NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Velmanase alfa for treating alpha-mannosidosis [ID800]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Chiesi Limited:
   a. Updated submission May 2023
2. **Clarification questions and company responses** July 2023
3. **External Assessment Report** prepared by ScHARR July 2023
4. **Technical engagement response** from Chiesi Limited
5. **Technical engagement response from consultees and commentators:**
   a. MPS Society
   b. Case study shared by MPS Society
6. **External Assessment Group critique of company response to technical engagement** prepared by ScHARR
7. **External Assessment Report Addendum**
8. **Consultee and commentator comments on the Draft Guidance** from:
   a. Chiesi, August 2022
   b. Chiesi updated response to DG, November 2022
   c. The MPS Society, August 2022
9. **Comments on the Draft Guidance received through the NICE website**

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

Summary of clinical and cost effectiveness in patients initiating treatment in childhood (aged under 18 years)

Submitted by Chiesi Limited: 5 May 2023

File name	Version	Contains confidential information	Date
ID800_velmanase alfa_HST resubmission_paediatric addendum_05May2023_redacted		No	5 May 2023

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Executive Summary

This addendum describes new data and analyses supporting the clinical and cost-effectiveness of velmanase alfa (VA) in an optimised population of patients initiating treatment in childhood (under 18 years). It also seeks to address NICE's concerns in the second Evaluation Consultation Document (ECD2)[1] published in July 2022. Prior to this addendum, Chiesi presented an original HST submission in January 2018[2], and further analyses and clinical data were submitted in May 2019 and March 2022.[3,4]

Key updates in this addendum include:

- Narrowing the scope to patients initiating treatment in childhood (under 18 years) to optimise the cost effectiveness of VA using the current model (see Section A)
- New natural history data in untreated patients from the AllStripes study and a caregiver survey reporting disease progression of AM and its impact on quality of life (QoL) on patients and parent carers (see Section B and Appendix A)
- A summary of paediatric efficacy data presented to the FDA, including new efficacy analyses and correlation with the oligosaccharide surrogate marker (see Section C)
- A rhLAMAN-11 analysis of new clinical data from rhLAMAN-07/-09 reporting improvements in mobility, lung function and QoL in patients treated with VA up to 12 years, and real-world data from the caregiver survey supporting delayed disease progression and improved QoL in children treated with VA (see Section C)
- A simplified economic model with a new paediatric base case (all patients initiating treatment under 18 years) incorporating new clinical data to reduce uncertainty and more appropriate inputs for a paediatric population (see Section D)
- A simplified proposal for managed access, aligned with the data collection plan to be implemented by NHS Scotland after VA was accepted by the SMC into the ultra-orphan pathway in September 2022 (see Section E)

Taken together, the new clinical data, updated modelling and revised positioning strengthen the case for VA being plausibly cost-effective in patients who initiate VA in childhood. If clinical uncertainty remains in this population, Chiesi have submitted a viable data collection plan to address the issues raised by NICE in ECD2. A fair and equitable approach to managed access is especially important for patients with AM due to the very small population with no pharmacologic treatment option. When assessing uncertainty, the ultra-rare nature of AM and the low budget impact should be considered alongside the challenges associated with modelling a complex, multisystem and heterogeneous disease that affects individuals differently.

Nature of the condition

AM is an ultra-rare, lysosomal storage disorder (LSD) caused by impaired α--mannosidase enzyme activity due to mutations in the *MAN2B1* gene[5]. AM is a chronic, multi-morbid, progressive disease characterised by cognitive impairment and skeletal deformities, resulting in immobility and a reduced QoL. As α-mannosidase is present in all cells[6], oligosaccharides accumulate throughout the body.[5] 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 death. A recent study of AM

patients reported median age of death of 45 years (range 18-56 years), with 47% of deaths due to pneumonia[7]. Progressive functional impairment can result in severe immobility or wheelchair dependence, which impacts independence and activities of daily living. The impact on caregivers is underestimated who themselves experience reduced QoL, which worsens over time[8]. Parent caregivers of children with AM experience a high burden, and siblings have a 25% chance of also having AM as an autosomal recessive genetic disorder.

AM is an ultra-orphan disease, estimated to affect up to 1 in 500,000 worldwide[9,10]. In England, the MPS Society estimate there are 30 patients, with <1 new case of AM expected annually, with approximately one-third of patients currently under 18 years.[11]

Impact of VA in children

There are no disease-modifying treatments for AM currently available in England, and best supportive care (BSC) focuses on relieving symptoms[12]. Allogeneic haematopoietic stem cell transplant (HSCT) is an option for some very young patients when clinically indicated but is associated with significant mortality[5,9,13]. 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[14].

Efficacy and safety of VA was studied in the rhLAMAN clinical programme, including: rhLAMAN-05[15], a 12-month randomised placebo-controlled trial; rhLAMAN-10[16,17], an integrated analysis of 33 treated patients up to 48 months; and rhLAMAN-08, in 5 patients aged <6 years[18]. Real-world data were collected in the Etoile-Alpha study[19,20] and case reports[21,22], with ongoing data collection in the AM Sparkle registry[23].

Clinical evidence shows VA slows the natural deterioration of AM by improving walking ability, delaying disease progression and improving QoL. In rhLAMAN-10[17], children treated with VA up to 48 months showed statistically significant improvements from baseline in serum oligosaccharides, immunoglobin G (IgG) levels, 3-minute stair climb test (3-MSCT), 6-minute walk test (6-MWT) and lung function (%predicted FVC). VA also improved QoL (EQ-5D), disability status (CHAQ-DI), upper limb function/dexterity (BOT-2) and reduced rates of infection.[17,24] rhLAMAN-10 analyses showed greater benefit with VA in patients initiating in childhood when compared with those starting as adults, highlighting the importance of early treatment. New rhLAMAN-11 analyses[25] incorporating long-term rhLAMAN-07/-09 data show improvements in 6MWT, 3MSCT, %FVC and EQ-5D in children are sustained for up to 12 years into adulthood. At last observation (LO) in rhLAMAN-11, only [redacted] patient initiating VA in childhood was classed as seriously impaired on CHAQ-DI, compared to [redacted] patients at baseline.

Value for money

Updated cost effectiveness analyses compared VA + BSC vs. BSC alone in an optimised subgroup of patients initiating treatment in childhood (under 18 years). The new base-case (with PAS) results in an ICER of £101,073 per QALY. Scenario analyses show a range of potentially plausible ICERs from £49,449 to £240,050 per QALY.

Section A – Decision problem

Table 1. Statement of the decision problem

	Updated scope issued by NICE	Variation from scope presented in this addendum	Rationale for variation from scope
Population	People with AM	People with AM initiating VA in childhood (aged under 18 years)	Optimises the cost-effectiveness of VA with the current model. Supported by the biological plausibility of early treatment with ERT in childhood is more likely to show improvement.
Intervention	VA 1mg/kg IV once-weekly		
Comparator(s)	Established clinical management without VA (including, where clinically indicated, allogeneic HSCT)	Allogeneic HSCT is not considered as a relevant comparator in this submission	As justified in previous submission and addendum
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) • HRQoL (patients and carers)	As per scope	N/A

Section B – Nature of the condition

1 Disease progression in paediatric patients

1.1.1 AllStripes Study (US and UK)

AllStripes is a retrospective natural history study of untreated AM patients in the US and UK.[26] Interim data from [redacted] patients ([redacted] % male, median age [redacted] years [IQR [redacted]]) show all have mobility difficulties: most (n=[redacted], [redacted] %) were able to walk unaided at one time, but gradually [redacted] ([redacted] %) had lost the ability to walk unaided.[27] Of the [redacted] patients who used mobility aids, all used a wheelchair; [redacted] used other devices including a lift, crutches, a knee scooter and a walker boot. In this study, the age at which patients lost the ability to walk unaided varied widely, ranging from [redacted] years. Further data on symptoms, diagnosis, healthcare resource use, use of mobility aids and mobility journeys will be available at study end. The mobility journey of an untreated US patient from age [redacted] years is shown in Figure 1, with further detail in the interim report.[27]

Figure 1. AllStripes: mobility journey of an untreated US patient

Source: AllStripes interim report, 2022 [27]

ADL = activities of daily living; AM, alpha mannosidosis

Note: scale from walking at age [redacted], diagnosis at [redacted] years, ataxia/difficulty walking at [redacted] years, relying on a walker at [redacted] years, primarily using wheelchair at [redacted] years, to bed/wheelchair bound at [redacted] years

1.1.2 2022 European and UK Patient and Caregiver Survey

An international online survey of patients and caregivers was distributed by clinicians and patient organisations to inform disease progression of treated and untreated patients aged ≥10 years. The protocol was approved in October 2022[28]; [redacted] interim responses were available for this submission,[29] with a further [redacted] responses collected for the final report (due Q2 2023). A summary of interim results is shown in Table 2, with detailed responses in Appendix A. This initial snapshot highlights the extreme heterogeneity of symptoms between patients, and in general, a slow decline of mobility and other symptoms over time. These data are also supportive of the transition probabilities for untreated patients used in the model that were elicited from an expert panel of clinicians with experience of managing children with AM.

Table 2. Interim caregiver survey responses (n=21)

Carer respondent (n=6), untreated patients											
Region	Patient age now/ diagnosed		Mobility* (rated 0-10: now, 5 years ago, 10 years ago)			Patient QoL* (rated 0-10: now, 5 years ago, 10 years ago)			Carer QoL* (rated 0-10: now, 5 years ago, 10 years ago)		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer respondent (n=1), patient treated with HSCT											
Region	Patient age now/ diagnosed	Age at HSCT	Mobility* (rated 0-10: now, 5 years ago, 10 years ago)			Patient QoL* (rated 0-10: now, 5 years ago, 10 years ago)			Carer QoL* (rated 0-10: now, 5 years ago, 10 years ago)		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient respondent (n=1), patient treated with VA											
Region	Patient age now/ diagnosed	Years treated with VA	Mobility* (rated 0-10: now, 5 years ago, 10 years ago)			Patient QoL* (rated 0-10: now, 5 years ago, 10 years ago)			Carer QoL* (rated 0-10: now, 5 years ago, 10 years ago)		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Carer respondent (n=13), patient treated with VA											
Region	Patient age now/ diagnosed	Years treated with VA	Mobility* (rated 0-10: now, 5 years ago, 10 years ago)			Patient QoL* (rated 0-10: now, 5 years ago, 10 years ago)			Carer QoL* (rated 0-10: now, 5 years ago, 10 years ago)		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Abbreviations: EE, Eastern Europe; NE/UK, Northern Europe or UK; SA, South America; SE, Southern Europe; VA, velmanase alfa

Source: RDRP, 2023[29]

*Note: Mobility is rated where 0 is no problem walking about and 10 is unable to walk about; QoL is rated where 0 is the best QoL imaginable and 10 is worst imaginable.

#Patient self-rated mobility 8 now, 7 at 5 years ago and 5 at 10 years ago but stated in free text: "*Walking has become easier since ERT. Prior to this I needed a wheelchair when my knees and ankles were inflamed after walking too much*" so it is assumed the ratings are reversed: 5, 7 and 8.

§Received VA for 6 months in 2022 aged 17 years, but then discontinued

¶Patient stated they had been receiving ERT treatment for 10 years 4 months, but as they were only diagnosed at age 9 and are now aged 15 years, it is assumed this is the age that they started ERT.

2 Impact of AM on the QoL of children and parent carers

As an ultra-rare disease, the true QoL burden of AM is poorly defined. The impact of AM on both patient and carer health-related QoL (HRQoL) was described in previous submissions[2], including a published UK MPS Society survey of 9 patients and carers,[8] and caregiver feedback from rhLAMAN-10 was published as a poster in 2021[30].

Interim results of the caregiver survey of European and UK patients[29] provides further evidence on the substantial impact on parent carers of children with AM, supporting the validity of the use of new paediatric-specific carer disutility values in the updated modelling estimates. In the study, parents of children with AM describe the increasing impact on both patient and carer QoL as patient mobility declines over time (see Table 2). Many parents describe being fulltime carers due to the substantial caring needs of children with AM, including lifelong requirements for personal care, house adaptations, and specialist schools for those with cognitive impairment.

Section C – Impact of initiating VA in childhood

3 Results of relevant new clinical evidence

Subgroup analyses by age of treatment initiation for rhLAMAN-05[15], rhLAMAN-10[16,17], the multidomain responder analysis[31] are published, and unpublished results of the real-world Etoile Alpha study[20] were provided in the previous submission, but are included in Appendix B for completeness. New clinical evidence comprises: analyses requested by the FDA including a multicomponent analysis of rhLAMAN-05[32] and paediatric efficacy analyses of rhLAMAN-10 to support the association of oligosaccharides and improved clinical outcomes; a rhLAMAN-11 analysis including new long-term data from rhLAMAN-07/-09 trials[25]; and new real-world data, including case series and the caregiver survey[29] that report improved functioning and QoL in children treated with VA.

3.1 FDA paediatric efficacy analyses

3.1.1 rhLAMAN-05: New FDA Multicomponent Analysis

VA was approved by the FDA in patients of all ages on the 16th February 2023.[33] A new multicomponent analysis of rhLAMAN-05 using O'Brien's test statistics was requested by the FDA to identify multicomponent endpoints.[32] Results report both an O'Brien's ordinary least squares (OLS) statistic, as well as a generalised least squares (GLS) statistic, which accounts for correlation among endpoints to form a multi-component endpoint, resulting in greater power. This approach is particularly useful in heterogenous diseases where a single efficacy endpoint may not be feasible to be measured in all subjects, so a combination of endpoints is more useful.

