validated by UK clinical experts. Treatment costs consider both the shift to home care and the increase in weight in the cohort as they age. The budget impact analysis assumes monitoring costs are included within the cost of providing BSC. Future resource implications relative to BSC (such as long-term reductions in procedure costs, health-state costs and associated PSS and societal costs) are not captured due to the short time horizon.

Section E – Impact of the technology beyond direct health benefits

1 Impact of the technology beyond direct health benefits

1.1 Impact on healthcare resource use

Chiesi is not aware of any additional costs associated with VA treatment over and above those already incurred in clinical practice for the treatment of patients with AM with BSC. No additional NHS infrastructure is required to ensure the safe and effective use of VA in those centres which are already experienced in the diagnosis and management of LSDs. As is the case for other ERTs, VA will be offered to patients via homecare by the NHS once patients have been stabilised following initiation of treatment in the clinical centre. Homecare administration will be by a trained nurse as is standard practice for the administration of other ERTs in the UK.

To start treatment with VA, the start/stop criteria must be followed (see Section F): these include standard biochemical, enzymatic, disability and functional tests that can be performed in clinical practice at routine assessments of patients with AM, and no additional tests are required. For a patient to start and continue treatment with VA, a series of clinical measurements (serum oligosaccharides, 3-MSCT, 6-MWT, FVC, CHAQ disability index, CHAQ pain [VAS], EQ-5D-5L and LVEF) should be made at baseline and at 12-month intervals.

1.2 Impact on patient and carer indirect and societal costs

AM is a devastating condition with a significant mortality and morbidity impact on patients. Yet as a multi-morbid lifelong condition, the stabilisation of disease progression associated with VA treatment has potential to offer additional benefits beyond improved health, QoL and direct healthcare costs. As described in Section B and published in the UK MPS Society Survey[10], AM results in a substantial economic and societal burden on patients, caregivers and other family members.

UK KOL interviews and the UK MPS Society Survey[10] describe how AM has a substantial, albeit unquantifiable negative impact on the social well-being and finances of patients and caregivers, which worsens as the patient's walking ability deteriorates. For example, adults with untreated AM are unlikely to ever obtain full-time employment. Additionally, the amount of care required can limit job opportunities for carers and result in substantial out-of-pocket expenses. Therefore, the substantial and long-term impact on families and carers of a treatment that can slow disease progression should not be underestimated.

These potential wider benefits were described in an interview with a patient (and their carer) who had been treated with VA as part of the UK MPS Society Survey and in case reports from patients treated in Europe[10,19]. These potential benefits include improved physical symptoms, reduced joint pain, rates of ear infections and improved or maintained walking ability.

It is anticipated that treatment with VA may result in direct and indirect cost savings to patients, caregivers and wider adult social care and government services. Due to the complexity of benefits that are potentially available for a person (and their family) with AM, it is not possible to detail all aspects. Furthermore, the uptake of benefits and support will vary due to means testing and local availability. However, it is anticipated that there are 5 broad ways in which direct and indirect cost benefits could be realised by the ability of VA to slow disease progression:

- Increased productivity of patient and caregivers: with treatment, some patients and caregivers may have increased ability and opportunities for work, to work longer hours and maintain employment for longer, with fewer absences due to illnesses and medical appointments
- Education benefits: children and young adults with AM will have special educational needs that require the funding of assistance and adaptations to enable the child to attend school or college. A child who benefits from VA may require reduced educational support.
- Reduced need for out-of-pocket expenses: including reduced need for self-funded home modifications, disabled access vehicles, mobility aids, electric wheelchairs, private carers or respite providers that are required as mobility declines
- Local government disability and social care budgets: home adaptations via Disabled Facilities Grant payments may be reduced or postponed due to the benefit of VA. These grants cover adaptations such as widening doors, installing ramps, modifying bathrooms and installing a stair lift. Local councils also provide direct payments to arrange adult social care (homecare or residential). A patient with functional improvement or stabilisation may postpone or reduce these home adaptations or their need for adult social care.
- Welfare budgets: central government welfare includes disability and sickness benefits (disability living allowance (DLA) or personal independence payment (PIP), attendance allowances, employment and support allowances, vehicle tax exemption, parking benefits and travel/transport benefits). A patient benefiting from VA may not require as many of these benefits. Furthermore, the family of a patient may be able to maintain a higher level of employment which will have income tax benefits. Families on low incomes may be entitled to housing benefits and council tax reductions. A patient benefiting from VA may not require as many additional local council benefits, and their families may be able to achieve or maintain a higher level of employment.

1.3 Benefits not captured in updated cost-effectiveness analysis

While the model attempts to capture the negative health and QoL impact of AM without treatment and the positive impacts of VA on patient length and QoL in the QALY, some aspects that may affect patient and carer QoL and societal impacts, such as pain, minor infections, hearing impairment, mental health, psychiatric problems, and dental health have not been accounted for in the cost-effectiveness analysis due to lack of data.

For example, while VA is unlikely to provide direct neurological benefits, patients with greater functional and hearing capacity may be able to attend school more frequently or engage more productively at work, providing both economic and QoL benefits, as evidenced in some published case reports[19]. No data were identified to inform personal and caregiver expenditure in the AM population and were consequently not

included in the model; however, in reality, personal and caregiver expenditure is likely to be variable, and in some cases, can be large. Therefore, the full value of VA to patients, carers, family members and siblings, and society may not be adequately reflected in the QALY gains modelled.

VA is the only approved pharmacological treatment for AM; as such, as a disease-modifying therapy, VA offers both patients and carers the value of hope of the potential for symptom improvement and/or slowing of disease progression, and the hope of retaining mobility and independence for as long as possible. As this is not possible to quantify in the QALY, this additional value of hope offered by VA is not accounted for in traditional cost-effectiveness frameworks[64].

Finally, the QALY framework may be too narrow given the complex and multi-morbid impact of AM. In particular, people may retain dignity, independence, and capabilities via effective care and treatment and these valuable benefits may not be captured using standard instruments for estimating QoL utility values. A wellbeing or capabilities perspective may be more valid for chronic, multi-morbid, progressive disease characterised by cognitive impairment and skeletal deformities such as AM.

Section F - Managed Access Arrangements

1 Managed Access Arrangement

Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

Describe the specifics of the MAA proposal, including:

- The duration of the arrangement, with a rationale
- What evidence will be collected to reduce uncertainty
- How this evidence will be collected and analysed
- The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA
- Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)
- Funding arrangement, including any commercial proposals or financial risk management plans
- The roles and responsibilities of clinical and patient groups during the MAA
- What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed

Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

1.1 Key clinical uncertainties and how further data collection could address these

Given the paucity of long-term evidence, the limited clinical experience of VA, the ultra-rare nature of the condition and lack of natural history data for untreated patients, a number of uncertainties exist with the clinical effectiveness of VA.

As such, some of the inputs in the economic modelling (see Section D) are reliant on UK KOL expert opinion and assumptions. All assumptions have been tested and validated by clinical experts and (where possible) informed by clinical studies and/or experiences from relevant proxy conditions. However, the use of clinical expert opinion and assumptions does lead to uncertainty in the model and can limit its usefulness in informing decision-making regarding the cost effectiveness of VA. From the sensitivity analyses conducted, the main uncertainties in the model relate to the

following clinical uncertainties:

- Long-term disease progression with and without VA, including infection rates
- Impact of VA on delaying and/or stabilising disease progression
- Long-term survival rates and causes of mortality with and without VA, including incidence of death due to infection
- QoL of patients with AM, with and without VA treatment, overall and stratified by ambulatory health state
- Impact of VA in changing the clinical management of AM

Ongoing clinical studies described in Table 21 include ongoing trials with VA (rhLAMAN-07 and -09), natural history studies (the SPARKLE AM registry and the AllStripes study), as well as supporting data from the UK MPS Society registry. Taken together, these studies can provide sufficient data to address some of these uncertainties by incorporating these data into further statistical analyses. Table 66 describes specific data that could be collected over the next 3 years and analyses that could be incorporated into a restructured cost-effectiveness analysis as part of a resubmission after a period of managed access in 2025. Further details of uncertainties in the economic analysis are described in Section D1.3.6.

These suggested data collection inputs will be further refined in collaboration with NICE, the ERG, NHS England, clinical experts and the MPS Society during technical engagement and consultation.

Table 66. Potential data collection to resolve clinical uncertainties

Clinical uncertainty	Suggested data collection and analysis
rhLAMAN-05 is the only comparative data available of VA vs. placebo and was limited by 12-month follow-up and small patient numbers	An indirect comparison of data of patients treated with VA (rhLAMAN-10, Etoile Alpha and SPARKLE) could be performed with natural history data of untreated patients (AllStripes, SPARKLE and the MPS Society) to support the RCT data and be incorporated into any updated responder analyses
Natural history data and off-treatment progression	Natural history data of patients untreated with VA will be collected in AllStripes, SPARKLE and local UK registries, including the MPS Society Registry
Utility data with/without VA	EQ-5D-5L and/or CHAQ will be collected in rhLAMAN-07,-09, SPARKLE and AllStripes and incorporated into updated responder analyses
Infection rates with/ without VA	Infection rates and hospitalisations will be collected in rhLAMAN-07,-09, SPARKLE and AllStripes
Global responder analysis includes serum oligosaccharides as one of the domains which is a surrogate endpoint	Updated responder analyses will be performed using clinical domain data collected in the MAA as part of the SPARKLE study, which will be incorporated into a restructured economic model to allow more clinical data to be incorporated and less reliance on expert opinion

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; VA = velmanase alpha

1.2 Proposed eligibility and stopping criteria for a MAA

In order to provide guidance on the appropriate management of patients treated with VA, Chiesi have developed start-stop criteria, in collaboration with UK KOLs and patient groups. The following criteria were agreed at the Chiesi advisory board on the 15th of November 2018 and at subsequent discussions with additional healthcare professionals, including a clinician working in the NHS.

1.2.1 Eligibility

To receive treatment, patients must be made aware of the start-stop criteria for VA. Patients are required to attend appointed clinics 2 times per year for assessment. There may be some patients, e.g. those with cognitive impairment or other behavioural issues or challenges, who are not able to complete a full set of assessments at the appointed visits. In such cases, clinicians will be expected to make all possible efforts to gather as much of the required data as possible.

Excluded patients

Patients should not be offered VA if ≥1 of the following apply:

- Previous anaphylactic reactions to the drug or excipients
- Patients with severe AM
- Previously treated with HSCT/BMT successfully
- Concomitant life-limiting condition
- In the view of the MDT, patient has reached a disease severity which will not benefit sufficiently from treatment
- Patients with only neurological manifestations of disease
- Unable to comply reliably and consistently with the measurement requirements (e.g. due to coexisting severe neurological impairment)

1.2.2 Start criteria

All patients (adults and children) not meeting ≥1 of the following start criteria will continue to be monitored, and treatment only to be offered when ≥1 of the start criteria are met.

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

- Biochemical measurement of oligosaccharide levels to show these are raised with set thresholds that must be met, AND
- Enzymatic activity to confirm the diagnosis of AM, AND
- Meets threshold of disability (see Table 67 below) to demonstrate that patients are affected by non-neurological manifestations of AM to an extent that warrant consideration for VA treatment - minimum levels, and maximum thresholds will be set for treatment.

Table 67. Threshold of disability for starting VA treatment:

Patients must meet ≥1 of the following criteria from ≥1 of the following clinical domains:

Clinical domain 1: Mobility function	**Clinical domain 2: Lung function**	**Clinical domain 3: Cardiac function**	**Clinical domain 4: Upper respiratory tract infections**
• 6MWT: 2 SD below the mean normal for an age matched measurement and a max level. OR • Short physical performance battery test (SPPB) – score of 9 or less is defined as impaired (in COPD/elderly patients) OR • Patients who use mobility aids (walking aid, wheelchair) – patients should also carry out the 6MWT and SPPB where possible, or the SPPB alone where patients are unable to complete the 6MWT to gain a baseline measure	• Forced vital capacity (FVC) test: 2 SD below the mean normal for an age matched measurement and a max level. OR • Sniff nasal inspiratory pressure (SNIP) test: a minimum difference of 50cm of water compared to an age matched measurement. OR • Requirement for ventilatory aids	• Impaired LVEF <45% of normal, as assessed by echocardiogram or cardiac MRI Treatment for reduced LVEF should be optimised and stabilised prior to treatment with VA. LVEF to be reassessed and this level taken as a baseline for future assessments.	• In patients ≥12 yrs, having >2 episodes of respiratory infections per annum that required antibiotic usage and based on clinical judgement
For children <6 years, in addition to use of mobility aids, a physiotherapist assessment of mobility should be conducted and treatment may be considered if patients are not meeting functional milestones for their age	For children <6 years, who are unable to reliably comply with FVC and SNIP tests, treatment should be initiated based on clinical evaluation or use of ventilatory aids.		Children <12 years should not be excluded on an infection basis as they already typically experience around 6 to 8 infections per year, including high numbers of lung and ear infection.
Siblings of currently diagnosed AM patients: Screened siblings of those with evidence of non-neurological AM, who themselves are eligible for VA, will be discussed individually at a standing committee.			

1.2.3 Monitoring and stopping criteria

Baseline assessments should be taken from the starting criteria described in Table 67, plus additional assessments of the biochemical domains and clinical domains in Table 68 to gain a baseline measure before initiation of treatment, so disease progression can be accurately assessed at the required time points (12 months, 24 months and annually thereafter). The biochemical and clinical domains in the monitoring criteria are based on the minimal clinically important differences used in the responder analysis requested by the EMA and published by Harmatz et al. 2018[23].

12-month review

- All patients to achieve improvement in the biochemical domain (serum oligosaccharides) by 6 months

  AND

- Patients to meet 4 out of 5 of the clinical domains at 12 months to continue VA

24-month review

- Maintain improvement the biochemical domain (serum oligosaccharides)

  AND

- Patients to meet 4 out of 5 clinical domains at 24 months to continue VA

  AND

- In ≥1 of criteria used as an entry requirement, an improvement measure must be demonstrated at 24 months

Subsequent reviews

Stabilisation of 4 out of 5 clinical domains (in addition to stabilisation of oligosaccharides) each year from previous year is required to continue VA, and ≥1 of the 4 to be in a measure used as an entry criterion.

Other reasons to consider stopping VA treatment

- patient unable to tolerate infusions due to infusion-related severe AEs that cannot be resolved
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit
- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g. due to repeated recurrent chest infection or progressive and sustained lack of mobility, or coexisting severe neurological impairment
- the patient misses more than three infusions of VA in any 12-month period, excluding medical reasons for missing dosages
- the patient has reached a disease severity which will not benefit sufficiently from treatment in view of the MDT

Stopping criteria in children <6 years of age

Children <6 years would not be expected to meet clinical domain requirements due to difficulties of carrying out baseline tests. Until aged 6 years, oligosaccharides should improve to the defined degree, and clinical judgement of the MDT should enable treatment to continue until progression can be accurately monitored. Please see individual domains for guidance on age and expected improvements.

1.3 Commercial arrangements

Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)

Chiesi is open to discussing any infrastructure requirements to deliver the MAA with NHS England.

Funding arrangement, including any commercial proposals or financial risk management plans

A simple confidential PAS discount will be submitted as part of the MAA. Chiesi is open to discussing additional risk management plans with NHS England should this support initiation of the MAA and patient access to VA.

Roles and responsibilities of clinical and patient groups during the MAA

The MDT responsible for the care of an AM patient will complete baseline and follow-up tests; the MDT will assess results for use in start/continuation decision-making. If an MAA is accepted, discussions will be held between the MDT and the UK MPS Society on how best to monitor PROMs.

What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed

Chiesi would welcome negotiations with the relevant NHS commissioners to find a one-off, long-term funding agreement.

Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

The MAA provides clarity on how clinicians wish to implement VA in the AM clinical pathway in England and Wales. It reduces the uncertainty associated with patient selection, as KOL-led ‘start’ criteria will ensure only patients likely to benefit from VA are selected for treatment. Furthermore, it reduces the uncertainty associated with long-term effectiveness of VA, in that KOL-led outcomes for monitoring/stop criteria will ensure only patients achieving appropriate MCID thresholds will continue treatment, with relevant outcome data recorded. Although formal economic analyses cannot be presented (due to differences in the outcomes in the rhLAMAN programme and those defined by UK KOLs in the MAA), it is expected that the MAA will improve the cost-effectiveness of VA as only ‘responders’ achieving clinical outcomes will continue treatment. Also, these data will be incorporated into updated responder analyses that will be included in the resubmitted model that will be restructured to allow more data to be included, with less reliance on expert assumptions.

Table 68. VA Monitoring and Stopping Criteria

Domains	Improvement measure within/at 12 months	Improvement measure at 24 months	Measurement at yearly review thereafter
Biochemical domain			
Serum oligosaccharides	50% reduction from baseline within 6 months. Not meeting this would require investigation to confirm adherence and antibody development. Treatment to stop if not met and no reasonable explanation. At 12 months - Stabilisation (threshold of +10% from 6 month response)	Stabilisation (threshold of +10% from 6-month response)	Stabilisation (threshold of +10% from 6-month response)
Clinical Domain 1: Mobility function (meet one of the following):			
6MWT	For patients ≥2 SD below the mean normal for an age matched measurement at baseline – would require 5% improvement from baseline value (only baseline value is age matched) Other baseline results require stabilisation (max deterioration of 2% from baseline)	For patients ≥2 SD below the mean normal for an age matched measurement – would require 10% improvement from baseline value (only baseline value is age matched) Other baseline results require stabilisation (max deterioration of 2% from baseline)	Stabilisation (deterioration less than 2% of baseline or last measurement)
SPPB	For patients ≥2 SD below the mean normal for an age matched measurement – would require 1-point improvement from baseline value (only baseline value is age matched) Other baseline results – require stabilisation (no adverse point threshold change)	Require stabilisation (no adverse point threshold change)	Require stabilisation (no adverse point threshold change)
Clinical Domain 2: Lung function (meet one of the following):			
FVC – Adults (>18 yrs.)	For patients ≥2 SD below the mean normal for an age matched measurement at baseline – would require 3% absolute improvement on baseline (only baseline value is age matched) in an accredited lung function lab In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	For patients ≥2 SD below the mean normal for an age matched measurement – would require 3% improvement from baseline value (only baseline value is age matched) in an accredited lung function lab In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	Stabilisation of FVC Any reduction of FVC >5% should be considered for treatment withdrawal

FVC – Paediatrics	For patients ≥2 SD below the mean normal for an age matched measurement – would require 5% improvement from baseline value (only baseline value is age matched) In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	For patients ≥2 SD below the mean normal for an age matched measurement – would require 10% improvement from baseline value (only baseline value is age matched) In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	Stabilisation of FVC Any reduction of FVC >5% should be considered for treatment withdrawal
SNIP	Greater than 10% or 5cm of water improvement from baseline	Stabilisation (threshold of -5% from baseline)	Stabilisation (threshold of -5% from baseline)
Clinical domain 3: Cardiac function			
Ejection fraction	Stabilisation in ejection fraction (threshold of -10% from baseline)	Stabilisation in ejection fraction (threshold of -10% from baseline)	Stabilisation in ejection fraction (threshold of -10% from baseline)
Cardiac treatment should be optimised prior to initiation of treatment, and the ejection fraction taken after this optimisation of care used as the baseline for assessment.			
Clinical domain 4: Infections			
Infection rate (adults and children)	Improvement defined of a ≥50% reduction in antibiotic (AB) usage from baseline or Stabilisation in rate of AB usage if not a starting criteria (threshold of +10% from baseline)	Stabilisation in rate of AB usage (threshold of +10% from year 1)	
Clinical domain 5: PROMS (meet one of the following):			
CHAQ-DI (patient or proxy-completed)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)
EQ5D-5L or MPS HAQ (patient or proxy completed)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)
Pain: VAS pain	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)

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Velmanase alfa for treating alpha-mannosidosis: A Highly Specialised Technology Appraisal. Critique of the company's additional evidence submitted in March 2022

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Rider on responsibility for report

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Contributions of authors

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

1 Executive Summary

The manufacturer of velmanase alfa (VA) has resubmitted evidence related to the clinical and cost-effectiveness of VA in the treatment of people with mild to moderate alpha-mannosidosis (AM).

The cost-effectiveness evidence largely uses the assumptions preferred by the NICE appraisal committee, with two notable changes. The first is that the utility gain associated with VA treatment has been increased to 0.10, rather than 0.05, and the assumption that in people who respond to VA treatment that disease progression would be halted for a period of 5 years. Additionally, the company has included the costs of home infusion and has updated/inflated costs to the most recent time point.

The incremental cost effectiveness ratios (ICERs) presented in terms of cost per quality-adjusted life years (QALY) estimated by the company were £[redacted] for a paediatric population, £[redacted] for an adolescent population, and £[redacted] for an adult population.

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. Given these views, the ERG believes that the ICERs will be in excess of [redacted], and considerably more so in the case of adolescent and adult patients.

2 Introduction

VA (LAMZEDE) is indicated as an enzyme replacement therapy for the treatment of non-neurological manifestation in patients with mild to moderate AM.[1] The mild to moderate criterion is believed by the ERG to have been stipulated because 'patients with the most severe rapidly progressing phenotype (with a deterioration within one year and central nervous involvement) were excluded from exploratory and pivotal VA studies.

VA for treating AM was first appraised by NICE by the HST committee in April 2018. This meeting resulted in a negative evaluation consultation document (ECD).[2] In response to this document, Chiesi, the manufacturer of VA submitted further evidence which was critiqued by the (ERG) and which was considered by NICE at an HST meeting in June 2018. In October 2018 NICE announced that the HST evaluation had been put on hold whilst Chiesi developed '*an offering for submission to NHS England*'. Neither the further evidence submitted by Chiesi nor the ERG critique has been made publicly available but were provided to the HST committee for consideration in the June 2018 meeting. Salient points from these documents will be detailed within this report to reduce cross-referencing.

In May 2019, Chiesi submitted further evidence to NICE having considered the comments at the second committee meeting and the critique produced by the ERG.[3] This additional evidence included a patient access scheme (PAS) which was a simple discount of [redacted] on the list price. Further changes to the company's model that was submitted for the second appraisal committee were made to:

- The way that patients discontinuing treatment due to lack of efficacy was operationalised within the model.
- Adding the functionality for patients on best supportive care (BSC) to improve disease status, although this was not permitted in the company's base case.
- Assuming that patients on VA would receive a utility gain of 0.05 in line with the committee's preferred assumptions.
- Using a discount rate of 3.5% for costs and benefits in line with the committee's preferred assumptions.
- Inflating NHS and personal social services costs to 2017/18 and changing some sources for these data.
- Using a distribution for the weight of patients rather than assuming a fixed value for all patients.
- Changes to the disutility associated with the walking unassisted and the walking with assistance, health states in line with the committee's preferred assumptions.
- Other changes considered minor by the ERG

The manufacturer also detailed a potential managed access arrangement (MAA) which attempted to devise a start / stop criteria and MAA framework. These criteria remain unchanged from the company's resubmission in 2019. However, the company stated that '*formal economic analyses cannot be presented (due to differences in the outcomes recorded in the rhLAMAN clinical trial programme and those defined by UK KOLs [Key Opinion Leaders] in the MAA)*' although the company stated that '*it is reasonable to expect that the MAA will improve the cost-effectiveness of velmanase alfa as only those achieving significant clinical outcomes will continue treatment.*'

Revised analyses were provided by the company to address limitations identified by the ERG which were submitted on the 18th of July 2019. Based on these revised analyses the ERG believed that the "*ICER for velmanase alfa used for treating alpha-mannosidosis is in excess of* [redacted] *per QALY gained at the current price given the PAS. The undiscounted QALY gains, which may be used by the Committee in determining the appropriate cost per QALY threshold, are estimated to be below 3.00, although this could improve should the MAA select those patients who will benefit most from treatment. However, the ERG believe that this is unlikely to increase above 10.00 undiscounted QALYs*.[4]"

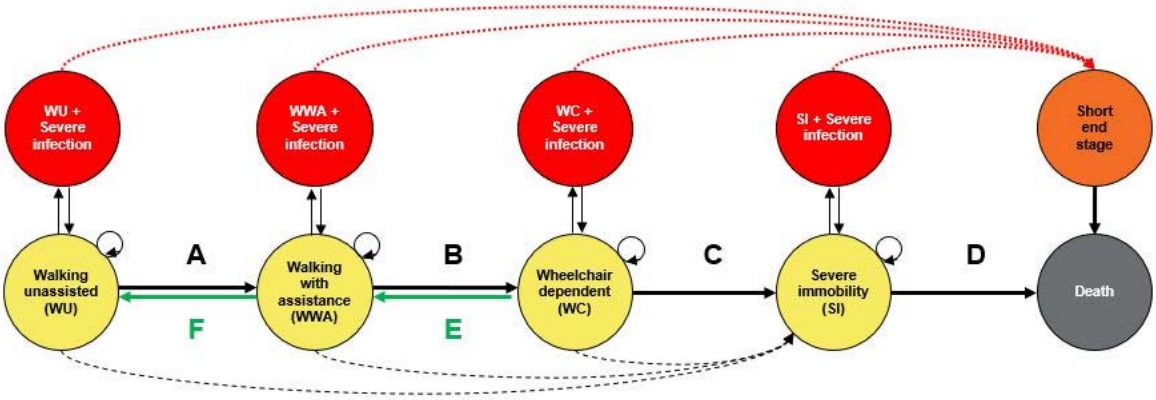
NICE produced a Final Evidence Document (FED) in October 2019, although this was subsequently withdrawn. In March 2022, the company resubmitted clinical and cost-effectiveness evidence related to VA. Key updates include: new data relating to the clinical effectiveness of VA from both clinical studies and real-world evidence; an increased PAS ([redacted]); and a proposal for a MAA and updated data collection plans.

The company submitted a revised economic model, which incorporated the NICE Appraisal Committee preferred assumptions in the withdrawn FED, with two key exceptions, and with costs changed to reflect current prices. The two exceptions were to: (i) increase the underlying utility benefit associated with VA, over and above the utility of each health state from the NICE Appraisal Committee's preferred value of 0.05 to a value of 0.10 and (ii) to assume that patients initiating VA who respond would not experience disease progression in the initial five years of treatment. The merits of these changes are discussed in the main text of this report.

The company's model structure remained unchanged which was a cohort Markov design, with 4 primary health states representing different levels of ambulatory status (walking unassisted, walking with assistance, wheelchair dependent, and severe immobility). The model included additional transitory health states for severe infection and a short end stage from which a patient could only move to death.

A schematic of the company's model, for reference, is provided in Figure 1. Death can occur from any state. As the NICE Appraisal Committee indicated in the withdrawn FED that '*the overall model structure was adequate for decision making*' the ERG does not comment further on model structure.

Figure 1: Schematic of the company's model



The ICERs, presented in terms of cost per QALY, estimated by the company were £[redacted] for a paediatric population, £[redacted] for an adolescent population, and £[redacted] for an adult population. All results presented in this report use the increased PAS price. The company states that '*As the current cost effectiveness model may not adequately capture the likely treatment effect of VA on pain, minor infections, respiratory function and psychiatric symptoms, these calculations may underestimate the true value of VA for patients with mild-to-moderate AM*' although the ERG notes that the increase in the underlying utility should account for some of these aspects from a health perspective.

3 Critique of the new analyses provided by the company

This section critiques the evidence relating to the two aspects where the company has preferred a different assumption compared to those of the NICE Appraisal Committee stated in the FED. These relate to an increased utility gain (from 0.05 to 0.10) for being on VA and assuming that patients who respond to initial VA treatment would not experience disease progression for five years.

3.1 Critique of the company's preference to use an underlying utility gain of 0.10 rather than the NICE Appraisal Committee's preferred value of 0.05

In the withdrawn FED, the NICE Appraisal Committee (Section 4.18) the quality-of-life benefit associated with VA treatment was discussed, with the company having chosen a value of 0.1 in its CS due to aspects of AM not fully accounted for in the model. The Appraisal Committee '*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.*'

The company has reverted back to a preference for a utility gain of 0.10 for patients receiving VA (which was estimated by Key Opinion Leaders) in its base case, rather than the 0.05 preferred by the Appraisal Committee. The company states that the rationale for this was the disease improvement and delayed progression observed in the Etoile Alpha study.[5] The ERG comments that the delayed progression has been explicitly incorporated in the company's revised model and allowing that to influence the utility gain over and above health state residency would introduce an element of double counting. As detailed in Section 2.2 Etoile Alpha is a small (n=[redacted]) retrospective study which makes establishing comparative data with patients receiving best supportive care (BSC) difficult.

The company presented data on the mean change from baseline at month 30 for measures of quality-of-life, although the number of patients contributing to these results is small (less than or equal to [redacted] patients for all measures). These data, which are shown in Figure 12 of the company submission (CS) are reproduced in Figure 2. [redacted]

[redacted]

The ERG believes that the data from Etoile Alpha indicates that treatment with VA may improve quality-of-life but that there is uncertainty in any increase in utility due to: (i) the fact that Etoile Alpha is a non-comparative study which may be prone to placebo, or Hawthorne effect bias, and; (ii) that patient numbers are small. A fuller discussion on the Etoile Alpha study is provided in Section 2.2.1. Clinical advice provided to the ERG suggests that patients would be receiving more medical monitoring and input in Etoile Alpha, based on experience with enzyme replacement therapies, the benefits of the better background care could be a significant proportion of patient improvement. Thus, there is considerable uncertainty in the ratio of improvements based on pharmaceutical treatment and improved standard of care, which may be disease specific.

The ERG comments that some data are reported for the five domains of the EQ-5D-5L and that these may be used to provide an indication of the improvement in utility associated with VA treatment, subject to the limitations listed previously, however, any improvement or worsening in health state (which would also affect utility) would need to be considered in any calculation. [redacted].

The ERG does not believe that the new evidence provided by the company is strong enough to refute the 0.05 value in utility associated with VA treatment preferred by the NICE Appraisal Committee, although ICERs using a 0.10 decrement whilst changing the assumed duration where there can be no disease progression for responders are provided for the Appraisal Committee's consideration.

Figure 2: Changes in Quality-of-life measures between baseline and month 30

3.2 Critique of the company's preference to assume that there is no disease progression for a period of 5 years for responders to VA treatment.

The company provided new clinical data as detailed in Table 3 of their submission (adapted to be Table 1 of this report). Of these studies, one related to paediatric patients (rhLAMAN-08) and is therefore not within scope for this appraisal. There were no new data for rhLAMAN-02, -03, or -04. These studies are therefore not considered further as they do not inform the assumption that patients have no disease progression for 5 years, since none reported outcomes beyond 2 years. New analyses were reported for rhLAMAN-05 and rhLAMAN-10 (rhLAMAN-10 was an integrated analysis of patients who were recruited to rhLAMAN-04 and -05). These related to infections (serum IgG levels, infection burden questionnaire, caregiver feedback). In the previous submission, rhLAMAN-10 reported outcomes for some patients up to 48 months, and the peer reviewed publication[6] of this study notes the mean time on treatment was 15.2 (range 11.7 – 53.4) months. This study therefore provides some data beyond 4 years, which may be useful to revisit with respect to the modelling assumption (see Section 2.2.3). A new retrospective registry study was reported (Etoile Alpha, n=16), which was cited as an evidence source to support the modelling assumption of patients who respond having no disease progression for a period of 5 years (CS Table 26), and is therefore given more consideration in this report (see Section 2.2.2). The company also described the ongoing SPARKLE study, a multi-national prospective cohort study looking at the long-term efficacy and safety of VA, for which there is only a second interim report of baseline characteristics and immature safety data, which are not relevant to the modelling assumption and not considered further here. A UK case report (n=1) and a case series (n=5) were also reported, along with case reports for all patients in the Etoile Alpha study, some of whom were on treatment for five years or more. These are considered in Section 2.2.3.

In addition to the empirical data from these studies, the company conducted an elicitation exercise in 2017 which is cited as support for the modelling assumption (CS Table 26), and critiqued here in Section 2.2.4. Newer clinical data (from studies such as Etoile Alpha) were therefore not available to the clinicians The elicitation exercise was not updated for the latest submission.

Table 1: List of clinical evidence of patients with AM treated with VA (adapted from Table 3 of the CS)

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	ERG assessment
rhLAMAN-02 (NCT01268358)	Phase I	Patients with AM (aged 5–20 years) N = 10	VA 6.25 U/kg VA 12.5 U/kg VA 25 U/kg VA 50 U/kg VA 100 U/kg	Change from baseline (no active or placebo comparator)	Original submission (Appendix 7)	No new data
rhLAMAN-03 (NCT01285700)	Phase IIa	Patients with AM (aged 5–20 years), N = 10	VA 25 U/kg VA 50 U/kg	Change from baseline (no active or placebo comparator)	Original submission, (Appendix 7)	No new data
rhLAMAN-04 (NCT01681940)	Phase IIb	Patients with AM (aged 5–20 years), N = 9	VA 1 mg/kg	Change from baseline (no active or placebo comparator)	Original submission, (Appendix 7)	No new data
rhLAMAN-05 (NCT01681953)	Phase III, 12-month core RCT with extension study up to 36 months	25 patients with AM: VA (n=15) • 7 children • 8 adults Placebo (n=10) • 5 children • 5 adults	VA 1 mg/kg	Placebo	Original submission, (Section 9 and Appendix 7)	No new data

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	ERG assessment
rhLAMAN-10 NCT02478840	Integrated analysis of all patients in rhLAMAN-04, -05 after-trial and CU studies	33 patients with AM: • 19 children • 14 adults	VA 1 mg/kg	Change from baseline (no active or placebo comparator)	Original submission, (Section 9 and Appendix 7) March 2022 CS includes a summary of new analyses in Section C1.3.1	New data but not of critical relevance to the model. rhLAMAN-10 previous analyses of relevance to new modelling assumption (no progression for 5 years).
Multidomain responder analysis	Post-hoc analysis requested by EMA	33 patients from rhLAMAN-05 and 10	VA 1 mg/kg	rhLAMAN-05: placebo rhLAMAN-10: change from baseline (no active or placebo comparator)	Original submission, (Section 9 and Appendix 7)	No new data
rhLAMAN-08 (NCT02998879)	Phase II paediatric study	5 patients with AM <6 years	VA 1 mg/kg	Change from baseline to Month 24 (40 months for 1	March 2022 CS Section C1.3.2	Population out of scope

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	ERG assessment
				patient)		
Etoile Alpha	Real-world retrospective registry study (France), conducted as a requirement of conditional market access by HAS	16 patients in 3 cohorts: 7 from rhLAMAN-07 1 from rhLAMAN-08 8 patients in nominative ATU	VA 1 mg/kg	Change from baseline (no active or placebo comparator)	March 2022 CS Section C1.3.6 and Appendix F	Of relevance to new modelling assumption (no progression for 5 years).
AM registry (SPARKLE)	Multicentre, post-authorisation noninterventional, prospective cohort study	All patients with AM	Not specified – all patients eligible irrespective of treatment (VA, BSC, HSCT, investigational treatment)	None	March 2022 CS, Section C1.3.10	Immature, no data of relevance
Case reports from rhLAMAN-05	Case report from rhLAMAN-05 (n=2)	2 patients with conducive hearing impairment	VA 1 mg/kg	Change from switch from placebo	March 2022 CS, Section C1.3.11	Of relevance to new modelling assumption (no progression for 5 years).
UK case report	Case report (n=1)	1 UK patient with AM	VA 1 mg/kg	None	March 2022 CS, Section C1.3.11	
Case report series	Case reports from 3 European centres (n=3,	5 adult patients	VA 1 mg/kg	None	March 2022 CS, Section C1.3.11	

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	ERG assessment
	Spain; n=1, Lithuania; Italy, n=1)					

Abbreviations: ADA, anti-drug antibody; AM, alpha-mannosidosis; ATU, temporary utilisation authorisation; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; BSC, best supportive care; CS, company submission; CSR, clinical summary report; CU, compassionate use; EMA, European Medicines Agency; HAS, Haute Autorité de Santé; HRQoL, health-related quality of life; HSCT, haemopoietic stem cell transplant; NPAF, new product assessment form; QoL, quality of life; RCT, randomised clinical trial; VA, velmanase alfa

3.2.1 Etoile Alpha

3.2.1.1 Description and critique of study design

Etoile Alpha is a real-world, retrospective, observational study conducted in France as a requirement of conditional market access. Basic study details are provided in Table 2. It followed 16 patients [redacted] up to June 2020. The mean treatment duration was [redacted] months. [redacted] patients were diagnosed younger than 6 years of age, although all commenced treatment with VA at or after [redacted] years of age. Patients were from [redacted]).