The endpoints included in various multi-component combinations in rhLAMAN-05 were 3MSCT, 6MWT, FVC% predicted, CHAQ-DI and CHAQ-VAS. For the analysis, all possible combinations of ≥2 endpoints were considered and both O'Brien's OLS and GLS statistics were computed. Only results limited to combinations with significance levels < 0.10 for ≥1 of the two tests were considered.

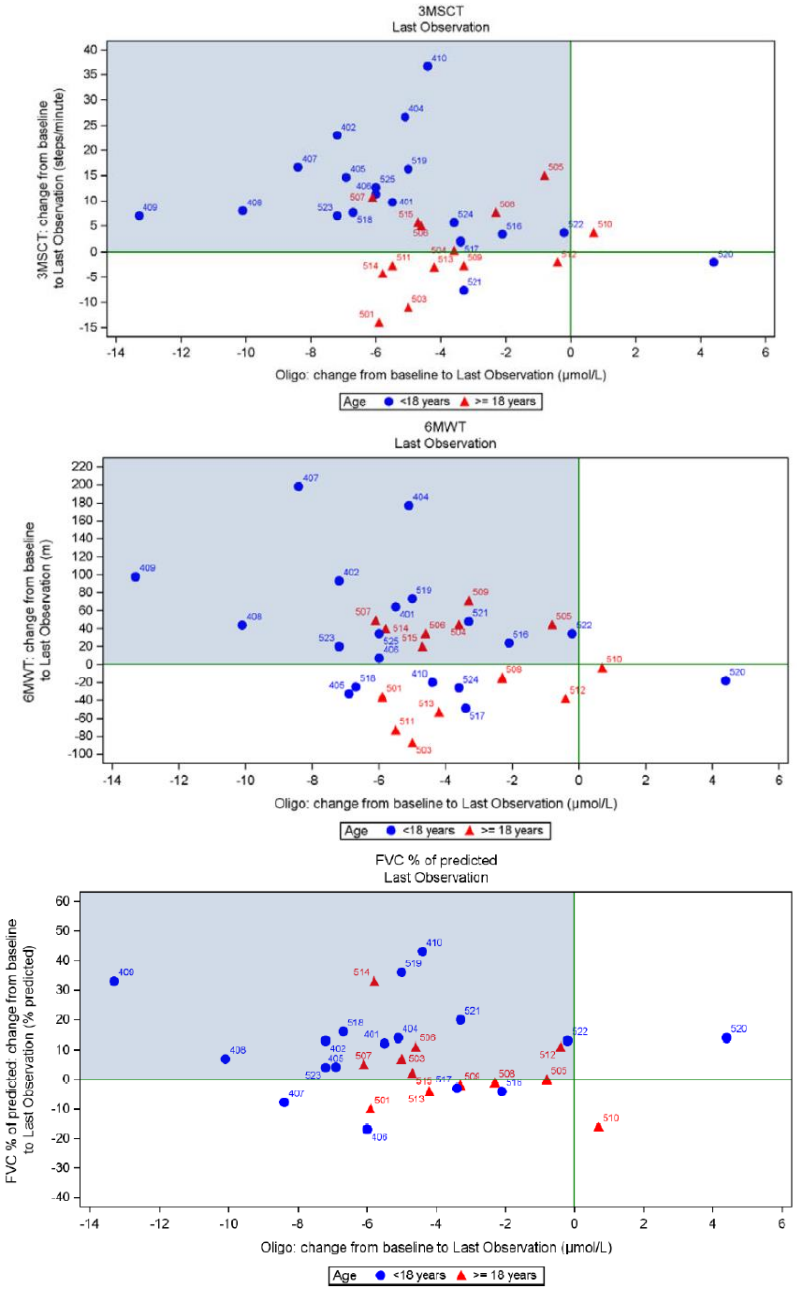
Overall in all age groups, the combinations of ([redacted]) and ([redacted]) were most significant for O'Brien's GLS statistic (p=[redacted]), reflecting the most statistically significant difference between VA and placebo groups. For paediatric subjects, the most significant combinations for O'Brien's GLS statistic were ([redacted]) and ([redacted]) (p=[redacted], equally). For adults, the combinations of ([redacted]) and ([redacted]) were most significant for O'Brien's GLS statistic (p=[redacted]). These combinations reflected the most statistically significant difference between VA and placebo by age group.

In conclusion, the most statistically significant difference between VA and placebo across all age groups and within paediatric and adult age groups was observed for a combination of [redacted] of the selected endpoints. This highlights that a selection of a single endpoint to determine efficacy for all subjects equally in a clinical trial for a heterogeneous disease like AM may not be appropriate. This new analysis also addresses some of the ERG's criticisms of the published multicomponent analysis[31] in Section 4.11 of the ECD2[1], as it removes the surrogate oligosaccharide endpoint, so is less prone to bias.

3.1.2 Correlation between Serum Oligosaccharides and Clinical Outcomes at Last Observation in rhLAMAN-10

Due to the progressive nature of AM and the irreversible tissue and organ damage that occurs over time, the efficacy profile of VA may differ in adults when compared with younger patients. As such, the correlation between serum oligosaccharide reduction and improvements in clinical outcomes (3MSCT, 6MWT and FVC % predicted) may be more evident in subjects with early disease (i.e., paediatric subjects), compared with those at advanced or irreversible stages of AM (i.e., particularly adult subjects). Figure 2 shows the correlation for all 3 clinical outcomes in rhLAMAN-10 by age group.

Figure 2. rhLAMAN-10: correlation between serum oligosaccharides and 3MSCT, 6MWT and FVC % Predicted



Abbreviations: 3MSCT, 3-Minute Stair Climb Test; 6MWT, 6-Minute Walk Test; m, metres; Oligo, oligosaccharides; FVC, Forced vital capacity.

Note: Age group based on subject's age on date of first VA dose. Actual date of first VA dose was collected for subjects enrolled in rhLAMAN-02, rhLAMAN-05 VA group, and rhLAMAN-05 placebo group who transitioned into rhLAMAN-07/-09. For subjects enrolled in rhLAMAN-05 placebo group who transitioned into Compassionate Use, date of first VA dose was estimated as the last day of dosing in rhLAMAN-05 + 7 days.

Source: Chiesi on file, FDA paediatric addendum 2022[32]

Results show most participants in rhLAMAN-10 fell wholly into the shaded upper left quadrant, demonstrating a favourable negative correlation between serum oligosaccharides and 3MSCT, 6MWT and FVC% predicted. By age group, a greater proportion of paediatric subjects aged ≥6 to <18 years than adults had an associated

improvement in both serum oligosaccharides and the clinical outcomes at LO. For 3MSCT, 17 of 19 (89.5%) paediatric subjects vs. 6 of 14 (42.9%) adults had an associated change. For 6MWT, 13 of 19 (68.4%) pediatric subjects and 7 of 14 (50.0%) adults had an associated improvement. For FVC %predicted, 12 of 17 (70.6%) paediatric subjects and 7 of 12 (58.3%) adults had an associated change at LO.[32]

3.2 rhLAMAN-11: integrated analysis of long term clinical trial data

The new rhLAMAN-11 analysis updates the published rhLAMAN-10 study using the same methodology[25], but integrates a further 7 years of follow-up data from 15 patients treated with VA in the rhLAMAN-07/-09 long-term extension trials (see Table 18 for trial designs and Figure 1 in Appendix C for parental studies).

rhLAMAN-11 integrates new data from rhLAMAN-07 (N=13) and rhLAMAN-09 (N=8). The analysis compares outcomes up to 12 years at last observation (LO) with baseline values on entering the rhLAMAN programme. The final rhLAMAN-11 analysis includes data from 33 patients: 19 patients initiating VA <18 years and 14 patients initiating VA ≥18 years. Compared to the previous integrated analysis, the follow-up is increased to up to 144 months in 2 subjects. Mean (SD) duration of treatment in rhLAMAN-11 until LO for the coprimary endpoint of 3MSCT was [redacted] years for <18 years and [redacted] years for ≥18 years. A summary of results are included below, with detailed results of rhLAMAN-11 included in Appendix C.

3.2.1 rhLAMAN-11: co-primary endpoints, by timepoint and age

Results show the significant reductions in serum oligosaccharides seen within 12 months in rhLAMAN-05 and maintained in rhLAMAN-10 up to 48 months (P<0.001 vs. baseline) were sustained in all patients to LO in rhLAMAN-11 (Table 3). For the 3MSCT coprimary endpoint, overall improvements vs. baseline were seen in rhLAMAN-10 up to 48 months (P=0.004), but were only significant in paediatric patients compared with adults (P<0.001 and P=0.784 vs. baseline, respectively). In rhLAMAN-11, significant improvements in 3MSCT vs. baseline were maintained long-term in paediatric patients for up to 12 years (p=[redacted] vs. baseline) (Table 4).

Table 3. rhLAMAN-10/-11: serum oligosaccharides by timepoint and age

Timepoint	Change from baseline	Overall N=33	<18 years n=19	≥18 years n=14
Baseline	Actual value (SD), µmol/L	6.90 (2.30)	7.63 (2.52)	5.91 (1.54)
rhLAMAN-10 to LO (up to 4 years)	Mean change (SD), µmol/L	-4.59 (3.23)	-5.26 (3.74)	-3.68 (2.20)
	Relative mean change (SD), %	-62.8% (33.61)	-66.6% (36.09)	-57.6% (30.46)
rhLAMAN-11 to LO (up to 12 years)	**Mean change (SD), µmol/L**	[redacted]	[redacted]	[redacted]
	Relative mean (SD) % change	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation. New data are shown in **bold**.

Sources: Lund 2018[16] and Chiesi data on file, Feb 2023.[25]

Table 4. rhLAMAN-10/-11: 3MSCT by timepoint and age

Timepoint	Change from baseline	Overall N=33	<18 years n=19	≥18 years n=14
Baseline	Actual value (SD), steps/min	53.60 (12.53)	53.00 (11.82)	54.04 (13.34)
rhLAMAN-10 to LO (up to 4 years)	Mean change (SD), steps/min	+6.39 (10.54)	+10.65 (10.32)	+0.60 (7.97)
	Relative mean change (SD), %	+13.8% (25.8)	+23.1% (27.3)	+1.1% (17.7)
rhLAMAN-11 to LO (up to 12 years)	**Mean change (SD), steps/min, p-value [95% CI]**	[redacted]	[redacted]	[redacted]
	Relative mean % change (SD), p-value [95% CI]	[redacted]	[redacted]	[redacted]

Abbreviations: 3MSCT, 3-minute stair climb test; SD, standard deviation. New data are shown in **bold.**
Sources: Lund 2018[16] and Chiesi data on file, Feb 2023.[25]

3.2.2 rhLAMAN-10/11: secondary endpoints by age

A summary of the secondary endpoint results in rhLAMAN-10 and -11 are shown in Table 5 and Table 6, respectively. Results show not only long-term disease stabilisation with VA treatment in paediatric patients, but long-term improvements in 6MWT and lung function from baseline to LO. As these are data up to 12 years and age-adjusted measures also show improvements, these results are unlikely to be due to growth. In children, improved EQ-5D was also maintained from baseline, supporting a long-term on-treatment utility benefit with VA. In all patients, a statistically significant improvement from baseline in serum IgG was maintained in rhLAMAN-11, a surrogate marker for immunological status, indicative of the reduction in infections observed in rhLAMAN-10[24] and in real-world studies[19].

Table 5. rhLAMAN-10: analyses by age-group up to 4 years

Endpoint	Patients (<18, n=19; ≥18, n=14)	Baseline; mean (SD)	Change from baseline to LO: mean, SD (%,[SD])	p-value [95% CI]
6MWT (metres)	**Paediatric**	**454.2 (86.3)m**	**+ 39.1 (67.6) m (11.9% [26.6])**	**P=0.002 [9.97; 36.25]**
	Adult	483.3 (95.6)m	+0.3 (50.5) m (0.7% [11.6])	P=0.021 [6.50; 71.66]
Age-adjusted 6MWT (% of predicted)	**Paediatric**	**69.34 (12.39)%**	**+1.87 (10.56)% (+5.37 [22.04])%**	**NR**
	Adult	68.64 (11.01)%	+0.21 (7.51)% (+1.09 [1.86]%)	NR
FVC (L)	**Paediatric (n=17)**	**2.24 (0.93) L**	**+0.9 (0.7) L (+45.9 [39.1]%)**	**NR**
	Adult (n=12)	3.23 (1.05) L	+0.2 (0.4) L (+3.5 (16.3)%)	NR

Age-adjusted FVC (% of predicted)	**Paediatric (n=17)**	**79.6% (16.4)**	**(11.6% [15.7])**	**P=0.007 [3.57; 19.67]**
	Adult (n=12)	92.5% (19.4)	(3.0% [12.4])	P=0.418 [-4.85; 10.85]
EQ-5D-5L	**Paediatric (n=10)**	**0.697 (0.184)**	**+0.083 (0.136)**	**NR**
	Adult (n=14)	0.568 (0.142)	+0.027 (0.134)	NR
Serum IgG (g/L)	**Paediatric**	**8.68 (6.10) g/L**	**+3.24 (1.92) g/L (+51.72 [33.28]%)**	**NR**
	Adult	8.14 (2.32) g/L	+2.91 (1.31) g/L (+38.61 [21.62]%)	NR

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; FVC, forced vital capacity; IgG, immunoglobulin G; LO, last observation; SD, standard deviation.