Efficacy data were reported at "*baseline or the nearest value to the baseline*" (CS p28), and at the last observation "*which could be any timepoint from month 6, to month 18, or 24, or 30, or 33, or 54*" (CS p28). The ERG was unclear whether the "*nearest value to the baseline*" had to be before treatment commenced. It was also unclear to the ERG the precise timepoint of outcome assessment for each patient. Time on treatment was reported for each patient, but since the longest time on treatment was [redacted] months (approximately [redacted] years), but the latest timepoint mentioned in the CS was 54 months (approximately 4.5 years), it is unclear whether time on treatment is indicative of the timepoint of outcome assessment.

The CS states that due to the small sample size and quantity of missing data, inferential statistics were not reported. The ERG agrees that statistical analysis would have been challenging and would have either relied on a great deal of imputed data with limited data to base this on, or would have excluded some patients from some analyses, introducing a risk of attrition bias. However, the company has relied upon interpretation of mean values over time without statistical tests to reach their conclusions, meaning these conclusions are associated with a high degree of uncertainty.

A number of outcomes were planned for Etoile Alpha (see Table 2). A summary of patient characteristics and key outcomes (selected based on their relevance to the start/stop criteria) is provided in Table 3. Further outcome data are available in the CS and CSR, but notably no data are presented for [redacted], indicating a high risk of selective reporting bias. In Table 3, the ERG has sub-grouped the individual patient data into paediatric/adolescent and adult subgroups. Since it was not reported at what time point outcomes were measured, the table is ordered according to time on treatment, but it is unclear whether this can be taken as indicative of the time of outcome assessment, for the reasons noted above.

Table 2: Summary of the methodology of Etoile Alpha

PICO item	Details
Population	To be eligible for enrolment in the retrospective registry, patients must have fulfilled both of the following inclusion criteria: • Every patient receiving or having received VA therapy in France as part of VA development or clinical use (nominative ATU) • Evidence of a signed informed and non-opposition letter indicating that the patient (or parents or a legally acceptable representative according to local regulation)
Intervention	VA 1mg/kg once-weekly
Comparator	Baseline measurement, or measurement nearest to baseline.
Outcomes	Data was collected at diagnosis, baseline and several yearly timepoints thereafter. • Biochemical variables: – Assessment of changes in levels of serum oligosaccharides (µmol/L), of changes in brain biomarkers and in serum immunoglobulin class IgG concentrations • Functional variables: – Assessment of changes in 3-MSCT, 6-MWT and 2-MWT • Respiratory variables: – Assessment of changes in pulmonary exploration tests: FVC (L and %), FEV1 (L) and PEF (L/s) • Complementary variables: – Urinary oligosaccharides (µmol/L), BOT-2 test, WISC test • Cognitive and audiometric variables: – Assessment of changes in the cognitive test Leiter-R (total score and score per area) – Assessment of changes in the PTA test – Imaging and spectroscopy: • Assessment of changes in neurological and structural functions by MRI and MRS • QoL: If QoL data available, QoL assessed through two questionnaires: CHAQ and EQ-5D-5L – CHAQ-DI disability index and assessment, quantified from 0 (lack of affection) to 3 (very severe affection) – CHAQ-VAS score pain related to the level of pain collected by an EVA graduated from 0 to 100 then transformed in a score from 0 to 3 – CHAQ general state VAS: general state quantified from 0 to 3 – For the 3 scores, a rise of the score will be related to a worsening in terms of disability, pain, or general state – EQ-5D-5L associated to patient state (mobility, autonomy, maintenance of usual activities, pain, discomfort, anxiety, and depression) • Safety variables of interest – AEs, SAEs

	– Reason for a possible stop of LAMZEDE – Infusion related reactions – Immunogenicity: Presence of anti-velmanase-alfa IgG antibodies

Abbreviations: 2-MWT = 2-minute walk test; 3-MSCT = 3-minute stair climb test, 6-MWT = 6-minute walk test; ATU = temporary utilisation authorisation; BOT-2 = Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ = Childhood Health Assessment Questionnaire; CHAQ-DI = Childhood Health Assessment Questionnaire Disability Index; FVC = forced vital capacity; IgG = immunoglobulin G; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PEF = peak expiratory flow; PTA = pure tone audiometry; SmPC = summary of product characteristics; QoL = quality of life; VA = velmanase alfa; VAS = visual analogue scale; WISC = Wechsler Intelligence Scale for Children

Table 3: Key patient characteristics and outcomes from Etoile Alpha. Compiled by the ERG from the CS and CSR

Patient	Age (years)	Age at time of diagnosis (years)	Age at VA exposure (years)	Duration of VA use (months)	Serum OS % change from baseline to last month of evaluation	3-MSCT (mean absolute value)		6-MWT (mean absolute value)		FVC (L)		LVEF % Change from baseline at the last available month
						Baseline (m)	last available month (m)	Baseline (m)	last available month (m)	Baseline	Last available month	
Paediatric/adolescent												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
Adults												
[redacted]												
[redacted]												
[redacted]												
[redacted]												

Average												
Median												

3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; FVC, forced vital capacity; LVEF, left ventricular extraction fraction; m, meter; VA, velmanase alpha

3.2.1.2 ERG critique of Etoile Alpha results

"Responders" in Etoile Alpha: The modelling assumption relates to responders to VA. It is unclear which patients in Etoile Alpha would be classed as responders in the context of the model, and therefore how generalisable the results are.

Unclear time of outcome assessment: Because it is unclear when the outcomes were assessed, it is not possible to tell which data relate to treatment for 5 years or more, making interpretation of the data with respect to the assumption of no disease progression for 5 years difficult. To aid an appraisal of the extent to which this data supports that assumption, the ERG has re-ordered patient data according to time on treatment (Table 3). It can be assumed that those on treatment [redacted] a) if the list of timepoints in the CS is comprehensive, the longest timepoint reported is 4.5 years, and b) patients may have missing data points that mean the actual timepoint of assessment is less than 4.5 years.

[redacted]. It could therefore be concluded that [redacted].

[redacted] It is also possible that childhood growth has confounded these outcomes, since no age standardisation has been performed (see *Age standardisation for outcomes where childhood growth can lead to improvement* below).

The ERG acknowledges that the analysis they have performed is exploratory in nature and without access to more precise data relating to the generalisability of the study to "*responders*", and the disease course and timepoints of outcome assessment in each patient, conclusions are subject to a high degree of uncertainty. The ERG encourages the company to provide a more robust and transparent analysis (e.g., including all time points for all patients who are classed as responders) to account for these and any other limitations (discussed in the following paragraphs) possible.

Severity of disease at baseline: Previous clinical advice to the ERG (received in 2018) indicated that patients diagnosed prior to 6 years of age usually have severe disease (which is not included in the licensed indication for VA). This [redacted]. The ERG notes that in the CSR [redacted] patients [redacted]. [redacted] in the context of a progressive disease and a single arm study is likely to disadvantage the treatment as patients may be worsening from baseline more rapidly.

Age standardisation for outcomes where childhood growth can lead to improvement: Some of the outcomes reported may be impacted by growth as a child gets older. For example, in normal children, the distance walked during the 6-MWT increases from around 500-540 to 660 meters in males and females from the age of 3 to 11 years old. After this, the value plateaus for females, but males continue to improve to around 730 meters at age 16.[7] Age-standardised values for the 6-MWT were provided for rhLAMAN-10 in the previous assessment (where age standardised results were less favourable, see Appendix 1), but do not appear to have been used here. The company state that the disease "*disables individuals early in life"* and that *"it is remarkable that the walking distance with time had not declined and had slightly increased, suggesting amelioration of disease under treatment with VA*" (CS p49). However, the ERG believes that without a comparator arm or a historic control (see also next section, *Lack of a comparator arm)*, and against a backdrop of the opposing influences of growth and disease, it is extremely difficult to tell how much of the observed improvement or stabilisation is due to growth that would have occurred in the absence of VA treatment, and how much is due to the effects of VA treatment on disease progression. Whilst the ERG was satisfied with the company's explanation during the previous assessment that the 3-MSCT is not affected by age, growth may affect other outcomes such as FVC; [redacted].

Lack of a comparator arm: Comparisons to baseline are subject to common drawbacks of single-arm observational studies, as detailed on p43 of the original ERG report. These include: a) regression to the mean, where patients may have e.g. an infection at baseline, but get better over time independent of the treatment; b) inability to account for the placebo effect due to, for example, increased monitoring and clinical input or a Hawthorne effect where people know they are being studied; c) inability to account for the effect of the introduction of symptomatic relief at key stages in disease progression, such as steroid use improving lung function; and d) training effects, where patients become more proficient at performing the tests as they get used to the expectations of the test, resulting in spurious improvements. Comparison to historic controls might not help to ameliorate all these issues, since some, for example,

the placebo effect and training effects, may be specific to the experimental design. The counterfactual, of how patients would have fared on BSC rather than VA is unknown.

Comparability to start/stop criteria: As already noted, the generalisability to patients classed as responders in the model is uncertain. Furthermore, the generalisability of the results of this study to patients who will meet the start/stop criteria to be used in clinical practice is unclear. Application of the start criteria may result in a less severe cohort compared to Etoile Alpha, whilst application of the stop criteria is likely to select for patients with better outcomes. The ERG thinks application of both the start and stop criteria are likely to enhance the efficacy of the treatment in clinical practice compared with the results reported in Etoile Alpha, and may select for patients more likely to have stable disease for 5 years on treatment, but the extent to which they will do this remains unclear.

Outcomes in Etoile Alpha included most of the clinical criteria used in the start/stop rules, but notably the short physical performance battery test (SPPB) and the sniff nasal inspiratory pressure (SNIP) were not reported, and the impact of treatment on these outcomes over a 5-year period is unclear.

Missing data: [redacted]. The reasons for the missing data are unclear, but could be associated with better or poorer outcomes, if, for example, patients stop attending monitoring if they are too poorly, or alternatively, when they are well and do not see the need. The impact of the missing data points is unclear.

3.2.2 rhLAMAN-10 and other studies from the previous submission

rhLAMAN-10 was an integrated analysis of all patients in rhLAMAN-04, -05 after-trial and compassionate use studies (n=33). The study design is summarised in Table 1. Outcomes are reported in Appendix 1, and were reported at 6 (n=33), 12 (n=24), 18 (n=11), 24 (n=10), 36 (n=7) and 48 (n=9) months. Mean outcomes were generally stable or improved across the timepoints. However, the degree of attrition/missing data at each timepoint made it difficult to have confidence in the conclusions, and the single arm design has limitations as discussed in Section 2.2.1. Missing data were not accounted for by the company, but the ERG thought it was possibly due to patients not having reached later timepoints due to time since enrolment (administrative censoring). If available, an updated analysis could help to support, or refute, the assumption of no disease progression for 5 years on treatment for VA responders.

The ERG notes that mention was made in the original submission to rhLAMAN-09. The ERG was informed by the company that this was a follow-up study of patients in Poland and Norway (response to clarification question A18b, 2018), to ensure they could remain on-treatment in the absence of a compassionate use programme in those countries. The ERG notes that in the previous submission (CS 2018, p83), the company state that efficacy outcomes would be assessed annually in this study. This

study appears in the current CS as an ongoing study (CS Table 21), and is described as being conducted in a single centre in Denmark, with five patients enrolled, and an expected completion date of March 2023. It is unclear to the ERG why this study is no longer being conducted in Poland and Norway. The ERG is of the opinion that this study could conceivably include relevant patients with sufficient follow-up to evidence the assumption of no progression for 5 years on treatment (since efficacy outcomes were assessed annually), and would encourage the company to provide any relevant analyses.

3.2.3 Case reports

A number of case reports were provided, as detailed in Table 1. Case reports are generally considered a low level of evidence for estimates of population-level efficacy since they do not have a comparator arm and relate to small numbers of patients. There is also a high risk of cases having been selected for positive outcomes and due to their open label nature, they may be subject to outcome assessment bias. However, in general the accounts of the improvements experienced by patients are extremely positive and indicate that the treatment has made tangible improvements to their lives. The extent to which this can evidence whether disease progression is halted for 5 years for patients who respond to treatment is, however, limited by the non-comparative nature, limited numbers and non-standardised reporting of all relevant outcomes.

In total, 24 patients are reported in the case reports. Of these, [redacted] related to patients who were on VA treatment for 5 or more years:

- one UK patient showed improvement from baseline to 5 years in outcomes relating to the musculoskeletal system, immune system, cognition, social skills, mobility and co-ordination
- 5 adults in 3 European centres showed delay in disease progression, retention or improvement in walking ability, and maintenance of function and school/work attendance over time, contrary to the usual disease course. One patient was on treatment for 10 years and showed mild progression of sensorineural hearing loss and maturation delay, but other AM manifestations remained stable. Another two (siblings) were on treatment for 7 years, with a 60–70-day treatment withdrawal during COVID-19 lockdown. During the withdrawal, both patients showed worsening of gait/mobility and problems with social interaction, but these effects were reversed upon recommencement of treatment. Both patients have had no infections or hospitalisations and walk unaided. The remaining two patients were on treatment for less than 2 years (6 months and 18 months)
- Hearing impairment outcomes improved in two patients who were treated for 12 and 15 months
- Of the 16 patients in Etoile Alpha, [redacted] were on treatment for [redacted]. The accounts provided indicate that the symptoms patients presented with [redacted].

3.2.4 Expert elicitation

The company provided data on the elicitation exercise undertaken in 2017, which showed the pooled estimates of the additional time that patients would stay in heath states due to the positive impact of VA. A summary of the elicited data, split by age group, for the additional time in years that patients would reside in the walking unassisted state and in the walking with assistance state before deteriorating is presented in Table 4. Note that all patients in the model start in one of these two states, with the majority in walking unassisted. [redacted]. This casts doubt on the company's preferred assumption that there would be no disease progression for 5 years. The ERG highlights that the company's model applies the additional time in state shown in Table 4 after it is assumed that treatment progression has been halted for 5 years.

Table 4: Summarised pooled data elicited from clinicians regarding the additional time (in years) in a health state due to VA treatment

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Numbers in brackets represent a 95% credible interval.

† The average number of years in this state for BSC was 11.4 years independent of age group

†† The average number of years in this state for BSC was 10.2 years independent of age group

As raised in previous ERG reports, the ERG believes it is unclear whether the additional time spent in better health states due to VA treatment explicitly incorporates the fact that patients could improve health state. The ERG maintains its view that the base case analyses presented by the company are likely to be favourable to VA treatment.

The relatively slow elicited rate of progression between health states for people on BSC may also cause difficulties with inferring complete lack of disease progression for patients who respond to treatment with VA. The model assumes that there is an 8.4% chance each year that patients in the walking unassisted health state transit to a walking with assistance health state. As such, 65% of people in the walking unassisted health state receiving BSC would remain there over a 5-year period and thus data on mobility taken from single-arm studies or registries for people receiving VA could be misleading.

The ERG notes that the elicitation exercise was performed in the absence of newer data, such as the Etoile Alpha and the values may change if the elicitation exercise was undertaken in 2022.

4 Cost-effectiveness results

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

4.1 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 5 (for paediatric patients), in Table 6 (for adolescent patients) and in Table 7 (for adult patients) assuming that there is no MAA in place. [redacted] The incremental undiscounted QALYs were under [redacted] for all scenarios evaluated by the company.