Source: Lund et al., 2018[16]; Borgwardt et al., 2018[17]

Table 6. rhLAMAN-11: efficacy analyses by age-group up to 12 years

Endpoint	Patients (<18, n=19; ≥18, n=14)	Baseline; mean (SD)	Change from baseline to LO: mean, SD (%,[SD])	p-value [95% CI]
6MWT (metres)	**Paediatric**	**454.2 (86.3)m**	[redacted]	[redacted]
	Adult	483.3 (95.6)m	[redacted]	[redacted]
Age-adjusted 6MWT (% of predicted)	**Paediatric**	**69.34 (12.39)%**	[redacted]	[redacted]
	Adult	68.64 (11.01)%	[redacted]	[redacted]
FVC (L)	**Paediatric (n=17)**	**2.24 (0.93) L**	[redacted]	[redacted]
	Adult (n=12)	3.23 (1.05) L	[redacted]	[redacted]
Age-adjusted FVC (% of predicted)	**Paediatric (n=17)**	**79.6% (16.4)**	[redacted]	[redacted]
	Adult (n=12)	92.5% (19.4)	[redacted]	[redacted]
EQ-5D-5L	**Paediatric (n=10)**	**0.697 (0.184)**	[redacted]	[redacted]
	Adult (n=14)	0.568 (0.142)	[redacted]	[redacted]
Serum IgG (g/L)	**Paediatric**	**8.68 (6.10) g/L**	[redacted]	[redacted]
	Adult	8.14 (2.32) g/L	[redacted]	[redacted]

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; FVC, forced vital capacity; IgG, immunoglobulin G; LO, last observation; SD, standard deviation.

Source: Chiesi data on file, Feb 2023.[25]

3.2.3 rhLAMAN-10/11: change in disability status by age over time

Change in mobility status and use of walking aids in rhLAMAN-10 and rhLAMAN-11 were measured using CHAQ-DI (Table 7 and Table 8). Long-term results up to 12 years show the disability status of children treated with VA had not progressed during this time, supporting a long-term delay in disease progression in the model. In addition, [redacted] children were severely impaired at baseline, whereas only [redacted] remained in this

category at LO, showing improvement in disability status over time with VA. In contrast, some adults experienced worsening of disability status, highlighting the importance of early treatment with VA. These results provide robust clinical inputs in the model for the delay in disease progression (6 years) and also support the expert assumptions on the %backwards transitions with VA and lack of forwards transitions, reducing the uncertainty on the improvement in walking status seen in children treated with VA.

Table 7. rhLAMAN-11: CHAQ-DI by Age Group

		Baseline	Last observation			
			Duration until LO (yrs)	Actual value	Change from baseline	%change from baseline
<18 years	n Mean (SD) Median Min; Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥18 years	n Mean (SD) Median Min; Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Chiesi data on file, Feb 2023.[25]

Table 8. rhLAMAN-10/-11: change in CHAQ-DI status, by age and time

	Statistic	< 18 years (N=19)	>= 18 years (N=14)	Total (N=33)
Baseline				
Not/Poorly Impaired	n (%)	8 (42.1)	3 (21.4)	11 (33.3)
Impaired	n (%)	5 (26.3)	8 (57.1)	13 (39.4)
Seriously Impaired	n (%)	6 (31.6)	3 (21.4)	9 (27.3)
Total	n (%)	19 (100.0)	14 (100.0)	33 (100.0)
Last Observation in rhLAMAN-10 (up to 4 years):				
Not/Poorly Impaired	n (%)	10 (52.6)	2 (14.3)	12 (36.4)
Impaired	n (%)	8 (42.1)	7 (50.0)	15 (45.5)
Seriously Impaired	n (%)	1 (5.3)	5 (35.7)	6 (18.2)
Total	n (%)	19 (100.0)	14 (100.0)	33 (100.0)
Last Observation in rhLAMAN-11 (up to 12 years):				
Not/Poorly Impaired	**n (%)**	[redacted]	[redacted]	[redacted]
Impaired	**n (%)**	[redacted]	[redacted]	[redacted]
Seriously Impaired	**n (%)**	[redacted]	[redacted]	[redacted]
Total	**n (%)**	[redacted]	[redacted]	[redacted]

Note: patient status is categorized on the following CHAQ-DI scores: not impaired/poorly impaired = 0-≤1, impaired = >1- ≤2 and seriously impaired = >2 to 3. The questionnaire asks for each topic whether help is needed and the use of aids or devices is questioned. If either help or any aids or devices are used for the topic, the score should be at least 2 ("with much difficulty"). This means that a score of 0 or 1 will be changed to a score of 2 if help or aids are used, while scores of 2 or 3 will remain as they are.
Source: Borgwardt et al., 2018[15] and Chiesi data on file, Feb 2023.[25]

3.3 New real-world data in children: 2022 caregiver survey and case reports

In the UK, no children with AM have been treated with ERT, so clinical paediatric experience of VA in LSD centres is lacking. In the previous submission, patient case reports from Etoile Alpha highlighted improvements seen in children treated long-term with VA (included in Appendix B for ease of reference).[19] Interim responses of the European caregiver survey included 6 patients treated with VA since childhood (see Table 2 and Appendix A).[29] These real-world data support the results of rhLAMAN-11 and highlight how early treatment with VA can prevent the deterioration in walking ability, with long-term stabilisation or improvements in mobility reported by treated patients, whereas patients who were untreated can experience disease progression.

New case reports of children in Europe treated with VA include 3 infants treated with VA as a bridging treatment for HSCT[32] and a 7-year-old in Italy treated for 18 months.[34] The 7 year old treated with VA showed substantial improvements in hyperactivity, 6MWT, comprehension, verbal expression and hearing loss. A net reduction in respiratory infections was reported with antibiotic use reduced from 20 times a year before treatment to 3 times a year, with no apnoea or night desaturation, no more electrical abnormalities on EEG, and improved QoL of the family was reported.

4 Measurement and valuation of health effects

4.1 Updates to QoL data used in cost-effectiveness analysis

Changes to the utility values in the updated base-case analysis are shown in Table 9. Other utility values are unchanged from the previous submission, as the committee's preferred values from ECD2.

Table 9. Summary of updates to utility values

State / variable	Utility value / disutility	Justification and references
VA on-treatment respiratory utility benefit	0.2 utility gain per +1L[35] = +0.9L[16] x 0.2 = **0.18**	HST committee preferred assumption of utility gain for respiratory benefit in HST2/HST19[35]; rhLAMAN-10 +0.9L FVC in patients <18 years[16]; respiratory gains are not included in the model as accepted in ECD2[1]
Health state caregiver disutility – WU	0.08 x 1.5 = **0.12**	Updated with paediatric-specific caregiver disutility values from type 2/3 SMA from TA755[36] Calculated for 1.5 caregivers – multiple caregivers are appropriate for children with AM who are cared for by their parents and have a 25% chance of an affected sibling – see caregiver survey (Table 2)
Health state caregiver disutility – WWA	0.08 x 1.5 = **0.12**	
Health state caregiver disutility – WC	0.16 x 1.5 = **0.24**	
Health state caregiver disutility – SI and SES	0.16 x 1.5 = **0.24**	

SMA = spinal muscular atrophy; WU, walking unassisted; WWA, walking with assistance; WC, wheelchair bound; SES = short end stage; SI = severely impaired

Children treated with VA in rhLAMAN-10 reported a statistically significant +0.08 utility gain from baseline in the 10 of 19 children who completed the EQ-5D-5L, a benefit that was maintained long-term in rhLAMAN-11. In ECD2[1], the committee accepted that the observed ED-5D utility gains may be underestimated due to difficulties in assessing QoL in children with AM with cognitive impairment, as well as the potential non-mobility QoL benefits of VA not accounted for in the model, such as improvements in lung function, minor infections, pain, minor surgeries, psychiatric complications, and within-state mobility improvements. In HST2/HST19 for MPSIVa, the committee accepted a surrogate utility benefit for increased respiratory function in a similar walking state-based model for an LSD with similar natural history to AM, with a +0.2 utility gain per 1L gain in FVC.[35] For these reasons, an on-treatment respiratory utility gain of 0.18 has been kept in the company base-case, calculated from the +0.9L gain observed in rhLAMAN-10 in 17 children at LO. A scenario analysis using an on-treatment respiratory utility gain of 0.256 calculated from the greater long-term +1.28L gain observed at LO from rhLAMAN-11 is also presented in Table 15.

Caregiver disutilities have been updated with paediatric-specific disutilities that were accepted for TA755 for type 2/3 SMA to better reflect the new population. In type 3 SMA, varying degrees of muscle weakness appear between 18 months and 18 years: people with this condition can have a normal lifespan and walk or sit unaided, but many lose mobility and other functions over time.[36] Disutilities used in the previous submission were for caregivers of older adults with MS and are not in line with HTA recommendations from Pennington et al. 2022.[37] As reported in the caregiver survey (Table 2), children with AM are mostly looked after by their parents and more than 1 child may be affected by AM; as such, the base case now includes 1.5 caregivers across health states. The caregiver survey also highlighted the heavy QoL carer burden that worsens as patients' mobility declines. A scenario analysis of 2.2 caregivers in line with the committee's preferred assumptions in TA755 is also presented in Table 15.

Section D – Value for Money

1 Updated economic analysis

In the original submission, Chiesi developed a de novo economic model that compared VA and BSC in terms of costs and QALYs in all patients with AM. The Markov model included data from 33 adults and children treated with VA in rhLAMAN-10 and the multi-domain responder analyses[31], and although limited, represented a substantial proportion of the diagnosed AM population. The Committee concluded in ECD2 that *"… the overall model structure was adequate for decision-making".*[1] In this addendum, the structure of the walking-based model is the same, but has been updated to better reflect the new optimised subpopulation of patients who initiate VA in childhood (under 18 years). In addition, the model includes more clinical data from rhLAMAN-11 in children treated with VA up to 12 years, supported by real-world data from the Etoile Alpha study[19], the caregiver survey and case reports[21].

The revised model uses a simplified and conservative 6-year delay in disease progression to account for the observed effect of VA in the relevant subpopulation, using the mean treatment duration of children treated with VA in rhLAMAN-11 (mean 6.3 years, range 1.0-11.8 years). Previously, expert elicitation assumptions from 2017 were used to estimate the transition probabilities with VA in 3 separate subgroups, before the availability of long-term data and subject to uncertainty. In this updated model, these VA-specific transition probabilities have been removed to reduce the uncertainty in the treatment effect. Instead, as a conservative assumption, both arms use the same transition probabilities estimated by clinical experts for patients treated with BSC, with the treatment effect of VA accounted for by the simplified delay in disease progression and the greater % of patients who backwards transition (ie. improve walking ability and change health state). The new clinical data from rhLAMAN-11 and the single population increase the certainty in these expert estimates for %backwards transitions and lack of forward transitions with VA, evidenced by improvements in CHAQ-DI in children up to 12 years, supported by long-term mobility improvements observed in children in real-world studies[20]. The model also keeps the on-treatment respiratory utility benefit (0.18) from the previously submitted base case, to account for long-term improvements in age-adjusted lung function observed in children in rhLAMAN-11 and the elimination of respiratory infections seen in clinical trials and real-world studies. Finally, caregiver disutilities have been updated to paediatric-specific values to more appropriately reflect the QoL burden of parents who care for a child with an ultra-rare genetic disorder, often with affected siblings, in line with similar HST assessments.

Updated cost effectiveness analyses compared VA + BSC vs. BSC alone in an optimised subgroup of patients initiating treatment in childhood (under 18 years). The new base-case (with PAS) results in an ICER of £101,073 per QALY. Scenario analyses show a range of potentially plausible ICERs from £49,449 to £240,050 per QALY.

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

A summary of the updates to the model is shown in Table 10. A detailed summary of the clinical variables used in the updated model is included in Appendix D.

Table 10. Updated model inputs

Parameter		Assumption	Source(s)
1	**Disease progression delay**	In multi-domain responders, there is a **6-year delay** before disease progression can occur.	rhLAMAN-11: mean treatment duration of [redacted] years in 19 children treated with VA – see Section 3.2.3
	Disease progression	After the 6-year delay in progression, multi-domain responders treated with VA now have the same rate of progression as those on BSC, since **the 2017 expert elicitation estimates for VA have been removed to reduce the uncertainty –** however this may underestimate the treatment benefit of VA as treated patients are likely to have a slower rate of progression than untreated patients.	2017 UK Expert Elicitation Panel[38]
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), eg. from WWA to WU:	2017 UK Expert Elicitation Panel[38]; unchanged but now supported by improvements in CHAQ-DI in rhLAMAN-11[17]; supported by Etoile Alpha and real-world case series
	Years 1 and 2	During 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	**VA on-treatment respiratory utility gain**	Improved clinical outcomes for VA-treated patients vs. BSC-treated patients translates into greater HRQoL. An **on-treatment respiratory utility gain of 0.18** is calculated from the +0.9L FVC gain in the paediatric subgroup in rhLAMAN-10 and the +0.2 utility gain per 1L FVC in HST2/HST19 Numerous QoL aspects of AM are incompletely captured in the model structure including lung function, lack of minor infections, pain and within state mobility gains	rhLAMAN-10: FVC gain; HST2/HST19 on-treatment respiratory utility gain – see Table 9
4	**Caregiver disutility**	Paediatric-specific caregiver disutilities have been applied for each health states in line with type 2/3 SMA: **WU, 0.08; WWA, 0.08; WC, 0.16; SI/SES, 0.16.** Parent caregivers experience a significant disutility due to caring for child(ren) with multiple and extensive clinical needs (e.g., behavioural, mobility-related, selfcare, activities of daily living) – updated to **1.5 caregivers** to account for both parents and siblings, with a 25% chance of affected siblings	TA755[36] type 2/3 SMA caregiver disutility; Caregiver survey – see Table 9

Abbreviations: FVC = forced vital capacity ; SMA = spinal muscular atrophy; UK = United Kingdom; VA = velmanase alfa; WU, walking unassisted; WWA, walking with assistance; WC, wheelchair bound; SES = short end stage; SI = severely impaired.

1.2 Results of updated economic analysis

1.2.1 Base-case results

Base-case results for VA vs. BSC in the optimised paediatric cohort are presented below. The settings for the base-case are shown in Table 11. With PAS, the ICER for VA vs. BSC was £101,073 in the new optimised population, as shown in Table 12 and Table 13. Deterministic results are presented in the base-case, due to linearity in the economic model and Probabilistic Sensitivity Analyses are presented in Section 1.2.2.

Table 11. Updated base-case model settings

Parameter	Setting
Perspective	NHS England and Personal Social Services
Time horizon	Lifetime (100 years)
Population	Paediatric (patients initiating in childhood under 18 years)
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 for 1.5 caregivers

Abbreviation: NHS = National Health Service

Table 12. Cost-effectiveness results: patients initiating in childhood

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
VA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£101,073

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

Table 13. New company base case: impact of changes from previous submission: patients initiating treatment in childhood

	Incremental (VA-BSC)		
	Costs	QALYs	ICER
Company's previous paediatric base case	[redacted]	[redacted]	£88,912
1) Removing VA-specific transition	[redacted]	[redacted]	£85,380

	Incremental (VA-BSC)		
	Costs	QALYs	ICER
probabilities and increasing delay in disease progression to 6 years			
2) Updating baseline starting distribution to reflect new population and starting criteria (no WC)	[redacted]	[redacted]	£87,029
3) Updating on-treatment utility benefit to reflect paediatric respiratory gain observed in rhLAMAN-10 (0.18)	[redacted]	[redacted]	£100,095
4) Updating carer disutility values to those appropriate for children from type 2/3 SMA	[redacted]	[redacted]	£91,040
5) Increasing the number of caregivers to 1.5 to reflect the new population	[redacted]	[redacted]	£78,274
6) Combining 1), 2), 3) 4) and 5): new company base case	[redacted]	[redacted]	£94,716
7) Revising the transition matrix and correcting a linking mistake	[redacted]	[redacted]	£104,596
8) Combining 6), 7), and 8): new company base case	[redacted]	[redacted]	£101,073

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

1.2.2 Updated sensitivity analysis results

Updated results from the univariate sensitivity analyses were plotted in a tornado diagram to visualise the order and magnitude of the impact of each parameter on the ICER (Figure 3). 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 annual probability of withdrawal, and the mortality rate from severe infection. 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 15.

Figure 3. Tornado diagram: new paediatric cohort

Probabilistic Sensitivity Analysis: New paediatric cohort

The results of the PSA (based on 1,000 simulations for the paediatric cohort are shown in Table 14 and Figure 4. The cost-effectiveness acceptability curve (CEAC) is shown in Figure 5. The probability of being cost-effective at a threshold of £100,000 per QALY is [redacted]

Table 14. Base case PSA results – new 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]	£100,153 (CI: £54,381 : £153,102)

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

Figure 4. Base case PSA scatterplot of VA vs BSC – new paediatric cohort

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

Figure 5. Base case PSA CEAC – new paediatric cohort

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

Scenario Analysis: new paediatric cohort

Results of the scenario analyses are shown in Table 15. These scenario analyses show 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.

1.2.3 Summary of updated cost effectiveness analysis

The changes made to the model for this addendum reflect the new optimised population of patients initiating VA in childhood, with inputs that are more appropriate for paediatric patients with AM and their parent carers. New long-term clinical data from the paediatric subgroup in rhLAMAN-11 increases the certainty of the inputs and the robustness of the results. The new base-case with-PAS ICER of £101,073 per QALY is more robust, but may be conservative, as it uses a simplified 6-year delay in disease progression that removes outdated expert elicitation assumptions for additional time in health states with VA. Long-term data show the delay in disease progression may be substantially longer than 6 years, with children treated with VA up to 12 years showing improved functioning from baseline. Scenario analyses show a range of potentially plausible ICERs from £49,449 to £240,050 per QALY.

Table 15. Key Scenario Analyses

Scenario	Scenario detail	ICER	Rationale and impact of new clinical data on plausibility
Base case	-	£101,073	New base case uses a conservative 6-year delay in disease progression (evidenced from the mean [redacted] year treatment duration in rhLAMAN-11) then the same transition probabilities as BSC
Include personal and caregiver expenditure		£103,004	Including personal and carer expenditure has a negligible impact on the ICER. There are very limited data that report personal expenditure for families caring for a disabled child. The value is likely to be very specific to each family and their own personal circumstances.
Include caregiver productivity loss	Include caregiver productivity losses due to reduced earnings	£153,717	Including caregiver productivity loss increases the ICER. The model includes the functionality for time spent caring for a person with AM to be distributed between professional care (costed as a PSS cost) or personal care (potentially accounted for as reduced productivity. As patients become less mobile, a greater proportion of their caring is provided professionally, so the impact of including caregiver productivity is there is a reduction in the productivity loss as a patient becomes less mobile, which may be a counterintuitive situation. In reality, it may be the case that as a person becomes more disabled, they may require professional care as well as a carer to retire or reduce their working hours to provide care. The provision of personal caregiver and professional care will be a complex case-by-case situation that takes into account the caregiver finances, employer benefits, social care provisions locally, the ability of caregivers to provide significant care etc. As such, caution should be taken when considering this scenario.
Time horizon 50 years	-	£96,343	New AM mortality data show a median age of death of 45 years (range 18-56 years), with 47% of deaths due to pneumonia[7]. Reducing the time horizon of the model from 100 to 50 years reduces the ICER.
No annual withdrawal	No treatment discontinuation for responders until entering 'WC' health state	£240,050	Removing annual discontinuation after year 1 increases treatment costs and the ICER. Clinical trial and real-world data support discontinuation rates in paediatric patients. Clinical advice suggests this scenario is not plausible for a once-weekly IV infusion and stopping rules for ERTs are routine practice in NHS LSD centres.
Permanent delay in progression	A permanent delay in disease progression in VA responders until treatment discontinuation	£49,449	New rhLAMAN-11 data and real-world evidence suggest not only a long-term delay in disease progression of at least 6 years, but trial data in children support disease improvement up to 12 years, which suggests that a permanent delay in disease progression is plausible and that the base case is conservative.
Discontinue if WC dependent	Treatment is discontinued upon entering the 'WC dependent' health state	£102,213	Including a stopping rule upon WC dependence has a negligible impact on the ICER. Clinical practice suggests this scenario may be plausible for a once-weekly IV infusion and stopping rules for ERTs are routine practice in NHS LSD centres.
UK MPS Society Health State Utilities	MPS Society Survey utility values are used for HSUVs	£78,722	HSUVs for AM are subject to uncertainty due to the small and heterogeneous patient population. Using alternative sources of HSUV collected from a relevant patient population in the UK reduces the ICER.
rhLAMAN-11 utility benefit	Include long-term on-treatment respiratory utility benefit from rhLAMAN-11 **(+0.256)**	£86,180	Long-term rhLAMAN-11 results show statistically significantly improved lung function (FVC and FVC % predicted) from baseline – new results show greater improvements in FVC in children at last observation in rhLAMAN-11 (up to 12 years) compared with rhLAMAN-10 (up to 4 years) which show long-term improvements in respiratory function with VA are sustainable and plausible, which are supported by real-world data.
Exclude carer disutility	Exclude carer disutility	£94,760	Removing carer disutility reduces the ICER as patients on VA live longer which impacts carer QoL.
Include 2.2 caregivers		£88,224	Caring for a child(ren) with AM impacts on multiple caregivers, including other parents, grandparents and siblings as shown in the new caregiver survey. In TA755, 2.2 caregivers was accepted for a similar genetic disorder (type 2/3 SMA). As such, the base case with 1.5 caregivers may be conservative and a scenario with 2.2 caregivers is plausible.

Abbreviations: BSC, best supportive care; HSUV, Health State Utility Values, ICER = incremental cost-effectiveness ratio; LSD, lysosomal storage disorders; MPS = mucopolysaccharidosis; VA = velmanase alfa; WC, wheelchair dependent

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.

In 2023, the UK MPS Society Patient Registry comprised 23 living patients with AM in England and Wales, however, it is thought there are approximately 30 patients with AM in total, with approximately one-third aged under 18 years.[11] As previously, we have assumed 1 new AM case per year as a midpoint estimate. The UK MPS Society Patient Registry reports that 85.7% of AM cases in England and Wales were diagnosed when the person was under 18 years.

Annual mortality probabilities for patients under 18 years are taken from the economic model. The budget impact calculations assume that 13.3% of patients will discontinue due to being a non-responder; after Year 1 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 16.

Chiesi has estimated market share figures for paediatrics ([redacted]), which are assumed to be constant across the next 5 years. The total number of patients/treated patients is presented in Table 16. It is estimated that in Year 1, [redacted] patients will be treated with VA, increasing to [redacted] patients by Year 5.

Table 16. Patients initiating VA in childhood: treated patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	10	11	12	13	14
Incident population	1	1	1	1	1
Total patients	11	12	13	14	15
Mortality	1.00%	1.00%	1.00%	1.00%	1.00%
Net number of patients	11	12	13	14	15
Market share	[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]

Budget impact calculations for the new cohort is provided in Table 17. These calculations take into account the increase in treatment cost as weight increases in children. Administration costs follow the assumptions in the economic model, with an annual cost of [redacted] in Year 1 (incident population) and [redacted] in subsequent years due to the switch to homecare provision.

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

Table 17. Budget impact – paediatric cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	£7,867.77	£7,182.75	£7,182.75	£7,182.75	£7,182.75
Annual drug budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative drug budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact		[redacted]	[redacted]	[redacted]	[redacted]

2.1 Benefits not captured in updated cost-effectiveness analysis

While the model attempts to capture the negative health and QoL impact of untreated AM and the positive impacts of VA on patient length and QoL in the QALY, some QoL and societal aspects impacting patient and carers, such as pain, 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[21]. 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.

Section E – Proposal for Managed Access

Table 18 describes clinical studies with VA (rhLAMAN-07/-09), and natural history studies including untreated and treated patients (SPARKLE registry and the AllStripes study) that together will provide additional evidence to address NICE's uncertainties in the clinical effectiveness of VA. The table provides details of patient-reported outcome measures (PROMs), real-world data, and patient eligibility and an estimation of patient numbers for each study.

This data collection plan for VA in England is aligned with the data collection plan that will be implemented in Scotland until 2026 as part of the ultra-orphan pathway.[39]

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

Key uncertainties identified 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
- HRQoL 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

During a period of managed access, most data will be collected in the SPARKLE registry. All patients with AM in England and Wales can be recruited into the SPARKLE registry for the purposes of data collection. SPARKLE is an ongoing European registry with 60 patients recruited so far and ~100 total participants expected. The protocol was published by Hennerman et al. 2020.[23] Yearly interim analyses of SPARKLE data are prepared and submitted to the EMA; two-year safety data in 40 patients are already available, and data from the SPARKLE 2026 interim report will be submitted and used to inform a restructured economic model as part of a resubmission at the end of any managed access period.

Table 19 describes data that can be collected over the next 3-5 years and analyses that could be used to update the current cost-utility analysis to address key uncertainties as part of a resubmission at the end of a managed access period.

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 18. Clinical data sources

Study name (acronym)	Study design	Eligible population (N)	Intervention	Comparator	Outcomes to be collected	New data to be generated during managed access (Est. completion date)
rhLAMAN-07 (NCT01908712)	Open-label, long-term safety and efficacy trial in France	Patients in France treated with VA (N=16)	VA 1mg/kg	None	Safety (primary), including the following: • Adverse Events • Anti-drug antibodies • Efficacy (secondary), including the following: – Serum oligosaccharides – 6MWT – 3MSCT – FVC – BOT-2 – Leiter-R – PTA – EQ-5D-5L – CHAQ DI and VAS	Up to 12 years of follow-up data will be available from 21 patients treated long-term with VA (LPLV September 2022, final CSR in Q1 2023 for both trials)
rhLAMAN-09 (NCT01908725)	Open-label, long-term safety and efficacy trial in Europe	Patients based in Norway and Poland and previously completing rhLAMAN studies (N=8)				
AM registry (SPARKLE)	Multicentre, post-authorisation non-interventional, effectiveness and safety, prospective and retrospective real-world study	Patients based in Europe with a confirmed diagnosis of AM Up to N ~ 100 expected, 60 recruited – includes centres in the UK	All patients with AM (VA, BMT, HSCT, investigational treatment, best supportive care)	None	Outcomes to be collected as part of routine clinical practice, which can include the following: • Serum oligosaccharides • 3MSCT (steps in 3 mins) • 6MWT (m) • 2MWT (m) (below age 4) • FVC (L and % of predicted) • EQ-5D-5L • Zarit Burden Interview	Real-world registry with 3 additional years of follow-up (5 years total) in at least 16 treated and 24 untreated patients will be available by end 2025. 4 sites recruited in England (1 pending in Wales). Any new patients treated with VA in England can be recruited in collaboration with specialist LSD centres.