Table 5: The company's revised base case results - paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	[redacted]	14.564	[redacted]	-	-	-	
VA	[redacted]	16.740	[redacted]	[redacted]	2.175	[redacted]	[redacted]

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

Table 6: The company's revised base case results - adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	[redacted]	14.355	[redacted]	-	-	-	
VA	[redacted]	16.590	[redacted]	[redacted]	2.236	[redacted]	[redacted]

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

Table 7: The company's revised base case results - adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	[redacted]	13.921	[redacted]	-	-	-	
VA	[redacted]	16.248	[redacted]	[redacted]	2.328	[redacted]	[redacted]

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

To inform the committee the ERG has shown the impact of two changes in the company's model that differ between the company's base case and the preferred assumptions of the NICE Appraisal Committee and also the impact of excluding costs associated with home infusions as was the case in earlier submission. These are shown in Table 8 to Table 10.

Table 8: 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]	[redacted]
1) Changing utility gain to 0.05	[redacted]	[redacted]	[redacted]
2) Assuming halt in disease progression for 1 year in responders to VA	[redacted]	[redacted]	[redacted]
3) Removing the costs of home infusions	[redacted]	[redacted]	[redacted]
4) Combining 1), 2) and 3)	[redacted]	[redacted]	[redacted]
5) Combining 1) and 2)	[redacted]	[redacted]	[redacted]

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

Table 9: 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]	[redacted]
1) Changing utility gain to 0.05	[redacted]	[redacted]	[redacted]
2) Assuming halt in disease progression for 1 year in responders to VA	[redacted]	[redacted]	[redacted]
3) Removing the costs of home infusions	[redacted]	[redacted]	[redacted]
4) Combining 1), 2) and 3)	[redacted]	[redacted]	[redacted]
5) Combining 1) and 2)	[redacted]	[redacted]	[redacted]

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

Table 10: Impact of changes from the Appraisal Committee's preferred assumptions and in incorporating costs for home infusions – adult patients

	Incremental (VA- BSC)		ICER
	Costs	QALYs	
Company's base case	[redacted]	[redacted]	[redacted]
1) Changing utility gain to 0.05	[redacted]	[redacted]	[redacted]
2) Assuming halt in disease progression for 1 year in responders to VA	[redacted]	[redacted]	[redacted]
3) Removing the costs of home infusions	[redacted]	[redacted]	[redacted]
4) Combining 1), 2) and 3)	[redacted]	[redacted]	[redacted]
5) Combining 1) and 2)	[redacted]	[redacted]	[redacted]

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

4.2 Exploratory results run by the ERG

The ERG compared the new model with the previous version and found that the majority of changes in parameter values or structure were acceptable or correctly programmed. A noteworthy change was the addition of costs related to home infusions (£132.50 per infusion) which will be unfavourable to VA treatment. The ERG is content that the costs of home infusion and the updating of prices is appropriate and has used these in its exploratory analyses.

In contrast to the company, the ERG prefers to source the cost per hour associated with home care assuming a face-to-face basis provided to social services, rather than the non-face-to-face costs associated with private purchasers (page 133 of Jones and Burns[8]). Further the ERG assumed that the first 12 hours of care in a day would be sourced at the daytime rate, with additional hours sourced at a night-time rate. These changes increased the cost per year of care to £12,972 for walking unassisted, £38,028 for walking with assistance, £143,700 for those in a wheelchair state, and £229,920 for those with severe immobility. The increase in the costs of care resulted in the ICER for the company's base case becoming more favourable to VA treatment.

When using the carer costs preferred by the ERG the ICER compared to the company base case decreased by approximately [redacted], due to a reduction in incremental costs. The ICERs became [redacted] for paediatric patients, previously [redacted], £[redacted] for paediatric patients, previously [redacted], and [redacted] for paediatric patients, previously [redacted].

Having changed the carer costs 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.

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, and the 0.05 value preferred by the Appraisal Committee in the FED. The results are contained in Table 11 for a paediatric population, Table 12 for an adolescent population, and Table 13 for an adult population. The incremental undiscounted QALYs were under [redacted] for all scenarios evaluated by the ERG.

Table 11: ERG exploratory results for a paediatric population

Description	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]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12: ERG exploratory results for an adolescent population

Description	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]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13: ERG exploratory results for an adult population

Description	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]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.3 Additional uncertainties that remain unaddressed

Within previous ERG reports, the ERG highlighted a number of limitations within the modelling; three of which remain. No changes to the model were made by the ERG as these were not possible within the project timescales.

1) The ERG believes that the model output will fail to match the input data elicited from clinicians The elicitation exercise (undertaken in 2017) asked clinicians to estimate the additional time each patient would spend in each health state if treated with VA. These values are used directly in the model. However, logically the model will not produce the answers elicited from the expert clinicians for two reasons: (i) where patients improve health states in the VA arm, they would have to progress from the improved state to the original state and then would have a further additional time in the original health state, for example, Table 4 reports that VA would provide an adolescent with an additional [redacted] years in the walking with assistance health state. However, if the patient were simulated to improve to the walking unassisted health state, then they would on average, have an additional [redacted] years in the walking unassisted state before spending another [redacted] years in the walking with assistance health state. and (ii) events such as reaching the Short End Stage through infection or the severe immobility state through surgical complications will change the life expectancy of each patient. While a formal analysis of this has not been conducted, the ERG believes that the actual increase in life expectancy will be higher than that predicted by the clinicians. It is unclear whether the experts in the elicitation exercise had considered these factors in their estimates, and it is also noted that the original question (Qol2, p12 of the UK Expert Elicitation Panel document[9]) appeared to ask about the absolute time in each state for patients on VA, rather than the additional time.

The company responded in the second clarification round[3] that '*The Company agrees that where patients improve, then progress to their original health state, they will spend additional time in that state; however, no changes have been made in line with the ERG comment in question from the previous ERG review; this is because the Company believes that the method of elicitation was clear in that the additional time in state on velmanase alfa was to be independent of other factors which may influence it, including severe infections and complications which may arise as a result of major surgery.*' The ERG still maintains its view that the base case analyses presented by the company will likely be favourable to VA treatment.

2) Amending the model to allow patients on BSC to improve

The model submitted by the company assumed that it was not possible for patients on BSC to improve disease status despite the fact that within rhLAMAN-05[10] two of five patients who were initially walking with assistance became device or third party-independent at 12 months. (Company response to initial clarification questions A44).[11] The company stated that this was a simplifying assumption and assumed an improvement in the VA arm over and above that of BSC. In an earlier submission, at the request of the ERG, the company performed exploratory analyses to investigate the impact on the ICER of assuming a 10% chance of improvement for those treated with BSC and increasing the chance of improvement, from wheelchair dependent to walking with assistance and from walking with assistance to walking unassisted, for those treated with VA from 20% to 30% within the first two years. These results indicated that the ICER increased by 3-4%,[4] highlighting that assuming that no-one could improve with BSC treatment, and assuming an improvement rate for VA that was the differential in improvement is favourable to VA treatment.

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

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

5 Critique of the proposed MAA

The ERG, in conjunction with its clinical advisors has provided a critique of the MAA proposed by the company. A critique is provided in this section; the ERG anticipates that any discussions on the MAA will be undertaken by people experiences in such matters.

The company has proposed an MAA to collect further evidence to reduce uncertainty within the decision problem, noting that the current model had to rely considerably on clinical expert opinion. The company stated that the following clinical uncertainties had the most impact on the ICER:

- Long-term disease progression with and without VA, including infection rates
- Impact of VA on delaying and/or stabilising disease progression
- Long-term survival rates and causes of mortality with and without VA, including incidence of death due to infection
- QoL of patients with AM, with and without VA treatment, overall and stratified by ambulatory health state
- Impact of VA in changing the clinical management of AM

The company states that the MAA '*reduces the uncertainty associated with patient selection, as KOL-led 'start' criteria will ensure only patients likely to benefit from VA are selected for treatment. Furthermore, it reduces the uncertainty associated with long-term effectiveness of VA, in that KOL-led outcomes for monitoring/stop criteria will ensure only patients achieving appropriate MCID* [Minimal clinically important difference] *thresholds will continue treatment, with relevant outcome data recorded*'. The company anticipate that the MAA will improve the cost-effectiveness of VA as '*only 'responders' achieving clinical outcomes will continue treatment'*.

In addition to the MAA, Table 66 in the CS details the suggested data collection and analyses anticipated that would reduce clinical uncertainty. This is reproduced in Table 14.

Table 14: The company's proposed potential data collection to resolve clinical uncertainties

Clinical uncertainty	Suggested data collection and analysis
rhLAMAN-05 is the only comparative data available of VA vs. placebo and was limited by 12-month follow-up and small patient numbers	An indirect comparison of data of patients treated with VA (rhLAMAN-10, Etoile Alpha and SPARKLE) could be performed with natural history data of untreated patients (AllStripes, SPARKLE and the MPS [Mucopolysaccharide] Society) to support the RCT data and be incorporated into any updated responder analyses
Natural history data and off-treatment progression	Natural history data of patients untreated with VA will be collected in AllStripes, SPARKLE and local UK registries, including the MPS Society Registry
Utility data with/without VA	EQ-5D-5L and/or CHAQ will be collected in rhLAMAN-07, -09, SPARKLE and AllStripes and incorporated into updated responder analyses
Infection rates with/ without VA	Infection rates and hospitalisations will be collected in rhLAMAN-07, -09, SPARKLE and AllStripes
Global responder analysis includes serum oligosaccharides as one of the domains which is a surrogate endpoint	Updated responder analyses will be performed using clinical domain data collected in the MAA as part of the SPARKLE study, which will be incorporated into a restructured economic model to allow more clinical data to be incorporated and less reliance on expert opinion

Abbreviations: CHAQ, Childhood Health Assessment Questionnaire; VA, velmanase alfa

The proposed MAA has defined starting and stopping criteria which the company says "*were agreed at the Chiesi advisory board on the 15th of November 2018 and at subsequent discussions with additional healthcare professionals, including a clinician working in the NHS.*" Patients starting treatment must be made aware of the start-stop criteria associated with VA and are required to attend clinics twice a year for assessment.

Treatment with VA would only be started in patients who met **all** of the following criteria.

- Biochemical measurement of oligosaccharide levels to show these are raised with set thresholds (no stated) that must be met
- Enzymatic activity to confirm the diagnosis of AM
- Meeting thresholds of disability to demonstrate that patients are affected by non-neurological manifestations of AM to an extent that warrant consideration for VA treatment. The threshold

for disability is shown in Table 15 (adapted from Table 67 of the CS) and requires that a patient must meet at least 1 criterion from a least 1 clinical domain. Reference to children under 6 years of age has been removed as these are not included within the NICE scope.

Clinical advice provided to the ERG noted that it was unclear whether siblings of patients with a diagnosis of AM could be treated when largely pre-symptomatic, as '*evidence of non-neurological AM*' (see Table 15) has not been explicitly defined. Also, the term '*LVEF <45% of normal*' may be ambiguous, as 'normal' patients would not have a left ventricular ejection fraction (LVEF) at 100%, potentially implying that a patient would need to have severe heart failure before treatment could be started based on this domain.

Table 15: Criteria for starting VA treatment

Patients must meet ≥1 of the following criteria from ≥1 of the following clinical domains:

Clinical domain 1: Mobility function	**Clinical domain 2: Lung function**	**Clinical domain 3: Cardiac function**	**Clinical domain 4: Upper respiratory tract infections**
• 6MWT: 2 SD below the mean normal for an age matched measurement and a max level. OR • Short physical performance battery test (SPPB) – score of 9 or less is defined as impaired (in COPD/elderly patients) OR • Patients who use mobility aids (walking aid, wheelchair) – patients should also carry out the 6MWT and SPPB where possible, or the SPPB alone where patients are unable to complete the 6MWT to gain a baseline measure	• Forced vital capacity (FVC) test: 2 SD below the mean normal for an age matched measurement and a max level. OR • Sniff nasal inspiratory pressure (SNIP) test: a minimum difference of 50cm of water compared to an age matched measurement. OR • Requirement for ventilatory aids	• Impaired LVEF <45% of normal, as assessed by echocardiogram or cardiac MRI Treatment for reduced LVEF should be optimised and stabilised prior to treatment with VA. LVEF to be reassessed and this level taken as a baseline for future assessments.	• In patients ≥12 yrs, having >2 episodes of respiratory infections per annum that required antibiotic usage and based on clinical judgement
Siblings of currently diagnosed AM patients: Screened siblings of those with evidence of non-neurological AM, who themselves are eligible for VA, will be discussed individually at a standing committee.			

Patients would be excluded from starting treatment if they fulfilled one or more of the following criteria.

- Previous anaphylactic reactions to VA or excipients
- Patients with severe AM
- Previously successfully treated with haematopoietic stem cell transplant or bone marrow transplant
- Concomitant life-limiting condition
- In the view of the multidisciplinary team, the patient has reached a disease severity which will not benefit sufficiently from treatment
- Patients with only neurological manifestations of disease
- Unable to comply reliably and consistently with the measurement requirements (e.g., due to coexisting severe neurological impairment)

The clinical advisors to the ERG also commented that it would be useful for 'severe AM' to be explicitly defined and also that there could be some subjectivity in the multidisciplinary team (MDT) assessment of a patient.

For those who initiate VA treatment, the baseline values for the parameters listed in Table 15 should be recorded, in addition to the values for the parameters in Table 16, in order that disease progression can be assessed. Progression would be assessed at 12 months and at 24 months and yearly thereafter, with treatment stopped if the disease had sufficiently progressed. The parameters chosen to be monitored, were based on the responder analysis requested by the European Medicines Agency, which has subsequently been published in Harmatz *et al*.[12] These are divided into a biochemical domain and five other clinical domains: mobility function; lung function; cardiac function; infections; and patient-reported outcome measures.

To remain on treatment after 12 months, patients had to achieve an improvement in the biochemical domain at 6 months **and** have met the improvement measure in at least four of the five clinical domains.

To remain on treatment after 24 months, patients had to maintain the improvement in the biochemical domain at 6 months **and** have met the improvement measure in at least four of the five clinical domains **and** have met an improvement measure in at least one of the criteria used as an entry requirement (Table 15).

To remain on treatment at subsequent yearly reviews, patients had to have stabilisation of oligosaccharides **and** stabilisation of 4 of the five clinical domains **and** stabilisation in at least one of the four clinical domains used as an entry requirement.

Patients can stop treatment with VA for other reasons. In the CS, the company has provided the following examples.

- patient unable to tolerate infusions due to infusion-related severe AEs that cannot be resolved
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit
- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g., due to repeated recurrent chest infection or progressive and sustained lack of mobility, or coexisting severe neurological impairment
- the patient misses more than three infusions of VA in any 12-month period, excluding medical reasons for missing dosages
- the patient has reached a disease severity which will not benefit sufficiently from treatment in view of the MDT

Table 16: Parameters related to the stopping criteria for VA treatment

Domains	Improvement measure within/at 12 months	Improvement measure at 24 months	Measurement at yearly review thereafter
Biochemical domain			
Serum oligosaccharides	50% reduction from baseline within 6 months. Not meeting this would require investigation to confirm adherence and antibody development. Treatment to stop if not met and no reasonable explanation. At 12 months - Stabilisation (threshold of +10% from 6 month response)	Stabilisation (threshold of +10% from 6-month response)	Stabilisation (threshold of +10% from 6-month response)
Clinical Domain 1: Mobility function (meet one of the following):			
6MWT	For patients ≥2 SD below the mean normal for an age matched measurement at baseline – would require 5% improvement from baseline value (only baseline value is age matched) Other baseline results require stabilisation (max deterioration of 2% from baseline)	For patients ≥2 SD below the mean normal for an age matched measurement – would require 10% improvement from baseline value (only baseline value is age matched) Other baseline results require stabilisation (max deterioration of 2% from baseline)	Stabilisation (deterioration less than 2% of baseline or last measurement)
SPPB	For patients ≥2 SD below the mean normal for an age matched measurement – would require 1-point improvement from baseline value (only baseline value is age matched) Other baseline results – require stabilisation (no adverse point threshold change)	Require stabilisation (no adverse point threshold change)	Require stabilisation (no adverse point threshold change)
Clinical Domain 2: Lung function (meet one of the following):			
FVC – Adults (>18	For patients ≥2 SD below the mean normal for an	For patients ≥2 SD below the mean normal for an	Stabilisation of FVC

yrs.)	age matched measurement at baseline – would require 3% absolute improvement on baseline (only baseline value is age matched) in an accredited lung function lab In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	age matched measurement – would require 3% improvement from baseline value (only baseline value is age matched) in an accredited lung function lab In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	Any reduction of FVC >5% should be considered for treatment withdrawal
FVC – Paediatrics	For patients ≥2 SD below the mean normal for an age matched measurement – would require 5% improvement from baseline value (only baseline value is age matched) In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	For patients ≥2 SD below the mean normal for an age matched measurement – would require 10% improvement from baseline value (only baseline value is age matched) In patients not meeting the requirement for FVC inclusion criteria, a reduction in FVC of >5% should be considered for treatment withdrawal.	Stabilisation of FVC Any reduction of FVC >5% should be considered for treatment withdrawal
SNIP	Greater than 10% or 5cm of water improvement from baseline	Stabilisation (threshold of -5% from baseline)	Stabilisation (threshold of -5% from baseline)
Clinical domain 3: Cardiac function			
Ejection fraction	Stabilisation in ejection fraction (threshold of -10% from baseline)	Stabilisation in ejection fraction (threshold of -10% from baseline)	Stabilisation in ejection fraction (threshold of -10% from baseline)
Cardiac treatment should be optimised prior to initiation of treatment, and the ejection fraction taken after this optimisation of care used as the baseline for assessment.			