Study name (acronym)	Study design	Eligible population (N)	Intervention	Comparator	Outcomes to be collected	New data to be generated during managed access (Est. completion date)
					• CHAQ DI and VAS • Rate and length of infection (requiring antibiotics or not) • Serum IgG, IgA and IgM • Rate of psychotic events • Height, weight, growth rate • Hearing test (PTA) • Procedures and medications • Safety: (S)AEs, ADA, IRRs	(15-year follow-up planned with yearly interim reports, estimated completion of SPARKLE in 2038)
All Stripes study	Retrospective natural history real-world cohort study in US, Canada and UK	Patients with AM with no prior HSCT (N=15, a subset of 5 patients without a confirmed genetic diagnosis will be separately analysed)	Not specified – all patients eligible irrespective of treatment (except HSCT)	None	Demographics, Diagnostic journey, Clinical evaluations QoL, AM symptoms and comorbidities, Biochemical properties, Infections and Immunological system, Mobility and Ambulation, Visual and Hearing Impairment, Neurocognitive decline, Respiratory and CV issues, Assistive devices, Surgeries and Procedures, Growth monitoring, Medications and Supplements, Hospitalisations	This real-world retrospective study will have reported with a minimum of 25 untreated patients, which will include patients managed in centres in the NHS in England (CSR expected Q1 2023)

Abbreviations: 3MSCT = 3-minute stair climb test; 6MWT = 6-minute walk test; 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; CHAQ = Childhood Health Assessment Questionnaire; CSR = clinical summary report; CU = compassionate use; DI = disability index; EQ-5D-5L = EuroQOL-5 dimensions-5 levels; FVC = forced vital capacity; HRQoL = health-related quality of life; HSCT = haemopoietic stem cell transplant; IRR = infusion-related reaction; LPLV = last patient last visit; PTA = pure tone audiometry; QoL = quality of life; RCT = randomised clinical trial; (S)AE = (serious) adverse events; VA = velmanase alfa; VAS = visual analogue scale

Table 19. Data collection and statistical analyses to resolve key uncertainties

Key uncertainty	Proposed data collection and analysis	When new data will be available
rhLAMAN-05 was limited by 12-month follow-up and small patient numbers	While the RCT is complete and the sample size cannot be increased, there will be data from other studies on at least 30 additional patients on treatment and at least 24 untreated in SPARKLE, including 6MWT, 3MSCT, FVC, adverse events, infections and QoL.	Analysis will be performed after the annual SPARKLE interim report published in February of each year, ready for a resubmission after a period of managed access.
rhLAMAN-05 is the only comparative data available of VA vs. placebo	An indirect comparison could be done using long-term functional and QoL data from all available data from treated patients (rhLAMAN-07/-09, Etoile Alpha and SPARKLE) compared with available data from untreated patients (SPARKLE). This analysis could provide evidence for the long-term functional and QoL improvements and delay in disease progression seen in patients treated with VA, when compared with long-term natural disease progression in patients treated with BSC only.	
Natural history of disease progression in untreated patients	The natural functional deterioration in untreated patients will be collected in AllStripes and SPARKLE, which can be used to further inform transition probabilities for untreated patients in the updated model instead of clinical expert opinion.	Analysis will be performed after the annual SPARKLE interim report published in February of each year, ready for a resubmission after a period of managed access
Infection rates and major surgery with and without VA	Infection rates and length of infections in treated and untreated patients will be collected in SPARKLE and AllStripes, and have been reported in treated patients in the rhLAMAN-11 and the real-world Etoile Alpha study. Rates of major surgery will be collected in AllStripes and SPARKLE.	
Baseline utility values of health states and the on-treatment utility gain of VA	EQ-5D-5L, CHAQ-DI and/or CHAQ-VAS pain will be collected in SPARKLE in treated and untreated patients to reduce the uncertainty in the health state utility values and on-treatment utility benefit of VA in an updated model	To be performed as part of the resubmission at the end of any period of managed access

Abbreviations: 3MSCT = 3-minute stair climb test; 6MWT = 6-minute walk test; CHAQ = Childhood Health Assessment Questionnaire; CSR = clinical study report; DI = disability index; FVC = forced vital capacity; RCT = randomised controlled trial; VA = velmanase alfa; VAS = visual analogue scale.

1.1 Summary

In conclusion, this plan describes new clinical data that will be collected over the next 3-5 years in the SPARKLE registry that will address the specific uncertainties identified by NICE in the ECD2. These data will inform a restructured model and full resubmission for VA by the end of 2026 that will be less reliant on clinical expert opinion and is more robust and acceptable to NICE.

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Clarification questions

1. **PRIORITY QUESTION:** We note that Chiesi's revision to the decision problem population states "*People with AM initiating VA in childhood (aged under 18 years)*" (Table 1, May 2023 CS).
    a. Are children under 6 included in this submission? If so, please clarify the outcomes in all analyses which include children under 6 or provide these data separately.

Yes – children under 6 years are included in the scope of this appraisal and are included in this submission – an updated scope was published by NICE in June 2022 including patients under 6 years to reflect the updated licenced indication for velmanase alfa. Clinical trial results including children <6 years were previously submitted in 2022, and new supporting data were included in this 2023 submission and are summarised as follows:

- rhLAMAN-08: 5 children <6 years treated with velmanase alfa – previously included in 2022 submission now published in Guffon et al., 2023[1]
- FDA analyses supporting the extrapolation of pharmacokinetic and efficacy data to patients <6 years[2]
- Additional case studies of patients treated with velmanase alfa including 3 infants treated with velmanase alfa as a bridging therapy for HSCT[2]

The key rhLAMAN-10/-11 analyses that provided clinical data for the economic model did not include patients <6 years, so subgroup data and separate economic analyses cannot be provided. As rhLAMAN-08 was primarily a safety trial and only included 5 patients, the results of rhLAMAN-08 cannot be used to populate the economic model.

The use of velmanase alfa in patients <6 years was discussed at length at the 4th committee meeting in June 2022 with clinical experts. Section 4.3 of the ECD2 published in October 2023[3] concludes that *"..although there was limited evidence in this age group, there was no biological reason to expect results to differ from those for people over 6. The committee concluded that the clinical evidence was likely to be generalisable across the population."*

    b. If patients under six are included in the submission, please clarify why HSCT is not a comparator?

The positioning of velmanase alfa in the treatment pathway in patients <6 years was also discussed at length at the 4th committee meeting in June 2022 with clinical experts (see section 4.3 of ECD2[3]). The positioning has not changed in that velmanase alfa is positioned in patients <6 years for those who are unsuitable for HSCT, therefore HSCT is not a relevant comparator for this appraisal: *"The committee noted that the company had positioned velmanase alfa treatment only for people in whom an allogeneic HSCT is unsuitable. It recognised that there was no data to compare velmanase alfa with an allogeneic HSCT, or for people who may use velmanase alfa as a bridge to a transplant. It concluded that it would not be able to make recommendations in people for whom an allogeneic HSCT would be considered as a possible treatment."*

In this submission, we provided 3 additional case studies of infants treated with velmanase alfa as a bridging therapy for HSCT.[2]

2. Are the same patients included in rhLAMAN-10 and rhLAMAN-11? If not, please clarify the differences?

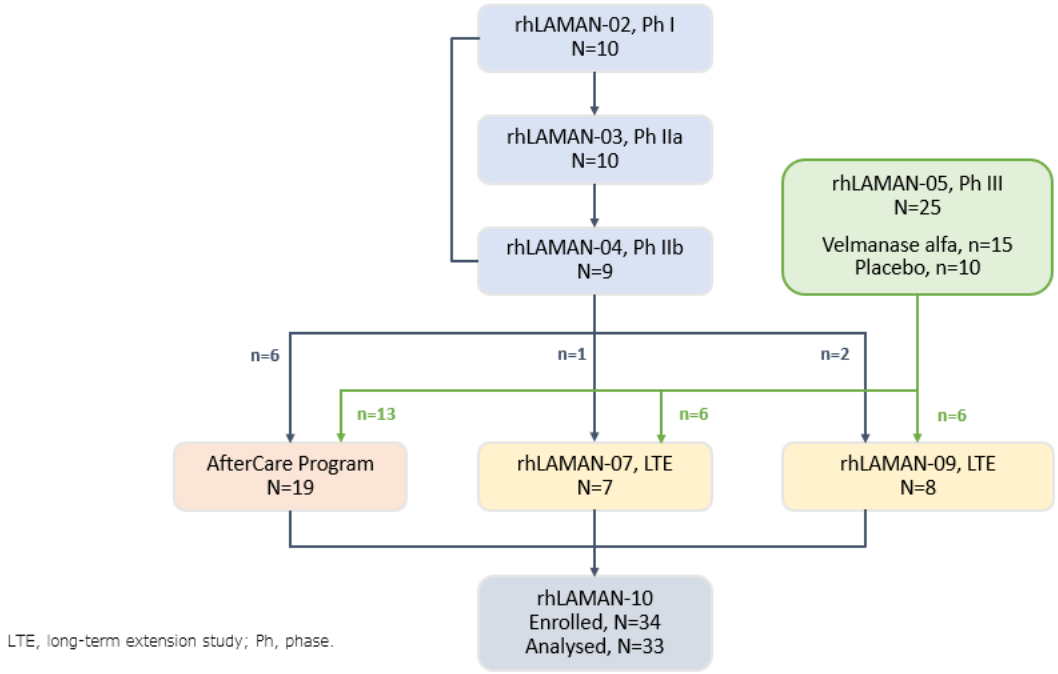
Yes - patients in rhLAMAN-11 were also included in rhLAMAN-10. rhLAMAN-11 updates the previously published rhLAMAN-10 analysis of 33 patients using additional years of data from a subset of 15 patients treated with velmanase alfa in the long-term extension studies rhLAMAN-07/-09 for up to 12 years. The interim report submitted in Feb 2023 describes the methodology and the results of the updated integrated analysis.[4]

After the integrated analysis of rhLAMAN-10 in 33 patients over 4 years was completed, two Phase 3b extension studies in Europe were still ongoing (rhLAMAN-07 and rhLAMAN-09). These studies included 15 subjects with AM in France, Poland, and Norway, offering treatment continuity up to September 2022 for subjects previously recruited in velmanase alfa studies. As these two Phase 3b extension studies have now been completed, the integrated analysis previously done on data collected until June 2015, has been repeated to include these data up to Sept 2022.

3. **PRIORITY QUESTION:** For rhLAMAN-11, for each timepoint, please clarify the numbers missing for reported outcomes and the reasons why. Please clarify the discontinuation rate per year.

For the discontinuation and different follow-up for the patient in the rhLAMAN-10 update (rhLAMAN-11), below is the flow of patients in the different studies:

- Figure 1: Patient disposition in rhLAMAN-10 (N=33)



LTE, long-term extension study; Ph, phase.

The rates of discontinuation by year in rhLAMAN-11 are not yet available as the CSRs are undergoing finalisation. In the rhLAMAN-10 analysis up to 4 years (n=33), no patient enrolled discontinued velmanase alfa. A total of 34 patients were enrolled in the rhLAMAN-10 study with 35 patient identifiers; one patient participated in rhLAMAN-02 and rhLAMAN-03 as Patient 403 and later was included in rhLAMAN-05 as Patient 520. This patient was counted only once. Of the 34 patients, one patient (Patient 502) participated in the rhLAMAN-05 trial in the placebo arm, and then received

velmanase alfa in the AfterCare program. The patient discontinued the treatment shortly after starting the AfterCare program. As such, no data for this patient was collected during the active treatment, and so this patient was excluded from all analyses.

Therefore, data from a total of 33 patients were included in the rhLAMAN-10 original analysis for patients treated with velmanase alfa in the AfterCare program (n=18), rhLAMAN-07 (n=7) and rhLAMAN-09 (n=8), representing a substantial proportion of the diagnosed AM population in Europe.

In the extension part of rhLAMAN-07 and -09, 2 of the 15 patients discontinued over the 12 year period of the trials. The 15 patients were followed-up in -07/-09 until 22 Sept 2022 when these two studies were closed and the additional data were integrated into the updated rhLAMAN-10 analysis (rhLAMAN-11). Thereafter these patients are being followed up in the SPARKLE study as well. In the refreshed rhLAMAN-10 report (rhLAMAN-11), we included the long-term data for the 15 patients that enrolled into Laman07 and Laman09. There were 2 patients that discontinued during L07 / L09. One patient preferred to move to the SPARKLE and was only followed-up in L09 for a short period (2 weeks), the other patient withdrew consent after 5.5 years of treatment – both patients are no longer treated (reasons unknown).

The final CSR for rhLAMAN-11 is not yet available to determine discontinuation rate by year.

4. Please clarify whether that the Feb 2023 appendix is intended to be used alongside the May 2023 resubmission.

Yes - the latest submission was completed in Feb 2023 - the updated cost effectiveness results provided in May 2023 were in response to early economic clarification questions from the EAG. All the clinical content from the Feb 2023 submission and the Feb 2023 appendix are still up to date and should be used alongside the updated cost effectiveness results provided in May 2023.

5. **PRIORITY QUESTION:** Across the history of this submission, and amongst submissions to other agencies (for example, the EMA and FDA), various stopping rules and multidomain responder analyses have been presented. Table 14 in the 2023 appendices cites the multidomain responder analysis in Harmatz *et al.* 2018 as the source data for discontinuations. Please clarify / provide:
    a. Which version of the stopping rules/multidomain responder analyses will be used in clinical practice? It is noted in the submission that NHS LSD centres are likely to apply stopping criteria – will this be their own criteria, or criteria suggested by Chiesi?

NHS LSD highly specialised centres routinely apply stopping rules for ERTs in UK clinical practice. Advice received from a UK clinical expert in 2022[5] stated that individualised treatment goals would be set for each patient, as there would need to be some flexibility to account for the different ways AM presents in patients, especially of different ages and severities.

Base case results use a 13.3% discontinuation rate (taken from the multidomain 'non-responder' rate from rhLAMAN-05 at 12 months in Harmatz et al. 2018[6]) followed by a 10% annual discontinuation rate, to estimate how applying stopping rules based on biochemical, clinical and QoL domains would affects the ICER (in this analysis, responders had to improve in 2 of 3 domains). Using stricter stopping rules decreases the ICER further as shown in scenario analyses: for example, using the non-'super responder' rate in Harmatz 2018 (super responders have to improve in all 3 domains), or stopping if patients become wheelchair dependent.

In clinical practice, stopping rules for velmanase alfa would need to be individualised and agreed by NHS LSD specialist centres; however, the analyses provided using results of the responder analysis estimate the effect of potential stopping rules, and scenario analyses using stricter stopping rules increase the plausibility of cost effectiveness further.

b. The results, for all outcomes for rhLAMAN-05, rhLAMAN-08 and rhLAMAN-11, when only paediatric patients who meet the anticipated clinical stopping rules are included. Of most importance are the analyses relating to serum oligosaccharides, 6MWT% predicted, 3MSCT, FVC, FVC % predicted, CHAQ-DI (and/or CHAQ-DI walking item responses, see Q8d) and EQ-5D-5L for patients who meet the responder criteria, or expected criteria in clinical practice (since it is noted that NHS LSD centres implement stopping rules).

As described above, stopping rules based on the multidomain responder analysis for rhLAMAN-05 at 12 months vs. placebo from Harmatz et al. 2018[6] are applied in the model. The current multidomain responder analysis does not include patients from rhLAMAN-08 and has not yet been updated to include the long-term data from rhLAMAN-11. The multidomain responder analysis for rhLAMAN-05 at 12 months vs. placebo was not separated by paediatric and adult subgroups, so the same 13.3% rate (+10% annual discontinuation thereafter) has been applied for all age groups.

c. The proportion of paediatric patients who are expected to meet the stopping criteria year on year, based on observed data from rhLAMAN-10/11).

The multidomain responder analysis has not yet been updated to include the long-term data from rhLAMAN-11. In addition, results for the multidomain responder analysis for rhLAMAN-05 have not been done for paediatric and adult subgroups, so the same placebo-controlled 13.3% rate (+10% annual discontinuation thereafter) has been applied for all age groups.

6. The 2022 CS included efficacy data for Etoile alpha patients. Please clarify why efficacy estimates from Etoile alpha are not included in this submission. Are patients in Etoile Alpha also in rhLAMAN-11? If so how many are adults and how many are children? Please provide the longitudinal outcomes for all outcomes, but especially serum oligosaccharides, 6MWT % predicted, 3MSCT, FVC, FVC % predicted, CHAQ-DI (and/or CHAQ-DI walking item responses, see Q8d) and EQ-5D-5L were for paediatric patients in Etoile Alpha who are not included in rhLAMAN-11. Please provide this as either as a separate analysis or integrated with the rhLAMAN-11 data. Please also provide these data for patients who meet the continuation rules, as per request in Q5.

This 2023 submission only includes new clinical data that have not been presented previously – results from Etoile Alpha were previously submitted in 2022 so were not included again in this submission, but have since been published as a conference poster in September 2022.[7]

Etoile Alpha was a retrospective study of all patients treated with velmanase alfa in France (N=16: n=9 starting treatment <18 years, n=7 starting ≥18 years). It included patients already on treatment in clinical trials and those started in the real-world on compassionate use as part of the French ATU managed access programme. In Etoile Alpha, there were 7 patients from rhLAMAN-07 who are included in rhLAMAN-11; the remaining patients comprised 1 patient from rhLAMAN-08 (paediatric <6 years study) and 8 patients from the ATU (4 children: patients 0101, 0102, 0201, 0301).

Individual patient data for all outcomes reported in the Etoile Alpha study were provided at the last submission – for paediatric data from the ATU that was not included in rhLAMAN-11, please refer to

the datasets provided for patients 0101, 0102, 0201 and 0301. Unfortunately, it is not possible to integrate the non-rhLAMAN-07 paediatric patients from Etoile Alpha into the rhLAMAN-11 analysis in the time available.

7. **PRIORITY QUESTION:** Please clarify whether there will be sufficient recruitment and follow-up of children aged 6-18 years across AllStripes and SPARKLE in order to conduct an indirect/matched comparison to resolve the key uncertainties noted in Table 19 of the May 2023 CS. We note that the mean age for AllStripes is 43, (IQR 18.5 years) and that data on children is extremely limited due to patients receiving BMT. Please clarify how well the outcomes recorded in AllStripes match the outcomes used in the rhLAMAN studies and in the economic model in order to conduct such an analysis?

The main source of data for an indirect comparison will come from the ongoing retrospective/ prospective SPARKLE study. Supporting natural history data from untreated patients in the retrospective AllStripes study will be also be used to validate inputs of any updated model. Please see further details below:

- **SPARKLE**: Baseline data from the 2nd interim report were published as a poster in 2022[8], a 3rd interim report was submitted to the EMA[9] and a 4th interim analysis[10] was performed for this request:
    - 3rd interim report: 30 sites activated in 17 countries, and a total of 74 patients enrolled across 28 sites in 17 countries. No patient had completed the long-term observation period of 15 years. Of the 74 enrolled patients, 39 (52.7%) patients had a time in study (from informed consent to DLP) of ⩾1 year and 35 (47.3%) patients had a time in study of <1 year. Of the 27 patients who were confirmed as treated with velmanase alfa, 13 patients had a treatment duration of⩾1 year and 14 patients <1 year; 5 patients received home infusions. No effectiveness data are available for the global treatment response (GTR) primary endpoint as this is assessed 3 years after the start of treatment and no enrolled patient had a follow-up of 3 years at the DLP.
    - 4th interim analysis (data lock Feb 2023): total 76 patients, 47 of which were <18 years at time of treatment initiation. Of paediatric patients, 14 of them were treated with velmanase alfa with a median duration of 248 days (range 1 – 1138 days), 8 were treated less than 1 year.

  Data for the individual tests that contribute to the GTR are available at retrospective visits, Baseline Visit and the 12-month Follow-up Visit as follows:
    - Serum oligosaccharides: Baseline Visit data are available for 18 patients. Data are available at a retrospective visit for 1 patient and at the 12-month Follow up Visit for 9 patients;
    - 3MSCT: Baseline Visit data are available for 11 patients. Data are available at a retrospective visit for 8 patients (of whom 6 patients had data available at >1 retrospective visit) and at the 12-month Follow up Visit for 5 patients;
    - 6MWT: Baseline Visit data are available for 25 patients. Data are available at a retrospective visit for 16 patients (of whom 9 patients had data available at >1 retrospective visit) and at the 12-month Follow up Visit for 12 patients;
    - FVC (% of predicted): Baseline Visit data are available for 14 patients. Data are available at a retrospective visit for 12 patients (of whom 9 patients had data available at >1 retrospective visit) and at the 12-month Follow up Visit for 7 patients;

- CHAQ Disability Index: Baseline Visit data are available for 22 patients and 12-month Follow up Visit data are available for 10 patients.

- **AllStripes:** final analysis is ongoing. The final dataset comprises 15 patients (4 treated with BMT, 11 untreated) from the UK, USA and Canada.[11] Although the mean (SD) age in the study is 31 (13) years, the natural history of untreated patients collected in the study will be useful to validate transition probabilities between walking states throughout the lifetime of an untreated AM patient, the age at which patients lose ability to walk unassisted, and the age at which walking aids/wheelchairs are needed. This can be compared with CHAQ data collected from patients treated with velmanase alfa in the SPARKLE registry and the rhLAMAN-11 updated analysis.

8. In relation to Table 14 of the appendix submitted in Feb 2023
    a. **PRIORITY QUESTION:** We note that a reference to rhLAMAN-10 is given to support the distribution of mobility at baseline. However, we were unable to find the distribution in the referenced article (Lund *et al*. 2018). Please could you clarify where these data have come from, and if it is from Lund *et al*. 2018 and we have missed it, please indicate where in the publication? We have found data in Borgwardt *et al.* 2018 for walking at baseline for rhLAMAN-10. Out of the youngest three patients (aged 7,7 and 9 years), one is in a wheelchair (aged 7), compared to 0% in the baseline distribution in Table 14. 5/19 patients need some assistance walking at baseline, which equates to 73.7% walking unassisted, compared with 78% as stated in Table 14.

    Please clarify how the baseline distribution is consistent with the data in Borgwardt *et al.* 2018 for modelling assumptions of a mean age at baseline of both 6 and 8 years of age. Please also clarify to what extent the inclusion criteria of the feed-in trials from which rhLAMAN-10 drew patients is likely to have skewed the distribution of mobility at baseline away from patients who need assistance to walk, compared to the anticipated use of the treatment in UK clinical practice. For example, rhLAMAN-05 excluded patients who could not walk unaided (rhLAMAN-05 CSR pg40).

The original submission included all patients with AM ≥6 years including adults - the original baseline distribution across health states was from the rhLAMAN-10 analysis from Borgwardt et al. 2018[12] – this equates to the following mobility distributions from rhLAMAN-10 by age group:

Table 1. Baseline distribution of mobility in rhLAMAN-10

	<18 years n=19	**≥18 years n=14**	**Total N=33**
Walking unassisted, n (%)	14 (73.7%)	9 (64.3%)	23 (69.6%)
Walking with assistance, n (%)	3 (15.6%)	4 (28.6%)	7 (21.2%)
Wheelchair, n (%)	2 (10.5%)	1 (7.1%)	3 (9.1%)

Source: Borgwardt et al. 2018[12] (page 5: *Overall, 30.3% (n=10/33) of patients required help from a person, walking aids, or a wheelchair at baseline (representing 26.3% of pediatric patients [5 of 19] and 35.7% of adults [5 of 14]; 3 patients (2 pediatric and 1 adult) used the wheelchair for long-distance mobility by the baseline assessment*))

It is correct that the basecase of the updated 2023 submission does not include any patients in the wheelchair (WC) health state – this is as a result of the new positioning of velmanase alfa in patients who initiated treatment <18 years (including those under 6 years who are unsuitable for BMT). This is to reflect: a mean baseline younger age of 6 years; any likely starting criteria in clinical practice in UK LSD centres (no treatment would be appropriate if already in a WC); and new real world evidence. To reflect a starting baseline distribution without the WC health state in the base case, the 2 paediatric patients in the WC health state from rhLAMAN-10 were distributed to the WWA state, resulting in the new basecase distribution used in the model – for clarification the new basecase is **WU: 75%; WWA: 25%; WC: 0%, SI: 0%.**

A clinical expert explained that once a patient is in a WC, it can be difficult to stop using the WC due to wasting of muscles which can make it difficult to move out of the WC state (a patient who is only partially WC dependent would still be classed as WC dependent according to the model), but explained that they had seen patients with LSDs go from using walking aids to no longer needing them as a result of ERT, in conditions such as Pompe disease.

In the final dataset of AllStripes retrospective natural history study of untreated patients[11], 14 of 15 patients (93.3%) were able to walk unassisted at one time (with the remaining 1 patient unknown). 12 of these patients (80%) reported that they had lost the ability to walk unassisted, with 7 patients reporting the age at which this occurred: mean (SD) 28.4 (15.4) years; median (range) 26 (3, 49) years. 11 of 15 patients (73.3%) reported using an assistive device or method for mobility, and 8 of 15 (66.7%) used a wheelchair. Although these real world data are limited and uncertain, this evidence suggests that if diagnosed early, most children with AM will be able to walk unassisted at the time of treatment initiation.

In the previous submission, the EAG requested a scenario analysis with the original distribution of rhLAMAN-10 – in this updated submission, using the rhLAMAN-10 <18 years distribution increases the ICER to £120,698. As the submission is now focused on the paediatric population and a younger starting age in the model of 6 years to reflect the new indication of all patients (including those <6 years if unsuitable for BMT) we believe in real-life clinical practice, paediatric patients would not be in WC state at baseline and the basecase distribution is more appropriate for the updated submission. If a patient was in a WC at baseline at 6 years, this is most likely a patient with severe AM who would not covered by the licensed indication of velmanase alfa (see section 2.2 of the ECD2). Potential starting criteria in UK clinical practice should also be considered, such as paediatric patients who are not already WC users.

b. **PRIORITY QUESTION:** Looking at the data on CHAQ-DI in the rhLAMAN-11 data (Feb 2023 appendices, Table 10), it shows that at baseline, the distribution of CHAQ-DI scores were (n, (%)): not/poorly impaired, 8 (42.1); impaired, 5 (26.3); seriously impaired, 6 (31.6), whilst at 72 months they were, respectively: [redacted] Please clarify how these data are consistent with an assumption of no disease progression for 6.3 years in the model.

The value of **6.3 years** was taken from the mean treatment duration in the rhLAMAN-11 analysis using last observation (LO) data for the 19 patients aged <18 years at treatment initiation. The snapshot of data at 72 months highlighted above is only for 4 patients who reported CHAQ-DI at that specific timepoint, so is too small a number to determine an overall change in a heterogeneous,

slowly progressive disease such as AM. The most appropriate data to use is the LO data from all 19 patients in the last row of Table 14.2.15.4 of the rhLAMAN-11 data provided, which incorporates all LO data including new long-term data from patients treated up to 12 years in rhLAMAN-07/-09. At LO in rhLAMAN-11 in patients <18 years, 9 patients were not/poorly impaired (47.4%), 9 patients were impaired (47.4%) and only 1 (5.3%) was seriously impaired. Two of these patients had been treated up to 12 years, with a mean treatment duration of 6.3 years for the 19 patients. As some patients showed improvement or disease stabilisation beyond 6.3 years (up to 12 years), the value of 6.3 years may be a conservative assumption in the real world setting, which is supported by the real world evidence from Etoile Alpha and case series.

c. The delay to progression is supported by "*mean treatment duration of 6.3 years in 19 children treated with VA*". Please confirm that "*mean treatment duration*" is the same as "*time on treatment*".

Yes this is correct.

d. **PRIORITY QUESTION:** Given that CHAQ-DI has been recorded in rhLAMAN-10 and -11 and includes a question about walking with assistance, please provide longitudinal data relating to walking with assistance. Please run a scenario analysis in the model using these data to estimate change in mobility health state.