Clinical domain 4: Infections			
Infection rate (adults and children)	Improvement defined of a ≥50% reduction in antibiotic (AB) usage from baseline or Stabilisation in rate of AB usage if not a starting criteria (threshold of +10% from baseline)	Stabilisation in rate of AB usage (threshold of +10% from year 1)	
Clinical domain 5: PROMS (meet one of the following):			
CHAQ-DI (patient or proxy-completed)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)
EQ5D-5L or MPS HAQ (patient or proxy completed)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)
Pain: VAS pain	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)	Stabilisation (threshold of +10% of baseline)

Whilst clinical advice to the ERG suggested that the 12-month, 24-month and subsequent yearly reviews was a reasonable framework to assess patients with AM, several comments were made relating to the proposed criteria for continuing with treatment.

The clinical advisors suggested that using change from the baseline value (5% at 12 months and 10% in year 2) for FVC for paediatrics would not necessarily accurately consider the FVC changes associated with normal growth. Further, it was commented that a 5% variation could be within the normal inter-test variability and performance especially in paediatric patients. There was also uncertainty in whether the SNIP test was validated in paediatrics.

In addition, there may be ambiguity over what is meant by the company by '*in ≥1 of criteria used as an entry requirement*' that was used by the company. It may relate to improvements in the specific criteria that allowed an individual to begin VA treatment as the alternative, which is an improvement in any potential domain, would be covered by the criterion that patients also needed to meet 4 of the 5 clinical domains.

6 Conclusions

The clinical benefits, and therefore the cost-effectiveness of VA treatment remain highly uncertain. The most favourable ICERs are [redacted] for paediatric patients, [redacted] for adolescent patients and [redacted] for adult patients but these are predicated on two key assumptions: (i) that there is a utility gain of 0.10 that arises for being on VA treatment in addition to any utility gains associated with being in a better health state and (ii) that for responders all disease progression is halted for a period of five years and that there are benefits in reduced progression after this time point.

The least favourable ICERs are [redacted] for paediatric patients, [redacted] for adolescent patients and [redacted] 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.

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. Given these views, the ERG believes that the ICERs will be approaching the least favourable ICERs, with all values in excess of [redacted], and considerably more so in the case of adolescent and adult patients.

7 References

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Appendix 1: Results of rhLAMAN-10

Table 17: Key clinical results from rhLAMAN-10[13]

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	

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
Relative (%) change from baseline (SD)			8.315 (18.32), p=0.036		9.317 (19.57), p=0.013		24.48 (18.76), p=0.001		2.487 (16.84), p=0.651		30.88 (32.72), p=0.069		39.11 (31.31), =0.006		13.77 (25.83), p=0.004	
6-MWT																
Actual value (SD)	466.6 (90.1)	33	474.6 (84.1)	24	492.4 (83.7)	31	499.9 (95.6)	11	486.6 (90.7)	10	471.2 (83.5)	6	522.6 (77.1)	9	489.0 (85.7)	33
Absolute change from baseline (SD)			17.6 (62.7), p=0.183		21.9 (65.2), p=0.071		55.5 (66.3), p=0.020		5.0 (58.5), p=0.793		59.3 (85.9), p0.151		69.7 (81.1), p=0.033		22.4 (63.2), p=0.050	
Relative (%) 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			NR		2.37 (9.98), p=0.196		NR		NR		NR		NR		1.16 (9.29), p=0.478	

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
baseline (SD)																
Relative (%) change from baseline (SD)			NR		5.87 (22.14), p=0.150		NR		NR		NR		NR		3.55 (18.30), p=0.273	
FVC % predicted																
Actual value (SD)	84.9(18.6)	29	87.1(18.6)	22	93.2(20.8)	30	84.8(23.6)	8	106.1(18.0)	8	78.8(22.0)	6	98.3(12.4)	7	93.121.7)	31
Absolute change from baseline (SD)			3.5(14.7), p=0.304	20	6.6(12.8, p=0.011	28	4.4(13.9), p=0.403		16.1(14.8), p=0.028	7	5.6(10.3), p=0.243		13.7(19.6), p=0.114		8.1(14.8), p=0.007	29
Relative (%) change from baseline (SD)			6.1(20.3), p=0.194	20	8.5(16.5), p=0.011	28	5.0(20.9), p=0.520		20.7(18.5), p=0.025	7	7.6(15.2), p=0.277		19.8(28.4), p=0.116		10.5(20.9), p=0.011	29
CHAQ disability index*																
Actual value (SD)	1.36 (0.77)	33	1.12 (0.71)	24	1.20 (0.70)	31	1.07 (0.75)	11	1.44 (0.79)	10	1.16 (0.60)	7	0.88 (0.64)	9	1.23 (0.66)	33
Absolute change			-0.11 (0.37)	24	-0.10 (0.36)	31	-0.14 (0.41)		0.16 (0.35)	10	-0.32 (0.62)		-0.10 (0.42)		-0.13 (0.440	

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
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 (72.270		-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

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
Absolute change from baseline (SD)			0.0647(0.1199)		0.0346(0.1044)		0.1950(0.1245)		0.0262(0.1303)		0.0993(0.1422)		NR		0.0505(0.1351)	
Relative (%) change from baseline (SD)			17.2811(32.8088)		6.9320(19.0980)		44.1743(28.6949)		7.2199(21.9332)		21.1495(32.1006)		NR		11.2291(24.7218), p=0.036	
EQ-5D-5L VAS*																
Actual value (SD)	67.9(18.2)	23	71.7(16.3)	15	69.0(16.6)	22	80.0(21.2)	2	70.8(14.3)	10	73.8(18.9)	4	NR		71.6(15.0)	24
Absolute change from baseline (SD)			5.7(16.9)	14	1.6(17.2)	21	6.5(4.9)		9.8(22.7)	9	-2.5(8.7)		NR		3.3(18.1)	
Relative (%) change from baseline (SD)			15.5(30.9)	14	7.7(32.2)	21	8.3(4.9)		26.6(43.3)	9	0.4(16.7)		NR		11.5(33.8)	
BOT-2 total*																

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
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**	

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
Leiter TEA AME*																
Actual value (SD)	6.514(2.176)	24	6.400(2.424)	15	6.860(1.992)	22	3.792(2.180)	2	6.817(1.529)	10	5.250(0.561)	4	NR		6.670(1.757)	24
Absolute change from baseline (SD)			0.100(1.331)		0.167(1.254)		-0.750(1.414)		0.108(1.665)		0.833(1.855)		NR		0.156(1.519)	
Relative (%) change from baseline (SD)			5.219(22.135)		5.849(19.657)		-19.42(34.413)		11.244(33.786)		33.225(47.595)		NR		9.345(32.485)	
Pure tone best ear*																
Actual value (SD)	52.57(12.36)	32	55.44(10.65)	22	53.35(11.41)	31	48.35(16.80)	11	54.76(8.72)	9	56.16(12.86)	7	47.62(13.76)	9	52.16(13.13)	33
Absolute change from baseline (SD)			2.05(4.72)		1.47(6.00)	30	-4.81(9.74)		2.05(6.55)	8	-0.76(8.78)		-3.73(6.21)		-0.49(6.58)	32
Relative (%) change from			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

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
baseline (SD)																
Serum IgG*																
Actual value (SD)	NR															
Absolute change from baseline (SD)															3.05 (2.39, 3.71), **p=<0.001**	24
Relative (%) change from baseline (SD)															44.07 (32.58, 55.57), **p=<0.001**	

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

* only statistically significant p values reported.

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Technical engagement response form

Velmanase alfa for treating alpha-mannosidosis [ID800]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

Technical engagement response form

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We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **17 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	Abigail Stevenson
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Chiesi Limited (company stakeholder)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response

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Utility gain associated with velmanase alfa treatment	Yes	Chiesi believe the new long-term data submitted from rhLAMAN-10, Etoile Alpha, and case reports strongly support an on-treatment utility gain of at least 0.1 for velmanase alfa. This is likely to be a conservative estimate due to the limitations of the walking ability-based economic model. The following response provides further evidence to support the additional utility gain with velmanase alfa and the new base case which includes an updated paediatric/adolescent utility gain of 0.25 and the same adult utility gain of 0.1 with velmanase alfa to reflect additional health gains observed in the long-term data from Etoile Alpha, and the limitations of the model in capturing these as utility gains. • The walking ability-based model, although deemed appropriate for committee decision-making, has limitations that means many of the multi-organ health benefits of velmanase alfa are not captured, and as such, the on-treatment utility benefit of 0.05 preferred by the ERG is an underestimate for velmanase alfa. In HST5, the ERG accepted a utility increment of 0.05 to capture the administration benefits of using an oral therapy compared to a twice daily ERT infusion (1). In addition, the minimally important difference (MID) for EQ-5D was determined to be 0.074 by Walters et al. (2); as many health improvements were reported with velmanase alfa that were clinically relevant to both patients and clinicians (see below), this would suggest that the on-treatment utility benefit with velmanase alfa should be above the MID for EQ-5D. • The ERG states a 0.1 utility benefit proposed by Chiesi likely double counts the utility benefit, as utility gains are already captured in the model health states – however, the ERG have not specified which health gains they consider to be captured in the model and which are not. To aid decision-making on the true utility gain, **we wish to clarify with the ERG which health benefits of velmanase alfa they believe are captured within the current 4 walking-based health states and which are not.** o Due to the limitations of the walking-ability based model, we believe that the following utility benefits are not fully captured in the model health states, and do not represent double counting, including: 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

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		health (anxiety and depression), cognitive function, psychiatric events and increased independence in activities of daily living. • **Within-state utility gains**: The model only has 4 health states (excluding death) based on walking status, and as such any 'within-state' improvements are not captured, and need to be represented fully by the on-treatment utility gain. Within-state improvements evidenced from clinical studies are shown below: o **rhLAMAN-10**(3): As the health states are so broad, the majority of patients in rhLAMAN-10 did not change state, but did show additional functional and QoL improvements with treatment. The majority of patients in rhLAMAN-10 were walking unassisted at baseline (70%), which increased to 82% by the end of follow-up; as such the majority of these patients did not change health state and their utility benefits are not captured fully in the model. Details of the patients that did change health state up to 4 years post-treatment in rhLAMAN-10 from Borgwardt 2018 (3). Of 33 patients at baseline, 23 (70%) patients were walking unassisted, while 10 required help from a person, walking aids, or a wheelchair (26.3% paediatric (5 of 19) and 35.7% adults (5 of 14)). By the end of follow-up, 4 of the 10 who required help no longer needed it, with only 6 patients (18.3%, 6/33) still requiring assistance or a wheelchair. Also noteworthy is that 3 patients (2 paediatric, 1 adult) who used the wheelchair for long-distance mobility by the baseline assessment were able to discontinue use at the end of the study period. From the original 5 paediatric patients who required assistance at baseline, 4 improved and 1 did not change. At follow-up, 2 paediatric patients who did not require assistance at baseline required assistance from another person in walking. However, both paediatric patients improved in overall function as measured by a reduction in the CHAQ DI. Conversely, 2 (22.2%) of 9 adult patients who did not use a wheelchair at baseline required use of a wheelchair at follow-up. Both patients had significant musculoskeletal impairments and previous orthopaedic surgeries. One patient underwent a lower limb amputation and required a walker and a wheelchair post-surgery, and the second patient had osteoarthritis and used a walker at baseline, but required a wheelchair at follow-up. A new scenario analysis has been performed to reflect the reported baseline distribution of walking status as reported in the final analysis of rhLAMAN-10 (3).

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		o As another example, the UK adult patient in rhLAMAN-10 (and further treated on compassionate use for over 6 years) showed substantial improvements in function (160m [+47%] improvement in 6MWT), cognition and QoL, and reductions in ear infections and pain, but all within the 'walking with assistance (WWA)' health state, which was published as a case report.(4) As this individual still uses orthopaedic boots despite substantial health improvements, they are still classed as being in the same 'WWA' health state. Post-treatment, this person's EQ-5D-5L utility value measured in the UK MPS Survey was 0.758 compared with 0.378 for patients on BSC(5). When compared with 0.577, the committee's preferred baseline utility health state for WWA, this represents an approximate 0.18 utility gain in an adult patient that would not be captured in the model. o **Etoile Alpha**: Baseline and post-treatment analyses on walking ability by patient and age-groups have been requested. Results from Etoile Alpha show substantial improvements in FVC, 6MWT and cognitive function from baseline, which is evidenced in the aggregated data and in the individual patient synopses (6)and case reports in the CSR (7). o **SPARKLE**: Baseline demographic data from the 14 patients with CHAQ-DI measurements in SPARKLE show [redacted]% of patients (n=[redacted]) with scores 0-1, [redacted]% (n=[redacted]) with scores 1-2 and [redacted]% (n=[redacted]) with scores ≥2. As a CHAQ-DI score ≥2 is used when a patient requires a walking aid, these data suggest that over [redacted] of patients in the SPARKLE registry were walking unassisted at baseline, so may not change health state if mobility improvements with velmanase alfa are realised (8). • **Transition probabilities**: the transition probabilities in the model were estimated by an expert elicitation panel in 2017 before the completion of rhLAMAN-10; as such their knowledge of the treatment benefits of velmanase alfa and the natural progression of untreated patients was limited. As such these probabilities may not accurately represent the treatment effect of velmanase alfa and the deterioration or the incidence of severe infections and mortality in untreated patients. A new scenario analysis has been performed to reflect the reported baseline distribution of walking status as reported in the final analysis of rhLAMAN-10 (3). Due to limited time, the expert elicitation panel exercise has not been repeated to update the

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		transition probabilities, and as such the transition probabilities in the base-case have not been changed. • **Utility with FVC and 6MWT**: Etoile Alpha and rhLAMAN-10 showed mobility improvements as well as improvements in lung function from baseline in both adult and paediatric patients (see Table 1 below). Quality of life measures were available only from a limited number of patients in both studies, however, 6MWT was captured for everyone in both studies, and FVC was captured for everyone in Etoile Alpha and most patients in rhLAMAN-10 (see Table 1) . Increased FVC has a strong association with both increased QoL and survival, and improved 3MSC, 6MWT and FVC are strongly correlated with improved EQ-5D-5L in another MPS disorder, Morquio Syndrome (MPSIVa).(9) o In HST2/HST19 for MPSIVa, the committee accepted a 0.2 additional utility gain for each 1L increase in FVC, and a 10% decrease in FVC was associated with a 15% increase in mortality. The HST2/HST19 committee also accepted a 0.02 utility gain per 10m increase in 6MWT(10). o Relying on this estimate, the [redacted]L (+[redacted]%) increase in FVC seen in Etoile Alpha would equate to a [redacted] utility benefit for improved respiratory function alone and a [redacted] utility benefit for the [redacted]m improvement. Combining 6MWT and FVC improvements would equate to a 0.254 utility benefit with velmanase alfa from the Etoile Alpha results. Similar improvements were seen in rhLAMAN-10, with greater improvements seen in the paediatric population (see Table 2 below). • **Disutility with pain**: In other MPS conditions, pain and fatigue is unanimously reported by all patients across many areas of the body, which substantially impacts on daily activity.(11) rhLAMAN-10, Etoile Alpha and case reports show reductions in pain and fatigue with velmanase alfa, although CHAQ-VAS data were limited. CHAQ-VAS Pain scores were reported in rhLAMAN-10 (3). At baseline in rhLAMAN-10, the mean CHAQ pain score was 0.618, with values of 0.761 at month 12 and 0.431 at last observation on treatment with velmanase alfa. The mean change from baseline to last observation was -0.173.There was no statistically significant change from baseline, but the mean change of 17% was greater than the minimal clinically important improvement of -8.2% defined by Dhanani et al (12). As any non-joint pain

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		would not be captured in the model, we believe these data also justify an increased utility benefit with velmanase alfa. • **Disutility with fatigue:** Fatigue was not specifically measured in rhLAMAN-10; however, 9 patients in Etoile Alpha and in case series reported considerably reduced fatigue, with less need for naps and improved ability to attend school or work. Fatigue is an important driver of HRQOL that is not specifically covered by the EQ-5D; its association with EQ-5D-3L was assessed in a large study of multiple sclerosis which found a moderate correlation. This suggests that the EQ-5D-3L domains of usual activities, pain/discomfort, and anxiety/depression were moderately correlated with fatigue suggesting that even though the EQ-5D-3L does not directly measure fatigue it captures it to some extent, but not completely. In comparison, levels of physical disability (as measured by EDSS) were only weakly correlated with levels of fatigue, and was experienced across levels of disability (13). This suggests that the utility changes of the walking-ability based model are unlikely to capture all aspects of fatigue in AM. • **Reduction in minor infections**: rhLAMAN-10, Etoile Alpha and case reports support the substantial reduction in the incidence of minor infections with velmanase alfa. This is likely reflective of increased serum IgG with treatment that is consistent across clinical studies; this statistically significant increase in serum IgG occurs rapidly with treatment within 1 year, as shown in rhLAMAN-05 (14). No respiratory infections were observed in the Etoile Alpha review period, with some patients reporting no longer needing to be on prophylactic antibiotics (supported by UK clinical expert interviews (15)). New natural history data in a cohort of 12 untreated Polish patients with AM over 14 years showed all untreated patients had recurrent infections (16). • **BOT-2 improvements**: A BOT-2 analysis of rhLAMAN-10 showed improvements in upper limb extremity function, fine motor deficits and running speed with velmanase alfa(17). For the combined adult and pediatric group there was a statistically significant improvement in BOT-2 total score of 13% (p =.035, 95% CI 1.0, 25.0) from baseline to last observation(17) A survey of patients and carers with MPSVI reported the additional upper and lower limb symptoms measured in BOT-2 as key disease aspects that impacted on activities on daily living, including