The longitudinal data and the matrix could potentially be constructed based on elements of the CHAQ from rhLAMAN-11 if there are sufficient data. However, since this would require analysis of patient level data, this analysis will need to go through a QC process that is not possible within the 5-day timeframe. The final CSRs for rhLAMAN-07 and rhLAMAN-09 including the patient-level data for the CHAQ responses up to 12 years are currently undergoing final QC. Please can the EAG clarify which CHAQ outcomes are required and Chiesi will endeavour to prioritise these datasets and provide these longitudinal data during technical engagement.

The overall rhLAMAN-11 CHAQ-DI scores presented in the Feb 2023 submission were interim analyses prepared for the addendum and present change in **overall CHAQ-DI score** over time, up to 12 years with a mean treatment duration of 6.3 years in patients who initiated treatment <18 years. The overall CHAQ-DI score measures all aspects of disability not just mobility (8 domains: dressing, arising, eating, walking, hygiene, reach, grip and activities), so does not always accurately reflect change in the 'mobility' health state of the model. However, it does provide strong supportive evidence of a delay in disease progression in children treated with velmanase alfa up to 12 years.

In overall CHAQ-DI, patient status is categorised on the following CHAQ-DI scores: not impaired/poorly impaired = 0-≤1, impaired = >1- ≤2 and seriously impaired = >2 to 3. The questionnaire asks for each topic whether help is needed and the use of aids or devices is questioned. If either help or any aids or devices are used for the domain, the score should be at least 2 ("with much difficulty"). This means that a score of 0 or 1 will be changed to a score of 2 if help or aids are used, while scores of 2 or 3 will remain as they are. In the overall CHAQ-DI score, all disability and assistance aids are considered for each topic, not just walking aids, such as a pencil grips, bathrails or raised toilet seats.

e. Please clarify how the UK KOL estimate of withdrawals from treatment compares to data on withdrawals from treatment gathered during the rhLAMAN studies.

The rates of discontinuations by year in rhLAMAN-11 are not yet available as the CSRs are undergoing finalisation (see answer to Q3). In the rhLAMAN-10 analysis up to 4 years (n=33), no patient enrolled discontinued the study. In the extension part of rhLAMAN-07 and -09, 2 of the 15 remaining patients discontinued over the 12 year period of the clinical trials.

The rates of discontinuation used in the model (13.3% in Year 1 and 10% annual discontinuation annually thereafter) reflect individualised stopping rules that will be used in clinical practice in UK NHS LSD centres, as described by the UK KOL in the expert interview conducted in 2022. As velmanase alfa is a once-weekly intravenous infusion with ERT, individualised stopping rules are routinely used; if patients are not experiencing symptom improvement/stabilisation with ERT and their disease is still progressing, it is unlikely they would continue with this treatment regimen.

f. Please clarify how rhLAMAN-10 and Etoile Alpha support an assumption of a 50% reduction in rates of severe infections, infection-related mortality and time in short end-stage state? The Borgwardt *et al.* 2018 analysis of infections in rhLAMAN-05 indicates a 22% reduction in infection rate per person comparing VA (infection rate per person 1.75) to placebo (infections requiring antibiotic use, rate per person 2.25). Please clarify why these data are not used to inform the reduction in severe infections.

The 22% reduction in infections observed within 12 months versus placebo in rhLAMAN-05 consists of **minor infections** (including ear and respiratory infections); however, costs and disutility for minor infections are not accounted for in the health states of the current model.

In the current model, only **severe infections** are included, defined as infections requiring hospitalisation – in the model, patients with severe infection enter a tunnel state for 6 months of associated patient disutility and costs (carer disutility is not included in the tunnel state however, so is also underestimated in the current model).

Long-term data on the incidence of severe infections and infection-related mortality in patients with AM with and without treatment with velmanase alfa are not available to inform the model, so estimates derived from the expert elicitation panel in 2017 are still the most appropriate to use.

In the final dataset of the AllStripes retrospective natural history study of untreated patients[11], 14 of 15 (93.3%) patients had documented reports of infections, and 6 of these (42.9%) reported hospitalisations due to the infection, which would be classed as severe. In addition, the natural history mortality study[13] reported infection-related mortality as a key cause of death in 15 untreated patients with AM: median age of death was 45 years, with 7 of 15 deaths (47%) due to pneumonia.

The 22% reduction in minor infections seen short-term with velmanase alfa over 12 months versus placebo in rhLAMAN-05 and the long-term sustained increase from baseline in serum IgG (a surrogate marker of humoral immunity) for up to 12 years in rhLAMAN-11 supports the plausibility of a 50% reduction in severe infections with velmanase alfa used in the model. A 50% reduction in mortality, complications and recovery time associated with severe infections in the model is also supported real-world data in Etoile Alpha and case reports detailed in the 2022 submission and below – as no severe infections were reported in these studies while patients were on treatment, a 50% reduction may be an underestimate.

- rhLAMAN-11: A statistically significant increase in serum IgG occurs rapidly within 1 year, as shown in rhLAMAN-05 versus placebo.[14] This substantial increase of a surrogate marker for

humoral immunity is maintained long-term up to 12 years in both children and adults as shown in rhLAMAN-11 (Table 5 and Table 6 of Feb 2023 submission)

- rhLAMAN-10 infection burden questionnaire: 21 of 32 caregivers in the pre-treatment period reported frequent infections as an important morbidity of AM that impacted patients' social interactions and QoL. 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.
- Real-world studies and case studies showed a substantial reduction in infections with velmanase alfa. No respiratory infections were observed in the Etoile Alpha review period (up to 9.5 years), with some patients reporting no longer needing to be on prophylactic antibiotics (supported by interviews with 2 UK clinical experts and a UK case study). This is in stark contrast to natural history data in a cohort of 12 untreated Polish patients with AM over 14 years that showed all untreated patients had recurrent infections (Lipinski et al, 2022 [15]), as well as the incidence of severe infections in AllStripes.
- Additional data on infection rates in treated and untreated patients are being collected in the ongoing SPARKLE study.

9. Please clarify what the justification for using a cohort age (in years) of 6 in the model (assuming patients under 6 are not treated). The mean age at diagnosis from Etoile Alpha is 7.5 and 5/16 (or 4/15 paediatric) patients were diagnosed at an age >6 years (see Etoile Alpha clinical study report Table 3), and could therefore not be treated from age 6 onwards.

As clarified in the response to Q1 and Q8, the new positioning of velmanase alfa is in patients who initiate treatment <18 years (including those under 6 years who are unsuitable for BMT), so a younger starting age is more appropriate. Data on age at diagnosis from the SPARKLE registry is also being collected to inform the most likely starting age in the paediatric population. Running a scenario with mean age of 7.5 increases the ICER to £109,751.

10. Clarify whether the formula in cell I220 should be 1-SUM(J220:Q220)-SUM(G220:H220)rather than the current formula. This sets R220 and AB35 both to 100% as we believe was intended. This will not affect the base case but would impact on any scenarios where people start in the WC health state.

As flagged by the evidence review, the model contained an error on the Matrices sheet. This affected the transition matrix for Best supportive care for the first cycle only, and only affected those transitions from the wheelchair bound (WC) state. All other transitions after the first cycle did not contain this error. As no patients started in the WC state in the base case or scenarios (see response to Q8), the error did not impact the reported results.

11. Clarify the potential logical inconsistency in assuming that VA has no impact on disease progression after 6 years compared with BSC, but that VA maintains the potential for improvement from the WC and WWA health states after 6 years whereas BSC does not.

The very conservative assumption that VA has no impact on disease progression after 6 years used to simplify the model is indeed countered by the very small benefit assumed in the potential for improvement from the WC/WWA states. The plausibility of this based on continued improvement seen up to 12 years in the rhLAMAN-11 study, and in real-world data in Etoile Alpha and case studies. In comparison, the carer burden survey[16], case series and natural history studies (such as AllStripes) report a slow progressive decline in untreated patients over time. As such, it is not realistic to assume any improvement from the WC/WWA states with BSC after 6 years. A scenario setting any improvement on VA to zero after 5 years was run, resulting in an ICER of £108,157.

12. Provide more detail for the reference for the costs for severe infection (both for ICU and general care). We could not locate these numbers from the current references. We believe that the value of £488.91 is more appropriated for cell F50 in the 'Costs' sheet but acknowledge that this will not impact on the ICER; please comment on this.

F50 is drug monitoring cost (adult); currently £175. Please see the detailed data used to calculate reference costs for severe infection:

Table 1 Data used to inform cost ICU unit (paediatrics)

Service Code	Service Description	Currency Code	Currency Description	Activity	National Average Unit Cost	NHS Table
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB01Z	Paediatric Critical Care, Advanced Critical Care 5	1924	£7,251.91	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB02Z	Paediatric Critical Care, Advanced Critical Care 4	9650	£3,697.11	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB03Z	Paediatric Critical Care, Advanced Critical Care 3	3169	£3,704.92	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB04Z	Paediatric Critical Care, Advanced Critical Care 2	11293	£3,534.00	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB05Z	Paediatric Critical Care, Advanced Critical Care 1	26008	£3,166.56	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB06Z	Paediatric Critical Care, Intermediate Critical Care	17905	£2,670.43	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB07Z	Paediatric Critical Care, Basic Critical Care	5725	£2,236.52	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB08Z	Paediatric Critical Care, Transportation	3960	£2,930.98	CC
CCU04	Paediatric intensive care unit (paediatric critical care patients predominate)	XB09Z	Paediatric Critical Care, Enhanced Care	7575	£1,941.17	CC
			Weighted average		**£ 3,102.49**	

Table 2. Data used to inform cost of ICU unit (adults)

Service Code	Service Description	Currency Code	Currency Description	Activity	National Average Unit Cost	NHS Table
CCU03	Medical adult patients (unspecified specialty)	XC01Z	Adult Critical Care, 6 or more Organs Supported	108	£1,471.39	CC
CCU03	Medical adult patients (unspecified specialty)	XC02Z	Adult Critical Care, 5 Organs Supported	782	£2,594.76	CC
CCU03	Medical adult patients (unspecified specialty)	XC03Z	Adult Critical Care, 4 Organs Supported	3812	£2,608.21	CC
CCU03	Medical adult patients (unspecified specialty)	XC04Z	Adult Critical Care, 3 Organs Supported	6541	£2,151.65	CC
CCU03	Medical adult patients (unspecified specialty)	XC05Z	Adult Critical Care, 2 Organs Supported	10311	£1,923.86	CC
CCU03	Medical adult patients (unspecified specialty)	XC06Z	Adult Critical Care, 1 Organ Supported	43015	£1,138.84	CC
CCU03	Medical adult patients (unspecified specialty)	XC07Z	Adult Critical Care, 0 Organs Supported	8122	£1,942.32	CC
			Weighted average		**£ 1,524.32**	

Table 3. Data used to inform cost of General care unit (paediatrics, adults)

Currency Code	Currency Description	Activity	National Average Unit Cost	NHS Table	LOS from 2017-18 Schedule - Not reported in current data
WJ06A	Sepsis with Multiple Interventions, with CC Score 9+	4,338	£9,150	Total HRGs	20
WJ06B	Sepsis with Multiple Interventions, with CC Score 5-8	3,085	£8,373	Total HRGs	16
WJ06C	Sepsis with Multiple Interventions, with CC Score 0-4	956	£6,901	Total HRGs	11
WJ06D	Sepsis with Single Intervention, with CC Score 9+	6,585	£6,095	Total HRGs	12
WJ06E	Sepsis with Single Intervention, with CC Score 5-8	7,453	£5,407	Total HRGs	10
WJ06F	Sepsis with Single Intervention, with CC Score 0-4	3,038	£4,647	Total HRGs	7
WJ06G	Sepsis without Interventions, with CC Score 9+	43,266	£3,390	Total HRGs	8
WJ06H	Sepsis without Interventions, with CC Score 5-8	80,519	£2,594	Total HRGs	6
WJ06J	Sepsis without Interventions, with CC Score 0-4	54,752	£1,953	Total HRGs	4
	Weighted average		**£ 3,084.22**		**6.8**
	Average cost per day		**£ 456.68**		

13. Clarify whether there were any observed improvements in health state across the evidence base for people receiving BSC in "*People with AM initiating VA in childhood (aged under 18 years)*" . If there were, please clarify why these probabilities are set to zero in the model. Clarify the concordance between any observed improvements across the evidence base in health state for the same population people receiving VA and the values assumed for improvement by KOLs.

As described in the response to Q11, the carer burden survey (Section 1.1.2 in the 2023 submission)[16], case series and natural history studies (such as AllStripes) all report a slow progressive decline in mobility in untreated patients over time. As such, it is not realistic to assume improvement from the WC/WWA states with BSC after 6 years.

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Velmanase alfa for treating alpha-mannosidosis (ID800)

EAG additional analysis following the company's submission of evidence in May 2023

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Declared competing interests of the author

No author has a conflict of interest to declare.

CONTENTS

TABLES

FIGURES

1 INTRODUCTION

This document summarises the latest company submission relating to the clinical and cost-effectiveness of velmanase alfa (VA) for treating alpha-mannosidosis. This highly specialised technology appraisal has been long-running with the initial committee meeting taking place on the 25th of April 2018 with a fourth committee meeting being undertaken on the 8th of June 2022. During this time, the company have made multiple changes including the population within the decision problem, the estimates of clinical gain for patients within the model and within the evidence base, which has been updated when new data became available.

For brevity, the EAG has focussed on the most recent company submission and has only referenced previous submissions where relevant, for example where the NICE Appraisal Committee had a stated preference within its last NICE Evaluation Consultation Document (ECD)[1] that was changed between previous company submissions and the latest company submission.