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		dressing, eating and drinking, ability to use a computer, use a pen/pencil and participate in sports.(11) As BOT-2 captures the additional functionality of upper limbs and the fine motor skills of lower limbs, these aspects are unlikely to be captured fully in the walking states. • **Utility and cognition**: Case reports from Etoile Alpha show all patients during the study had clinician-reported stability or improvements in cognitive impairment (referred to as mental retardation in the CSR) and language, with two patients reporting a reduction in psychiatric events and reduction in antipsychotic medication (eg. decrease in neuroleptics and decreased need for psychiatric treatment). New natural history data in 12 untreated polish patients with AM over 14 years showed a gradual exacerbation of intellectual disability and signs of psychiatric disorders (16). Cognition is an important driver of HRQOL that is not specifically covered by the EQ-5D; its association with EQ-5D-3L was assessed in a large study of multiple sclerosis which found a moderate correlation (13). This suggests that the EQ-5D-3L domains of usual activities, pain/discomfort, and anxiety/depression were moderately correlated with cognition suggesting that even though the EQ-5D-3L does not directly measure cognition it captures it to some extent, but not completely. In comparison, levels of physical disability (as measured by EDSS) were only weakly correlated with cognitive disability (13). This suggests that the utility changes of the walking-ability based model are unlikely to capture all aspects of cognitive function in AM. Taken together, Chiesi believe the multidimensional long-term health improvements and utility gains observed among patients in rhLAMAN-10, real-world data in Etoile Alpha justify a plausible additional on-treatment utility gain of at least 0.1. This is likely to substantially higher when the within-state improvements in mobility and lung function are considered, as well as other important health improvements are taken into account, such as minor infections, fatigue, pain, cognitive improvements and improved dexterity/upper extremity deficits. EQ-5D-5L utility gains observed in rhLAMAN-10 were not performed for all patients and are unlikely to capture all multi-organ improvements observed with velmanase alfa. For these reasons, we have submitted a new company base case incorporating a 0.25 utility gain for paediatrics/adolescents and maintained the adult on-treatment utility gain of 0.1. The clinical data used to justify these utility gains are summarised in Table 1 below:

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Table 1. Summary of utility gains with clinical data in rhLAMAN-10 and Etoile Alpha

	Absolute change in clinical outcome	Paediatric: <18 years **(calculated utility gain)**, n	Adult: ≥18 years **(calculated utility gain)**, n	All patients **(calculated utility gain)**, n
rhLAMAN-10 at last observation, N=33	*EQ-5D-5L*	*0.08, n=10*	*0.03, n=14*	*0.05, n=24*
	FVC, litres (utility gain if 0.2 utility per +1L)	0.9L **(0.18)**, n=17	0.2L **(0.04)**, n=12	0.4L **(0.08)**, n=28
	FVC, % predicted	*11.6%, n=17*	*3.0%, n=12*	*8.1%, n=31*
	6MWT (utility gain if 0.02 utility per 10m)	39.1m **(0.078)**, n=19	0.3m (-), n=13	22.4m **(0.045)**, n=33
Total calculated additional utility gain from rhLAMAN-10 (FVC + 6WMT)		**0.18 + 0.078 = 0.258**	**0.04**	**0.08 + 0.045 = 0.125**
Etoile-Alpha, N=16	*EQ-5D-5L*	*NA*	*NA*	*NA*
	FVC, L (utility gain if 0.2 utility per +1L)	NA	NA	[redacted] L ([redacted]), n=[redacted]
	FVC, % predicted	*NA*	*NA*	*NA*
	6MWT (utility gain if 0.02 utility per 10m)	NA	NA	[redacted] m ([redacted]), n=[redacted]
Total calculated additional utility gain from Etoile Alpha (FVC + 6WMT)		**-**	**-**	**0.22 + 0.034 = 0.254**

Sources: Borgwardt et al., 2018a (3); Borgwardt et al., 2018b (3); Etoile-Alpha CSR, 2021 (7); utility gain from HST2/HST19 (10)

Table 1 shows the improvements in EQ-5D-5L utility scores reported at last observation in rhLAMAN-10, alongside calculated utility gains from improvements in additional lung function and mobility from improved FVC and 6MWT measurements. The EQ-5D-5L scores are likely an underestimate of utility

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		gain (as explained in detail in the points above), and the difference between the EQ-5D-5L and calculated utility gain is likely due to the smaller number of patients providing EQ-5D-5L data due to the difficulties in performing this test in AM patients, especially those with cognitive impairment or in children. As only one patient in Etoile Alpha provided EQ-5D-5L at baseline and end of study, only the calculated utility gain from FVC and 6MWT in all patients from this study is shown – results for %FVC and by age group have been requested.
Disease progression after treatment with velmanase alfa in responders	Yes	Chiesi believe the new long-term data submitted from rhLAMAN-10, Etoile Alpha and case reports strongly support a plausible delay in disease progression of at least 5 years with velmanase alfa. This assumption is likely to be strengthened when final rhLAMAN-07/-09 data are available in [redacted], which will provide data in 21 patients treated for over 10 years. 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. Etoile Alpha includes data from [redacted] patients who are the same patients that have been followed up through rhLAMAN-03/04, rhLAMAN-05 and rhLAMAN-07 for up to 9.5 years. As these [redacted] patients show disease improvement or lack of disease progression with treatment for well over 5 years, the 5-year delay in disease progression is likely to be a conservative estimate. The long-term delay in disease progression seen in Etoile Alpha was also confirmed in a UK case report of a patient who has been continued on treatment after rhLAMAN-05 on compassionate use for 7 years(4). The modelling results also likely underestimate the delay in disease progression with velmanase alfa, since the expert elicitation exercise used to estimate transition probabilities in the model has not been updated since 2017 when long-term data were not available. The following points provides further evidence to support the delay in disease progression with velmanase alfa to reflect long-term data, and the likely conservative assumptions previously used to estimate the transition probabilities in the model. • **rhLAMAN-07** (France): includes [redacted] treated patients ([redacted] ongoing, [redacted] on home infusion), including [redacted] patients previously in clinical trials and [redacted] new patients from Etoile Alpha. [redacted] patients currently have ≥9 years of follow up data. Last patient last visit is due in [redacted], with final results expected in [redacted], which will be incorporated into updated responder

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		analyses • **rhLAMAN-09** (Poland and Norway): includes [redacted] treated patients ([redacted] ongoing, all hospital infusion). Includes [redacted] patients with ≥9 years of follow up data – including 2 siblings who had a 1-year treatment holiday due to Covid restrictions. Last patient last visit is due in [redacted], with final results expected in [redacted], which will be incorporated into updated responder analyses • **Etoile Alpha:** the mean treatment duration of the [redacted] patients in Etoile Alpha was [redacted] months (approx. [redacted] years); however, [redacted] patients included from the rhLAMAN-07 cohort all had a longer treatment duration of over 5 years, up to a maximum of [redacted]). Individual patient data are included as additional evidence to show the clinical improvements observed over time and delay in disease progression in these long-term patients (patients 0104, 0105, 0106, 0107, 0110, 0111, 0112) (6). • **Transition probabilities** in the model to estimate disease progression in untreated and treated patients were determined by an expert elicitation panel in 2017 before the completion of rhLAMAN-10 so their knowledge of the long-term treatment benefits of velmanase alfa and the natural progression of untreated patients was limited. As such, these probabilities may not accurately represent the treatment effect of velmanase alfa, nor new data on the natural deterioration, nor the incidence of severe infections and mortality in untreated patients. A new scenario analysis has been performed to reflect the reported baseline distribution of walking status as reported in the final analysis of rhLAMAN-10 (3). Due to limited time, the expert elicitation panel exercise has not been repeated to update the transition probabilities, and as such the transition probabilities in the base-case have not been changed. • Limited **UK clinical expert opinion** gathered since the availability of longer-term data (rhLAMAN-10 and Etoile Alpha) were in agreement that a delay in disease progression of at least 5 years was clinically plausible (UK clinical expert interviews 2022 (15)). • Patients who are eligible for velmanase alfa have mild-to-moderate AM, so have type 1 or type 2 phenotype and exhibit slow disease progression when untreated, which occurs over many years (18). In these phenotypes, it usually takes >2 years for disease progression and clinical

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		deterioration to manifest from a baseline, as such any observed delay in disease progression with treatment per se will take longer than the ERG's suggested 1 year. • **Definition of a responder/super-responder and impact on discontinuation rate**: in the base-case, the increased delay in disease progression with velmanase alfa is assumed to be 5 years, only in patients who respond to treatment. The definition of a "responder" is taken from the global treatment response (GTR) analysis that was performed by Chiesi as a post-hoc request from the EMA, with results published by Harmatz et al., 2018 (19). In the base case, a "responder" is defined as a patient with a response to ≥2 domains (pharmacodynamic, functional and/or QoL). In rhLAMAN-05, 13% of patients were non-responders after 1 year, and as such a 13% discontinuation rate at 1 year was applied to the model (with a 10% annual discontinuation rate thereafter). Chiesi are proposing stopping criteria in the MAA which aligns to "super-responders" in the GTR analysis (defined as those with a response to all 3 domains (pharmacodynamic, functional and QoL). As such, scenario analyses have been performed using discontinuation rates applied for patients who were non-"super responders" in the GTR at 1 year: in rhLAMAN-10 by age-group, this would equate to a 47.4% discontinuation rate in patients <18 years and a 64.3% discontinuation rate in those >18 years. The annual discontinuation rate used is the same 10% as previously. As the definition of a "super-responder" is used in these scenario analyses, the assumption of a 5-year delay in disease progression in patients who respond to treatment in all 3 domains is likely to be more clinically plausible than in patients who respond to only 2 domains, and may be supportive of a plausible delay of more than 5 years.
Appropriate population and inclusion of rhLAMAN-08 study	No	Chiesi have provided results of rhLAMAN-08 in the resubmission which were used to support the European paediatric license extension for the use of velmanase alfa in children under 6 years which was approved by the EC in November 2021. Chiesi anticipate that velmanase alfa would be used in this population in children under 6 years who are unsuitable for allogeneic haematopoietic stem cell transplant. In line with the licensed indication, patients under 6 years with the most severe rapidly progressing phenotype of AM (with a deterioration within 1 year and central nervous system involvement) would also be excluded. This severe type of AM is also known as type 3 AM, which is immediately recognised with skeletal abnormalities and obvious

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		progression, leading to an early death from primary neurological involvement or myopathy, usually by the age of 2 years (20). Chiesi wish to clarify that patients with type 1 and type 2 AM who are severely impaired due to disease progression are still eligible for treatment with velmanase alfa under the licensed indication.

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Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Availability of rhLAMAN-07/-09 long-term data	Section 2.2.2 and 3.2.2.	No	Final rhLAMAN-07/-09 data will be available in [redacted] ([redacted]), which will provide data in 21 patients treated for over 10 years. These data will be included in any updated responder analyses after any period of further data collection and should support the delay in treatment progression and on-treatment utility benefit. Etoile Alpha includes data from [redacted] patients for up to 9.5 years who are the same patients that have been followed up through rhLAMAN-03/04, rhLAMAN-05 and rhLAMAN-07.
Additional issue 2: Critique of Etoile Alpha methodology	Section 3.2.1.2	Yes	Chiesi accept the critique of Etoile-Alpha as a single-arm retrospective study; although the results may not provide high-quality robust data for the long-term efficacy of velmanase alfa, they support its plausible potential with uncertainties that can be addressed by further data collection and the additional long-term data that will be provided in rhLAMAN-09. However, 7 patients included in Etoile-Alpha are the same patients followed for over 9 years from their initial inclusion in clinical trials from rhLAMAN-02/-03/-04/ or rhLAMAN-05, and into rhLAMAN-07. Although Etoile Alpha has limitations, we believe that it confirms the positive trends seen in the initial controlled 12-month period of rhLAMAN-05 and supports long-term improvements in

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			clinical outcomes for over 5 years. Further responses on specific critique from the ERG to assist in committee decision-making are addressed in the points below: - Unclear time of outcome assessment o Etoile Alpha was a retrospective study of 3 cohorts of patients treated with velmanase alfa in France (rhLAMAN-07, rhLAMAN-08, or nominative ATU). Patients were followed from baseline, which is the first visit from when they started in the rhLAMAN trials, or the ATU. All final timepoints were assessed on the same date at the last visit (June 2020). o Individual patient data syntheses have been provided so improvements in patients treated for >5 years can be assessed – patients treated for >5 years (patients 0104, 0105, 0106, 0107, 0110, 0111, 0112) are provided in a separate folder o Aggregated data by specific timepoints have been requested. - Missing data points o As Etoile Alpha was a retrospective real-world study, not all tests performed in the clinical trial were performed in the real-world setting as there is no standard of care or guidelines for monitoring in AM; as such not all baseline assessments were performed for all patients. The 2MWT was specified but is a test that is generally used in children <4 years in place of the 6MWT; as all patients were over this age at the time of exposure to velmanase alfa, this test was not done. o The difficulties in performing utility or QoL measurements in AM has been discussed previously, as some patients are children and some have cognitive impairment. o 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. - Age-adjustment of results

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			o 6MWT and FVC results of Etoile Alpha confirm the positive trend seen in the controlled 12-month period of rhLAMAN-05 and the longer rhLAMAN-10 analysis. o The mean age at first exposure to velmanase alfa is 19.5 years, with only 5 patients starting treatment at under 10 years (the youngest being 6 years old at velmanase alfa initiation) o Although 6MWT results were not age-adjusted, on average patients improved in their 3MSCT and 6MWT by >20 steps for each, respectively from baseline. Over the average treatment duration of the study (4.5 years), untreated patients would be expected to experience a decline in 6MWT during this time, which was confirmed by UK clinical experts (15). o FVC results by % predicted are included in the individual patient synopses; aggregated data for FVC % predicted have been requested o The 45% improvement in FVC observed in Etoile Alpha is unlikely to be driven by growth of the 6 paediatric patients and 3 adolescent patients who started velmanase alfa before the age of 18. Natural history data from 22 AM patients under 18 years showed a decline in % predicted FVC over a 2-year period, showing a decline in lung function with age in paediatric patients(21). New natural history data in a cohort of 12 Polish patients with AM over 14 years also showed untreated children with AM grow slowly, finally reaching the 3rd percentile (or values below the 3rd percentile).(16). - Severity of disease at baseline o Chiesi agree 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. Patients with severe AM who are not indicated for velmanase alfa are those with the type 3 rapidly progressing severe phenotype of

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			AM (with a deterioration within 1 year and central nervous system involvement and who usually die within 2 years of age)(20). The patients included in Etoile Alpha who were classed as severely impaired are patients with type 1 or type 2 AM but who have severely advanced disease progression, who were usually older patients. o Patients with AM who are severely impaired but are type 1 or type 2 are still eligible for velmanase alfa treatment in the licensed indication and were included in Etoile Alpha. These patients still showed disease improvement or stabilisation from baseline over the study period, which provides supporting evidence that velmanase alfa can demonstrate a treatment effect even in older patients who are severely impaired o Chiesi wish to clarify that patients with type 1 and type 2 AM who are severely impaired due to disease progression are still eligible for treatment with velmanase alfa under the licensed indication. - Comparability to stop/start criteria o Chiesi is in agreement with the ERG that as Etoile Alpha includes patients with severe impairment who may not be eligible for velmanase alfa according to any agreed starting or stopping criteria, the efficacy of the treatment in clinical practice are likely to be enhanced compared with the results reported in Etoile Alpha, as such "super responder" criteria may select for patients more likely to have stable disease for 5 years or more on treatment (see additional issue 3 below). Chiesi is also in agreement that the precise extent to which the criteria will do this remains unclear, so any uncertainty could be addressed by further data collection.
Additional issue 3: Definition of a responder/stopping criteria in the	Executive summary, Section 3.2 and Section 5	Yes	A key change to the base case included in this resubmission is an assumption of a 5-year delay in disease progression in "responder" patients. The definition of a "responder" is taken from the global treatment response (GTR) analysis that was performed by Chiesi as a post-hoc request from the EMA, with results published by Harmatz et al., 2018 (19). In the base case, a "responder" is defined as a patient with

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model in line with the MAA			a response to ≥2 domains (pharmacodynamic, functional and/or QoL). In rhLAMAN-05, 13% of patients were non-responders after 1 year, and as such a 13% discontinuation rate at 1 year was applied to the model (with a 10% annual discontinuation rate thereafter). Chiesi has included stopping criteria in the proposed MAA which aligns to "super-responders" in the GTR analysis (defined as those with a response to all 3 domains (pharmacodynamic, functional and QoL). As such, additional scenario analyses have been performed to incorporate these stopping rules to show how these affect the ICERs across all age groups, which will be important in committee decision-making. In these scenario analyses, discontinuation rates were applied for patients who were non-super responders in the GTR at 1 year: in rhLAMAN-10 by age-group, this would equate to a 47.4% discontinuation rate in patients <18 years and a 64.3% discontinuation rate in those >18 years. The annual discontinuation rate used is the same 10% as previously. As the definition of a "super-responder" is used in these scenario analyses, the assumption of a 5-year delay in disease progression in patients who respond to treatment in all 3 domains is likely to be more clinically plausible than in patients who respond to only 2 domains , and may be supportive of a delay of more than 5 years.
Additional issue 4: Expert elicitation inputs for transition probabilities and baseline distribution of health states	Section 3.2.4	Yes	The ERG highlighted the results of the expert elicitation exercise in determining the transition probabilities between health states. In the estimates of the additional time that patients would stay in health states due to velmanase alfa, the ERG highlights that the upper 95% credible interval does not reach 5 years for any data point. Chiesi wishes to reiterate that this exercise was performed in 2017 before the availability of any long-term data with velmanase alfa. As such, the results of the expert elicitation are likely to underestimate the treatment effect of velmanase alfa, which further justifies the delay in disease progression of at least 5 years, which could plausibly be higher in super responders. Chiesi wish to respond to this issue in the following points with an additional analysis which were performed to address this issue: - The ERG noted that all patients in the model start in one of these two states,

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			with the majority in walking unassisted. o A scenario analysis has been performed so 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. 2018 (3) - As the expert elicitation exercise has not been updated in 2022, Chiesi agree with the ERG that the values for the transition probabilities may change as a result of the new long-term data. As the expert elicitation values have not been updated, these have not been changed in the base-case.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
1. On-treatment utility gain	1. On-treatment utility gain of 0.1 for all age groups 2. Company cost estimates for home-based social care	1. Updated paediatric and adolescent utility gain to 0.25 2. Updated to ERG's preferred cost estimates for home-based social care	ICERs resulting from the change described (on its own): - Paediatric: £88,912 - Adolescent: £126,214 - Adult: £185,872 Change from the company's original base-case ICER: - Paediatric: - £39,122 - Adolescent: - £52,226 - Adult: - £6,106
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ] - Paediatric: [redacted] - Adolescent: [redacted] - Adults: [redacted]	Incremental costs: [£££] - Paediatric: £[redacted] - Adolescent: £[redacted] - Adults: £[redacted]	Company revised base-case ICERs: - Paediatric: £88,912 - Adolescent: £126,214 - Adult: £185,872

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Sensitivity analyses around revised base case

The sensitivity analyses performed in the 2022 company addendum (Table 55, 2022 submission) have been updated to reflect the new base-case. New scenario analyses that have been added are highlighted in **bold**.

Scenario	Scenario detail	Paediatric ICER	Adolescent ICER	Adult ICER	Impact of new clinical data on plausibility
Base case	-	£88,912	£126,214	£185,872	
0% discount rate	0% discount rate for costs and benefits	£123,628	£149,144	£199,261	
1.5% discount rate	1.5% discount rate for costs and benefits	£104,454	£135,497	£178,983	
Include personal and caregiver expenditure	Include personal and caregiver expenditure	£90,562	£127,845	£188,055	
Include caregiver productivity loss	Include caregiver productivity losses due to reduced earnings	£130,785	£169,161	£247,104	
Time horizon 50 years	-	£86,077	£123,788	£183,404	
Time horizon 20 years	-	£143,284	£232,883	£719,254	
No annual withdrawal	No treatment discontinuation for responders until they enter the 'wheelchair dependent' health state	£180,756	£203,873	£318,255	New data from the MAA will inform the plausibility of this assumption
No delay in progression in VA responders	No delay in progression in VA responders	£127,478	£170,484	£269,215	New data from the MAA will inform the plausibility of this assumption
Permanent delay in progression in VA responders	A permanent delay in disease progression in VA responders until treatment discontinuation	£56,162	£88,248	£123,986	New data from the MAA will inform the plausibility of this assumption; this is supported by new clinical data in the Etoile Alpha study[18]

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Scenario	Scenario detail	Paediatric ICER	Adolescent ICER	Adult ICER	Impact of new clinical data on plausibility
Discontinue if wheelchair dependent	Treatment is discontinued upon entering the 'wheelchair dependent' health state	£84,251	£122,192	£179,128	
No reduction in severe infection probability	No treatment effect for VA in terms of reducing the probability of a severe infection occurring, and in reducing the mortality risk of a severe infection	£76,804	£116,137	£174,496	New data from the MAA will inform the plausibility of this assumption
No reduction in surgery benefit	No treatment effect for VA in terms of reducing the probability of mortality or serious complications arising from a surgical procedure	£88,563	£128,802	£193,705	New data from the MAA will inform the plausibility of this assumption
No homecare administration	No homecare administration, all VA infusions provided in hospital	£112,437	£149,253	£216,129	
Treatment monitoring in addition to BSC	Patients receiving VA require an additional two consultant consultations per annum	£89,868	£127,541	£188,342	
MPS Health State Utilities	MPS Society Survey utility values are used for the health state utility values	£72,039	£102,614	£144,418	New data from the MAA will inform the health state utility values
Exclude carer disutility	Exclude carer disutility	£89,455	£127,044	£187,623	
On-treatment utility = 0.00	On-treatment utility benefit for VA = 0	£162,420	£226,694	£241,141	New data from the MAA will inform the on-treatment utility assumptions, data from Etoile Alpha suggest this scenario is not plausible
On-treatment utility = 0.05	On-treatment utility benefit for VA = 0.05	£139,687	£195,981	£209,929	New data from the MAA will inform the on treatment utility assumptions; data from Etoile Alpha suggest this is a conservative scenario

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Scenario	Scenario detail	Paediatric ICER	Adolescent ICER	Adult ICER	Impact of new clinical data on plausibility
Withdrawal rate based on 'Super-Responders'	**Paediatric patients and Adolescents have a withdrawal rate of 47.4%, and Adults have a withdrawal rate of 64.3%, at 12 months, and an annual withdrawal rate of 10%.**	**£74,435**	**£108,786**	**£128,790**	New data from the MAA will inform the % of super-responders and rate of withdrawal in this scenario
Permanent delay in progression for VA patients who are 'Super-Responders'	**Those who are 'Super-Responders' in rhLAMAN-10 have a permanent delay in progression**	**£47,545**	**£77,820**	**£93,241**	New data from the MAA will inform the plausibility of this assumption
Updated baseline distribution	**Updated baseline distribution of walking abilities in rhLAMAN-10**	**£95,107**	**£130,413**	**£144,231**	
Increased improvement of 10% for VA and BSC	**Scenario analysis as requested by ERG**	**£92,290**	**£130,521**	**£194,824**	

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Clinical and patient expert technical engagement response form

Velmanase alfa for treating alpha-mannosidosis [ID800]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for information about you.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical or patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm on 17 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1

Table 1 About you

1. Your name	Dr Karolina M Stepien
2. Name of organisation	Salford Royal NHS Foundation Trust
3. Job title or position	Consultant in adult metabolic medicine
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with refractory or resistant cytomegalovirus infection? ☐ A specialist in the clinical evidence base for refractory or resistant cytomegalovirus infection or technology? ☒ Other (please specify): treating clinician in a tertiary centre
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Part 2: Technical engagement questions for clinical and patient experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue: Utility gain associated with velmanase alfa treatment	
Key issue: Disease progression after treatment with velmanase alfa	
Key issue: Appropriate population and inclusion of rhLAMAN-08 study	
Are there any important issues that	

have been missed in ERG report?	

Questions for engagement

Key Issue: utility gain associated with VA treatment	
Are you aware of any additional evidence to support a utility gain which is not included in the submission or resubmission?	No, all available evidence is mentioned in the report. Just to confirm the SPARKLE Registry has been opened and the recruitment is progressing well.
Are there any additional health benefits to patients and carers which are not captured in the economic model, but which are a likely outcome for responders who have velmanase alfa?	- frequency of admissions to the hospital with infections/ seizure and whether it has changed over time of the VA therapy - orthopaedic issues and surgeries (4 of our patients had orthopaedic corrective surgery this year), or any other surgeries i.e. hip in childhood/ adolescence/ adulthood (wheelchair dependence may depend on the advance joint disease) - analgetic agents use and whether it has changed with the VA treatment
Are the benefits mentioned above likely to affect children, adolescents and adults equally?	It may vary depends on co-morbidities and advanced symptoms Ear infections tends to be pronounced more in childhood, while adults have it sporadically Joint problems and advanced bone deformities and resulting pain are more prevalent in adults

Key Issue: Disease progression after treatment with velmanase alfa	
Does the company approach reflect what is expected in clinical practice (no disease progression for 5 years followed by delayed progression and extended time in earlier health states for responders to velmanase alfa)?	I think that '5 years' is only an arbitrary number of years. It would vary from one patient to another, with differences even among siblings. The sooner the VA treatment is started, the better for the disease progression to be arrested and for long-term complications to be prevented or delayed. Alpha mannosidosis is a slowly progressive condition and we have to consider that adult patients will develop age-related complications over time.
Is there a biological rationale which would support the company approach to delaying disease progression for 5 years?	Not aware of any biological rationale.
Please comment on the results of the expert elicitation exercise (Table 4 ERG report) given the new evidence from the Etoile Alpha study.	For adults the median time in both columns is much shorter as compared to children and adolescents. This is what we observe in our adult cohort of alpha mannosidosis patients where since the transition to our services (and no treatment) their mobility is deteriorating and they develop wheelchair dependence over time. As above, severe alpha mannosidosis related hip joint disease and subsequent weight gain, result in wheelchair dependence faster in adults as compared to children. This may change with VA treatment, in particular if pain is optimised with the therapy.
Is the delay in disease progression likely to be same across subgroups of children, adolescents and adults?	It is very individual, may depend on their genotype, enzyme activity at diagnosis. Some of our patients had subtle changes in childhood and the diagnosis was made/confirmed in their adolescence. There are still adult patients out there in whom the diagnosis was

	confirmed in their 30s. It only confirms that the condition is slowly progressive and patients have non-specific subtle clinical manifestation. The earlier the treatment has been started, the better for the patient. The treatment considered in adulthood may not reverse damage already done, but may help prevent infections and long-term antibiotic prophylaxis may be stopped, may help control pain and as a result analgetic agents may be discontinued as a result of it.
Key Issue: Appropriate population and inclusion of rhLAMAN-08 study	
Is the population included in rhLAMAN-08 relevant to the scope of the evaluation?	Paediatric population <6 years of age, as far as I understand it is not included in the scope of this NICE review
What would distinguish mild to moderate disease from severe disease in people under 6 years?	• Genotype/ phenotype • Clinical manifestations: delayed development and severe learning disability, frequency of ear infections, severity of bone deformities, severity of pain, frequency of admissions to the hospital with infections (chest) or seizure, rapidly deteriorating mobility, wheelchair dependence, not being able to stand up independently, bladder and urine dysfunction, history of surgeries (spinal, foot, hips).

	• The pace of the above symptoms would distinguish between mild, moderate and severe form, with the rapidly progressive symptoms in severe forms, often requiring palliative care input.
Would children under 6 be treated with velmanase alfa in clinical practice?	This is a question for paediatricians, but I do not see any reason why they should not be treated with VA.
Is the wider evidence (e.g. Etoile Alpha study) generalisable to children under 6 years?	This study was done on 16 patients including children and adults. It showed improvement in QoL and stability/ improvement in other parameters. There is lots of missing results. I am not sure whether it could be generalisable to children < 6 years of age. I note however that 8/16 patients were diagnosed at the age of 6 years or before and were treated and followed up afterwards for minimum 13 months, maximum 114 months with some positive response in some.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Alpha mannosidosis is a slowly progressive neurodegenerative condition

Patients live up to their adulthood and are likely to develop alpha mannosidosis as well as age related complications

Unmet needs of adults with alpha mannosidosis include pain, joint deformities and requirement for corrective surgery

VA therapy may help control pain and improve mobility (frequency of falls) and walking aids dependence

Adults with this condition have moderate to severe learning disability and require supportive care 24/7

Thank you for your time.

Your privacy

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Clinical and patient expert technical engagement response form

Velmanase alfa for treating alpha-mannosidosis [ID800]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for information about you.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical or patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm on 17 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1

Table 1 About you

1. Your name	Sophie Thomas
2. Name of organisation	The MPS Society
3. Job title or position	Senior Head of Patient Services and Clinical Liaisons
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with refractory or resistant cytomegalovirus infection? ☐ A specialist in the clinical evidence base for refractory or resistant cytomegalovirus infection or technology? ☒ Other (please specify): **(Patient organisation)**
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it **(Submitted 2018)** ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Commented [ST1]: Think these need to be changed as not reflective of the condition

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Part 2: Technical engagement questions for clinical and patient experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue: Utility gain associated with velmanase alfa treatment	See below
Key issue: Disease progression after treatment with velmanase alfa	See below
Key issue: Appropriate population and inclusion of rhLAMAN-08 study	See below
Are there any important issues that	See below

have been missed in ERG report?	

Questions for engagement

Key Issue: utility gain associated with VA treatment	
Are you aware of any additional evidence to support a utility gain which is not included in the submission or resubmission?	**Data from both the French Etoile alpha study and Sparkle registry is important for the committee to consider, despite being excluded by the ERG. Given the small patient numbers globally, evidence generated through both the registry and study will be vital to understand the disease pathway for both treated and non-treated patients.** Mortality in patients with alpha-mannosidosis (2022) https://rd-rp.com/wp-content/uploads/2022/03/LB-26-WORLD-2022-ePoster-Alpha-mann-mortality-FINAL.pdf Adam J et al (2019) Disease progression of alpha mannosidosis and impact on patients and carers https://rd-rp.com/wp-content/uploads/2020/05/06.12.19-Disease-progression-of-alpha-mannosidosis-A-UK-natural-history-survey-Manuscript.pdf Lund et al (2018) Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6326957/)

	Harmatz et al (2018) Enzyme replacement therapy with velmanase alfa: Novel global treatment response model and outcomes in patients with alpha mannosidosis (https://www.sciencedirect.com/science/article/pii/S1096719218301537?via%3Dihub)
Are there any additional health benefits to patients and carers which are not captured in the economic model, but which are a likely outcome for responders who have velmanase alfa?	Velmanase alfa has not only had a positive clinical effect on patients but these improvements have been maintained over a period of time. As with other ultra-rare progressively worsening disease the terms 'improvements' and 'maintaining' are extremely relevant end points, where a cure is not currently available. Patient reported outcomes and clinical evidence from the 2018 committee clearly demonstrated a treatment effect that had improved a number of areas of disease which was supported and verified by the clinical experts. The experts shared that like with other ERT's, improvements and changes to the course and presentation of the disease are only being fully understood now, but there has been a clear increase in utility benefits observed over time, especially if started in childhood. The utility benefits is further observed in a recent paper by L Borgwardt, where the efficacy and safety results of VA in various treatment arms was analysed with the conclusion stating *"These findings support the utility of Velmanase alfa for the treatment of Alpha Mannosidosis, with more evident benefit over time and when treatment is started in the paediatric age" (Borgwardt L. et al. J Inherit Metab Dis. 2018)*. Despite the committees uncertainties in 2018 regarding the longer term outcomes and benefits; we were pleased that they had recognised that VA was a promising and innovative treatment. The further studies as presented by the company should hopefully show the ongoing benefit of velmanase alfa for patients. It is the Society's view that any ongoing uncertainties can be balanced against clear assessment and monitoring criteria through the MAA.

	Treated patient summary Diagnosis - Diagnosed at 15 years; told prognosis was poor, intellect was set and in decline. Mobility – Wears orthopaedic boots (so still in walking with assistance group, although needs no assistance) Able to walk long distances without assistance, no longer needs to wear callipers, use a walking stick or needs the use of a wheelchair for long distances. Medical – Has more energy. Improved breathing and respiratory function. Less infections, improved hearing, no neurological decline and improved communication. (pre-treatment was having 2/3 infections a month) Quality of Life – More independent / able. Feels generally well, improved mobility and respiratory function has aided independence, confident and less reliant on parents / others for support. Social, travelled independently. Does voluntary work **Carer burden / impact** Reduced peer groups, socialisation of whole family becomes more difficult and isolated. Parental ability to socialise / go out / go on holidays is negatively impacted as individual will not want to go with parents but can't be left at home Constant Emotional support, guidance, assistance, encouragement, sympathy (given willingly) Takes its toll on parents, both physically and mentally Impact on mental health and wellbeing including depression Impact on employment / financial – reduced income / financial burden / reduced work / time off for appointments, education meetings etc

	<u>After treatment</u> Mental health improved / Relationships improve Seeing a future More sociable / work less impacted Borgwardt et al (2018) stated that the 'Prognosis for untreated adults is poor due to progressive neuromuscular and skeletal deterioration, impacting on ADL and increased carer burden'. 'For a treated patients, improvements in HRQof L reduction in disability pain, increased mobility.Dependancy on ambulatory devices or third party reduced' *Borgwardt et al (2018) Health Related Quality of Life, Disability, and Pain in Alpha Mannosidosis: Long-Term Data of Enzyme Replacement Therapy with Velmanase Alfa (Human Recombinant Alpha Mannosidase)* *https://journals.sagepub.com/doi/full/10.1177/2326409818796854* Additional health benefits discussed by KOL's include: serum oligosaccharides measures, reduction in infections, improved respiratory function, positive impacts on quality of life, more

	energy, less pain, improvement in bone density. These are not just important clinical and biochemical markers but are important to patient's activities of daily living and quality of life. Lund et al (2018) stated 'Serum oligosaccharides is of high relevance particularly in adults and the vulnerability of patients to infections with consequences of significant morbidity' *Lund et al (2018) Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6326957/)*
Are the benefits mentioned above likely to affect children, adolescents and adults equally?	It is important to understand that alpha mannosidosis is a highly heterogeneous progressive, debilitating disease. Age and presentation of symptoms at diagnosis could have an impact on treatment outcomes and patients will respond in different ways. Whilst treating early will give the best outcomes, it is important to consider that stabilisation is as good a response rate, as improvements. Timely treatment is critical whether it is treating a child or an adult. Borgwardt L et al (2018) paper showed improvements of those treated on the trial over a sustained period- supports treatment efficacy over a 5yr period. In our view this paper offers

	credibility to the authenticity of the case reports presented by the company showing significant improvement across multiple domains. Harmatz et al (2018) used a responder analysis model to demonstrate a clinically meaningful treatment effect with velmanase alfa that supports the early initiation and continued benefit of longer-term treatment of all patients with alpha- (this was a more sensitive evaluation method than those used in the clinical trial). In summary the responder analysis model demonstrated *'A greater improvement in 3MSCT, 6MWT, and FVC % was observed in pediatric patients, compared with adults in the rhLAMAN-10 analysis [12], suggesting that velmanase alfa produces greater clinical benefits in motor and pulmonary function when administered early in the disease course.* *New model In the specific case of velmanase alfa, the model makes it possible to observe a clear treatment effect over a short duration of treatment (12 months) in a mixed population of pediatric and adult patients, in comparison with placebo.* *Conversely, all patients who received velmanase alfa achieved a PD response and 10 out of 15 also had a motor function response (in the 3MSCT and/or 6MWT), while 5 of 15 had relevant FVC improvements. These results support the robustness of the approach, despite the small patient numbers and the inherent variability of the disease. Thus, velmanase alfa appears to improve outcomes across multiple variables compared with placebo in both pediatric and adult patients'.*

	Harmatz et al (2018) Enzyme replacement therapy with velmanase alfa: Novel global treatment response model and outcomes in patients with alpha mannosidosis (https://www.sciencedirect.com/science/article/pii/S1096719218301537?via%3Dihub)
Key Issue: Disease progression after treatment with velmanase alfa	
Does the company approach reflect what is expected in clinical practice (no disease progression for 5 years followed by delayed progression and extended time in earlier health states for responders to velmanase alfa)?	**Whilst we have limited experience in the UK, there is evidence as previously shared to confirm that in most cases disease stability was maintained for a period of 5 years with improvement in key outcomes, such as mobility, FVC and cognitive function. A MAA could be a way of providing some answers to the committee's uncertainties**
Is there a biological rationale which would support the company approach to delaying disease progression for 5 years?	**Meetings with KOL's attended previously concluded that a decreased of serum oligosaccharides was a good way of indicating treatment response. This has been evidenced through a number of studies also Lund et al (2018) for example.** ***Lund et al (2018)*** *Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6326957/)*

Please comment on the results of the expert elicitation exercise (Table 4 ERG report) given the new evidence from the Etoile Alpha study.	
Is the delay in disease progression likely to be same across subgroups of children, adolescents and adults?	As mentioned previously alpha mannosidosis is an extremely heterogeneous disease and therefore it will depend on a number of factors; onset of symptoms / time of diagnosis, mutation, CNS involvement etc Children, young people and adults have responded well to this treatment.
Key Issue: Appropriate population and inclusion of rhLAMAN-08 study	
Is the population included in rhLAMAN-08 relevant to the scope of the evaluation?	
What would distinguish mild to moderate disease from severe disease in people under 6 years?	**Mutation, family history (for siblings), age of diagnosis, presenting symptoms, onset of symptoms**
Would children under 6 be treated with velmanase alfa in clinical practice?	**Potentially although HSCT may be a preferred option for treating the CNS**
Is the wider evidence (e.g. Etoile Alpha study) generalisable to children under 6 years?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- It is important to understand that alpha mannosidosis is a highly heterogeneous progressive, debilitating disease.
- Presentation of symptoms at diagnosis could have an impact on treatment outcomes and patients will respond in different ways. Whilst treating early will give the best outcomes, it is important to consider that stabilisation is as good a response rate, as improvements.
- Age and Timely treatment is critical whether it is treating a child or an adult.
- Different models have been used to assess the efficiacy of velamanase alfa. They have also concluded that velmanase alfa '*appears to improve outcomes across multiple variables compared with placebo in both pediatric and adult patients'(Harmatz 2018)*
- Treatment has had a clear and positive impact on the quality of life of both patients and carers

Thank you for your time.

Your privacy

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Clinical expert statement

Velmanase alfa for treating alpha-mannosidosis [ID800]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Duncan Cole**
2. Name of organisation	**Cardiff and Vale UHB**

3. Job title or position	**Clinical Reader / Honorary Consultant in Medical Biochemistry and Metabolic Medicine**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? **(We would encourage you to complete this form even if you agree with your nominating organisation's submission)**	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here.	☐ yes (please go to question 24).

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Halt progression of the disease Improve mobility Improve quality of life Reduce the rate of infection (esp upper resp tract)
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Maintenance of current mobility Reduction of number of infections per year Improve quality of life scores
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, definitely. There is no currently licensed treatment that can impact disease progression.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Supportive care, including physiotherapy, orthopaedic intervention as needed, treatment of infections, support for learning disability
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	This is a very rare disease and I only see adult patients, and cannot comment on children's care. I suspect most other clinicians treat this disease in a similarly supportive way, although the frequency of review and monitoring tests done may vary. Note, I am based in Wales, and cannot specifically comment on practice in English centres.
• What impact would the technology have on the current pathway of care?	Significant – the pathway of care would be more closely aligned with other lysosomal storage diseases, and with clear assessment requirements, eligibility/exclusion criteria, and monitoring requirements. The treatment itself would require the same governance arrangements as other ERTs.
11. Will the technology be used (or is it already used) in	I'm not quite sure what this means, but I have experience caring for a patient with alpha mannosidosis who participated in the pivotal clinical trial, and has subsequently been on an aftercare programme. She is currently receiving the treatment via homecare and is reviewed regularly in the metabolic clinic. I would

the same way as current care in NHS clinical practice?	anticipate that this would be similar to how we would expect patients with this condition to be managed if the treatment was approved by NICE.
• How does healthcare resource use differ between the technology and current care?	Velmanase alfa requires starting in hospital in a day unit, and continuation via homecare, which requires additional resource from the NHS in terms of staff time, day unit space, etc. With regards to other resource use, reduced GP consultations for infections, pain etc; and reduced orthopaedic input for surgery would be expected.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics only – commissioned for ERT and related treatments for lysosomal storage disease
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities already exist, within commissioned treatment centres. Training in the new drug would be needed, but otherwise this would be handled in the same way as other ERTs, for which extensive experience already exists.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase	Possibly. It is not clear to me at present what impact it will have on longevity, but reduce the likelihood of severe infective episodes leading to sepsis.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. I have seen direct evidence of this from my clinical experience with a patient on this treatment.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not sure quite how to interpret this question, but the exact criteria for treatment will need to be agreed; as a minimum the patient will need to have a confirmed diagnosis of alpha mannosidosis.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The treatment is clearly more involved than supportive care for everyone, healthcare professionals and patients and their families alike. However, it is no different to other ERTs, which are generally well accepted, with clear follow-up / monitoring arrangements. For some patients, infusion reactions may be a problem, but this will be a minority and pre-medication is usually effective in managing this.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. There will be eligibility and exclusion criteria, and treatment goals will be set, which are reviewed on an annual basis (at a minimum). 6 monthly clinical reviews will be needed.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. I have seen improvement in cognitive and social functioning and independence in my patient since she has been on treatment, which also impacts her family who care for her substantially. I am not sure that this would be adequately captured in a QALY calculation.

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This is the only treatment aimed at the underlying disease that is available for this condition for adults. From my experience, it does make a significant impact on patients and their families.
• Is the technology a 'step-change' in the management of the condition?	Yes, the only alternative is supportive care for adults. With this treatment we have the possibility of altering the natural history of the disease.
• Does the use of the technology address any particular unmet need of the patient population?	As above – patients will progress without this treatment, becoming more disabled and requiring more support as they get older.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As noted above re: infusion reactions.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	In large part, yes, if we take this to mean assessments and approaches to supportive management. Serum oligosaccharide testing is not routine though.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improved or stabilised motor function and mobility - measured in trials Pulmonary function – measured in trials Quality of life – measured in trials Rate of infection – not measured but IgG measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No – the only reliable predictor of outcome on the trials was age, with younger patients improving more than older patients.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Trials do not adequately cover the impact on cognitive function and impact on daily living, or of impact on carers. This can be found in case reports and smaller studies.
22. How do data on real-world experience compare with the trial data?	My experience is consistent with the trial data, and if anything the outcomes for the patient I treat are better than the trial data would suggest.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. Is allogeneic HSCT usually performed in patients with apha-mannosidosis aged >5 years? If no, do you agree that allogeneic HSCT is not be a suitable comparator for velmanase alpha?	I am not a paediatrician, but can confirm that this would not be considered for adult patients; I don't think the data are good enough to support this approach. I don't think allogeneic HSCT would be a suitable comparator.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- The trial data in adults shows stabilised disease for mobility and lung function; this is a clinically relevant outcome as the disease is progressive.
- My patient has experienced improved cognitive function, social functioning and independence, and has had very few upper respiratory tract illnesses since starting velmanase alfa. This has had a major impact on her quality of life.
- There are no other treatments available to adults that can alter the natural history of alpha mannosidosis
- The treatment is safe and can be delivered successfully via homecare
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Information for inclusion / discussion – Onaissa Jamil

- Date of diagnosis - Aug 2015.
- My sister and I were diagnosed in 2015, this was a very new thing for us to understand

- Age when first symptoms identified?
- In childhood. Balance and coordination especially with fine and gross motor skills.

- Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition?
- There were many issues that my parents felt needed addressing such as milestones in learning at school and college. They kept on getting doctor appointments but no one knew what the exact cause was. We were given such diagnosis as Dyslexia, Dyspraxia, Dyscalculia and Learning Difficulties. My parents kept being sent to all doctors, specialists but no one could make the diagnosis until we were in our early 20s. Medically my sister and I had problems with hearing, speech and co-ordination. We have had lots of trips to the Ear Nose and Throat and Speech and Language Therapy.

- What was the impact of this on you and your family?
- This has been a very big shock and has taken some time to actually digest. We are still processing the whole situation. Mentally, not knowing what will happen in the future gives added stress but we look on the positive side of life! There have been many issues that have affected me and my family … some may be so simple but for me have had a big impact. Socialising with children at school was so difficult for my sister and me. Because we were seen as ‘different’ or having a ‘disability’ children would be very cruel with comments. Even teachers did not understand and we did not get the support we needed from education! But that did not put us down. My parents supported us throughout all of our education and tried to help with socialising with groups. Some were more successful than others! I have managed to gain a Degree in Textile Design. This was definitely not without its barriers!!
- Although socialising, making friendship groups, being included in parties and gatherings seem trivial, the feeling of not being part of that has had a huge impact on life. Luckily my parents are supportive and have given my sister and I love, support and positive thinking, so we have managed this part of our life.

- What is it like to live with the condition?
- When we were young at primary school age we would be in the lowest school groups and my sister got a key worker (to help with classes) but this was in secondary school. In my later college years I got some support. But because of my social skills of being shy and not able to make friends easily, I had a

difficult time. There were groups of girls in my class who were very unkind to me. At University I received support. I had a note taker for classes. My tutors had more understanding of my needs. I found it difficult to manage all the assignments. My mother and I would wonder if this was part of the condition. I generally do any job at a slower pace than others. So completing assignments and practical work took so long. This then impacted on stress levels because there were deadlines to meet. My mother did support me with talking to tutors and explaining the condition. Again because this is a rare condition, it was hard for us to make others understand.

- On a day-to-day basis, I try to do all things. But again I find things difficult. Simple things that others may think nothing about such as chopping and cutting vegetables. My mother has taught me how to do this safely.
- I now understand this is because of the fine and gross motor skills. My speech has always been slower than others. This has been difficult for me because I don't seem to communicate in the right way. I try to make people understand what I want to say. I understand in my head what I want to say but these words seem to come out a different way! People have been impatient when I speak because of their understanding of what I want to say. This makes me feel different and unusual. Again this might be something simple to others but it really does affect me.

- What do carers experience when caring for someone with the condition?

- We don't have any carers because we weren't diagnosed at a young age. My sister and I have had struggles through our education and life but we like to keep positive. My parents are our carers and we try to care for ourselves too.

- Please describe if you have had to adapt you and your family's life, taking into account the following;

  physical health – after the diagnosis, we have been advised to do exercises and eating healthily and look after our general health and well-being. This has been difficult at times because sometimes my sister and I don't feel like exercising but as time goes on, we realise the importance of staying fit and healthy.

  emotional wellbeing – it has been a struggle with making friends and getting them to understand what our needs have been. I have felt isolated at many times and this would feel sad. Over the years we have learned to research other groups of people who have similar needs. So we have contacted them and have now made some good friendships. I am now 30 years old. And I am going to be engaged this year. This again has not been easy but I am happy to say my finance to be, is very understanding and loving.

  everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life.

I have wanted to learn how to drive a car. I did have many lessons for many years with a driving instructor who specialises in teaching adults with additional needs. However, through many discussions and hard work, he did have a conversation saying how I was not able to progress. He knew about my condition and we discussed how my spatial awareness and safety was impacting on progress. Sometimes I would have good lessons and then others would not be able to do so well. I do not understand why I cannot progress this particular part of my life in wanting to learn how to drive. After having discussions with the driving instructor and my family, it seems that spatial awareness has something to do with this.

Through real hard work and effort from the Job Centre and an Organisation that helps young people with disability into work, I managed to keep a job at Asda for 4 years. I am really proud and happy to have achieved this. Sadly, during this time, there were many occasions where management did not understand my needs. This did have an effect on my confidence. At the beginning I was so proud I had a job. But as time went by, this started to feel more of a burden because of the way I was treated by some colleagues and Managers. Again my mother had to intervene and have meetings with the management to explain my condition and how this affects me. We made the decision to end this employment, one because of Covid and two, the negative impact it was having on me. I look back on this experience and take away the positive things and learn from the others.

After my Degree in Textile Design, I started my own business in Machine Knitting such as cushions, hats and scarves. I do try and put on craft fairs for Xmas with my products. I really am happy with this career move.

I am currently living with my parents. As I mentioned before I am engaged to be married next year. This will not be without its own issues, as we need to discuss many things with the Consultants at Salford Royal. It has been difficult meeting someone who is like-minded and is understanding. I hope this relationship will be a happy one.

At the moment we have had no adaptations to the home. If we need to in the future we will get advice about what to do.

I am currently not working but am concentrating on my machine knitting business. My dealings with money and finance are always overseen by my parents. I try to keep myself aware of scams and not to be a victim of vulnerable financial situations such as cold calling. But this is always a worry.

As I have said before, I did find it difficult to be part of friendship groups when I was younger. Now with lots of research, we are beginning to make good friends.

- If you are the parent of an affected child / young person, please also include their ability to go to school / college, develop emotionally, form friends and participate in school/college and social life.

- What is the effect on any siblings?
- Both my daughters have this condition and it has affected them in different ways.

- What do you think of current treatments and care available on the NHS?
- We have appointments every 6months for a check up in Manchester at Salford Royal. We also have blood tests, scans and weight and blood pressure taken.
- We have not been involved in any treatment as yet.

  What operations care / support have you received?
- As a child I suffered from Glue Ear and had grommets 4 times. I also had my tonsils out when I was 16. My hearing does suffer in the winter months due to colds. My ears then fill up with fluid and I do find it difficult to hear. I get my hearing checked out also.

- Is there an unmet need for patients with this condition?

- Yes. My family and I feel there could be a lot more support out there for this condition. Throughout my education no one knew what Alpha Mannosidosis was or is. There is some information on the Internet but this is quite general and can really give different responses if someone were to read this. There are so many ways this condition impacts on an individual. We have the example of my sister and I. She has different issues but at the same time have similar to myself. The spectrum is so big also. We have this condition mildly but others have it moderately. There could be videos that explain what this condition is, given by those who are affected. More literature can be available to explain what this is. As a parent, the most difficult and frustrating issue is understanding what is part of the condition and what could be deemed as a personality trait. Where does one draw the line in distinguishing these characteristics?

- What do you think are the advantages of the potential ERT treatment? (Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life.
- There are many advantages of potential ERT treatment. At the moment we are living ‘with a ticking time bomb’. Meaning we have no idea what is going to happen with us, as we get older. So at least with treatment we would have peace of mind.
- Emotionally we would be able to feel that we are part of the whole society and not just this very exclusive group of people with the condition.

- What do patients or carers think are the disadvantages of the ERT treatment? (Consider how the treatment is given and where this may be?

- What are the conditions of giving the treatment? Is this with a needle or through drugs taken orally?
- Would there be side effects?
- How does this affect each individual?
- What are the signs of the treatment working?
- How frequently would this treatment be given?
- These are some questions we would like answered.

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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.

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