The decision population in the company's submission has been restricted to non-adults (patients under 18 years of age) which differs from previous submissions where patients of all ages were considered. In another notable change, the company now states its belief that the use of VA in responders would delay disease progression for six years. This claim is critiqued within this document.

Section 2 summarises the evidence base for VA and new clinical effectiveness data that were not presented in previous submissions. Section 3 provides the EAG's critique of the modelling undertaken by the company. Section 4 provides cost-effectiveness results reported as incremental cost-effectiveness ratios (ICERs) expressed in terms of cost per quality-adjusted life year (QALY). Section 5 provides the EAG's conclusions.

2 SUMMARY OF THE EVIDENCE BASE AND NEW CLINICAL EFFECTIVENESS DATA

The existing evidence base presented in previous submissions and the new evidence submitted in the 2023 CS[2] and clarification response[3] are summarised in Table 1. This table also indicates which aspects of the economic model are informed by the new and existing data. Data that are new have been highlighted in blue in Table 1.

In Section 2.1 of the report, the EAG considers the new clinical evidence submitted by the company and the extent to which it supports key assumptions made in the economic model, namely the assumption of no disease progression for 6 years, the assumption in the model that patients on best supportive care (BSC) do not improve, and that patients commencing on VA treatment are 6 years of age.

In Section 2.2 of the report, the EAG summarises points that remained uncertain after the last committee meeting and provide its view on whether there is now greater certainty in these issues. In Section 2.3, the EAG considers ongoing studies and analyses and how these may address any outstanding uncertainties.

Table 1: The evidence base for velmanase alpha (VA) and its relationship to key modelling assumption uncertainties

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	EAG assessment
Early and aftercare studies						
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-07 (analysed in rhLAMAN-11)	Open label aftercare treatment with VA. Jan 2018 CS states "with annual centralised efficacy assessments", whilst March 2022 CS states "Open-label, long-term safety trial in France"	Patients from rhLAMAN -02, -03, -04 and -05 (N=10)	VA 1 mg/kg	None	Jan 2018 CS (no outcome data alone, integrated in rhLAMAN-10); March 2022 (no outcome data)	No new data
rhLAMAN-09 (analysed in rhLAMAN-11)	Open label aftercare treatment with VA. Jan 2018 CS states "with annual centralised efficacy assessments", whilst March 2022 CS states "Single-centre, open-label, long-term safety trial in Denmark"	Patients from rhLAMAN-02, -03, -04 and -05 (N=5)	VA 1 mg/kg	None	Jan 2018 CS (no outcome data alone, integrated in rhLAMAN-10) ; March 2022 (no outcome data)	No new data
Key studies and analyses that inform the assessment						
rhLAMAN-05	Phase III, 12-month core	25 patients with	VA 1 mg/kg	Placebo	Original	No new data

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	EAG assessment
(NCT01681953)	RCT with extension study up to 36 months	AM: VA (n=15) • 7 children • 8 adults Placebo (n=10) • 5 children • 5 adults			submission, (Section 9 and Appendix 7)	
FDA multicomponent Analysis of rhLAMAN-05	Post-hoc analysis requested by FDA	As for rhLAMAN-05	As for rhLAMAN-05	As for rhLAMAN-05	May 2023 CS, Section 3.1.1	Unclear relevance
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)	March 2022 CS Section C1.3.2	Of relevance to new scope, which includes children under 6
rhLAMAN-10 NCT02478840 rhLAMAN-11 (same patients as rhLAMAN-10, but longer follow up)	Integrated analysis of all patients in rhLAMAN-02, -03, -04, -05, -07 and -09 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 Feb 2023 CS (rhLAMAN-11)	rhLAMAN-11 of relevance to new modelling assumption of no disease progression for 6 years
Multidomain responder analysis of rhLAMAN-05 and -10	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

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	EAG assessment
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	No new data, but existing data of relevance to age at diagnosis. 7/33 (21%) patients in rhLAMAN-11 were in Etoile Alpha. An additional n=4 Etoile Alpha non-adult patients were of relevance to efficacy assessments Of relevance to new modelling assumption of no disease progression for 6 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; Interim report in May 2023 submission	Of relevance to managed access data collection (2023)
AllStripes 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	March 2022 CS, Table 21 Feb 2023 CS, reference pack[4]; May 2023 clarification response reference pack (Tables 1-24)	Of relevance to: • Age at diagnosis • Managed access •

Study name (acronym)	Study design	Population	Intervention	Comparator	Cross-reference to company submissions	EAG assessment
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 of no disease progression for 6 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, Spain; n=1, Lithuania; Italy, n=1)	5 adult patients	VA 1 mg/kg	None	March 2022 CS, Section C1.3.11	
Case report series	Infants treated as bridging treatment to HSCT (n=2)* Infant treated for 18 months (n=1, Italy)	3 infants	Unclear	None	May 2023 CS, Section 3.3	Relevant to committee comment on HSCT bridging therapy[5]
Expanded Access Programme (NCT04959240)	Compassionate Use Programme in the US	All eligible patients with AM	VA 1mg/kg	None	March 2022 CS, Table 21	Unclear relevance.

Text in blue indicates data newly submitted in the 2023 CS[2]

2.1 New clinical evidence submitted by the company

2.1.1 rhLAMAN-11

The 2023 CS[2] reports new data for rhLAMAN-11, which is an extension of rhLAMAN-10, comprising the same patients but with an additional approximate 7 years of follow up data for a proportion of patients (n=15) from rhLAMAN-07/-09, taking follow-up from a maximum of 4 years to a maximum of 12 years. Analyses have been provided for patients aged less than 18 years (n=19) and adults aged ≥18 years (n=14) separately. The analyses are presented in the 2023 CS Tables 3-7 (not reproduced here for brevity). The EAG focuses on the data relating to non-adult patients, since the company has positioned the treatment for this population only.

The company reported results for all key outcomes previously reported, namely serum oligosaccharides, 3-minute stair climb test (3MSCT), 6-minute walk test (6MWT), age-adjusted 6MWT, forced vital capacity (FVC) (Litres (L)), age-adjusted FVC (% predicted), EQ-5D-5L and serum immunoglobulin G (IgG).

The percentage changes from baseline in serum oligosaccharides and 3MSCT were [redacted] in the rhLAMAN-11 analysis (serum oligosaccharides - [redacted]) compared to the rh-LAMAN-10 analysis (-66.6% (SC36.09, p value NR); 3MSCT [redacted] compared to +23.1% (27.3) respectively)). The other outcomes (6MWT, age-adjusted 6MWT, FVC (Litres (L)), age-adjusted FVC (% predicted), IgG) were [redacted] between the rhLAMAN-10 and rhLAMAN-11 analyses, except for EQ-5D-5L where the improvement had [redacted] from +0.083 (SD 0.136, p value NR, n=10) to [redacted].

The EAG notes that rhLAMAN-11 and Etoile Alpha contain some of the same patients (see response to 2023 clarification question 6[3]), and results from the two analyses should not be considered independent.

2.1.1.1 Critique of rhLAMAN-11 analyses

2.1.1.1.1 CHAQ-DI evidence and the disease progression delay used in the economic model

The company support its assumption of a delay to disease progression for patients on VA with data from rhLAMAN-11. The 6-year delay is based on a) the mean duration of treatment/duration until last observation for the co-primary outcome 3MSCT (mean [redacted], median [redacted]) and b) the CHAQ-DI percentage change from baseline at last observation ([redacted]). (N.B. Negative change values for CHAQ-DI indicate disability has lessened).

The EAG has some concerns about how well the evidence supports the assumption of a delay of 6 years for a number of reasons.

CHAQ-DI is a composite outcome that may not be representative of walking states: Firstly, CHAQ-DI is a composite outcome which assesses disability across eight domains (dressing, arising, eating, walking, hygiene, reach, grip and activities), but is used in the model to inform the mobility health states. The EAG asked the company to provide data relating to walking from the CHAQ-DI; the company was unable to provide the results in the clarification response, but it did offer to prioritise specific outcomes if the EAG requested. However, there was insufficient time for the EAG to review all new documentation and make this request. It is therefore unclear if CHAQ-DI is representative of walking states. The company acknowledge this in its 2023 clarification response 8d[3]:
"*The overall CHAQ-DI score measures all aspects of disability not just mobility (8 domains: dressing, arising, eating, walking, hygiene, reach, grip and activities), so does not always accurately reflect change in the 'mobility' health state of the model*.".

Last observation is less than 6 years for more than half the patients in the analysis, and responses are heterogeneous: A further limitation of the analysis is that it is based on the median duration until last observation, but the [redacted], and therefore the mean of the last observation will be comprised of patients who have both much longer and much shorter times to observation. Furthermore, the results suggest that, [redacted] Figure 1, a reproduction of Figure 6 in the 2023 company appendices, shows the individual plots for patients contributing to the analysis, with blue lines showing non-adult patients. From this it can be seen that [redacted] patients appear to have follow-up data at or beyond 72 months (some lines merge making the total unclear), [redacted].

It is unclear which patients in the analysis would stay on treatment in clinical practice: The company states that non-responders will cease treatment after 12 months, and this is based on 13.3% being classed as non-responders from the multi-domain responder analysis reported in the first submission[6] and in a journal article[7] (not the super-responder analysis reported in the 2022 submission[8]). Looking at Figure

1, this seems roughly consistent with the proportion who have CHAQ-DI values worse than baseline at 12 months. The EAG requested analyses for all outcomes for rhLAMAN-05, rhLAMAN-08 and rhLAMAN-11, when only non-adult patients who meet the anticipated clinical stopping rules are included (clarification question 5b[3]), but the company were not able to answer this request. It is therefore unclear whether the patients who remain in the analysis beyond 12 months would remain on treatment in clinical practice. The company suggest that "*NHS LSD highly specialised centres routinely apply stopping rules for ERTs in UK clinical practice. Advice received from a UK clinical expert in 2022 stated that individualised treatment goals would be set for each patient, as there would need to be some flexibility to account for the different ways AM presents in patients, especially of different ages and severities.*". Therefore, it cannot be assumed that those who do not respond to treatment in the disability domain would stop treatment.

Too few patients are in the analysis at 6 years to provide certainty in the estimated effect: The EAG considered the data available at 72 months of follow-up as an alternative way to assess whether disease progression is halted for [redacted] years. In Appendix C of the 2023 company submission, data are reported for each time point, categorising patients into one of three categories: Not/poorly impaired (which the EAG have assumed to mean not/slightly impaired); impaired; and seriously impaired. At baseline, the proportion of non-adult patients (n=19) in these groups were [redacted] At the 72-month assessment point, [redacted] patients contributed data, and the respective proportions were [redacted] At time points beyond 72 months, the number contributing to any one analysis does not exceed five. Due to the small number in the 72-month analysis and beyond, it is difficult to draw any conclusion as to whether disease progression has been halted for [redacted] years, though the plots suggest that [redacted] and it is not clear which of these would remain on treatment (see previous paragraph). There are [redacted] patients in the 60-month analysis and the values at this time point between categories are [redacted] The EAG has low confidence in these results due to the [redacted] in the analysis. There are [redacted] in the 48-month analysis, and values at this time point are [redacted], and it is not clear which patients would remain on treatment.

No comparator arm: One final consideration is the lack of a comparator arm. It is not possible to tell what effects are due to VA and what may be due to other factors such as: regression to the mean; the training effects of doing walking tests and stair-climb tests multiple times; concomitant medications such as pain relief; patient growth for the 3MWT; and other BSC treatments such as surgery.

Figure 1: Individual plots of CHAQ-DI over time. (Reproduction of Figure 6 in the 2023 company appendices)

2.1.1.1.2 Other outcomes from rhLAMAN-11 and the disease progression delay used in the economic model

3MSCT, 6MWT, age-adjusted 6MWT, FVC, age-adjusted FVC (% predicted), EQ-5D-5L and serum IgG from rhLAMAN-10 and rhLAMAN-11 are summarised and compared in Section 2.1. The EAG notes the following about these analyses.

Limitations of last observation analyses: As with CHAQ-DI, the analyses reported relate to the last observation for each patient, not a specific time point. Therefore, similar concerns apply as outlined for CHAQ-DI, namely that the last observation is a mixture of different time points, responses are heterogeneous, it is unclear which patients would stay on treatment, and there appears to be too few patients in the analyses beyond 5 years to have confidence in the estimates. The EAG notes that [redacted] even where plots available in the 2023 CS appendices [redacted] (see 2023 CS Appendices Figures 2-7). The EAG asked for clarification on why patients were missing, but the company did not directly answer that part of clarification question 3.[3] The EAG therefore urges caution with respect to an interpretation of the broadly similar outcomes in rhLAMAN-10 and -11 as indicating that disease progression was halted for those additional years of follow-up. The EAG does note, however, that the plots in Figures 2-7 of the 2023 CS appendices [redacted] The EAG did not review the data at 5 and 6 years for each timepoint (as was done for CHAQ-DI in Section 2.1.1.1.1) due to time constraints, though notes that these data are available in the company's reference pack.

Additional concerns include a [redacted]

[redacted], though it is unclear if these differences are clinically or statistically significant, and there is considerable uncertainty due to the factors already noted for last observation analyses.

2.1.2 2022 European and UK Patient and Caregiver Survey

The company conducted a survey in 2022 of patients and caregivers and provided an interim analysis of n=21 patients in the 2023 CS, Section 1.1.2. The results are divided into untreated patients, patients treated with HSCT, and patients treated with VA. Respondents were asked to rate their mobility, patient quality of life (QoL) and carer QoL now, 5 years ago and 10 years ago. The company uses these data to support the extreme heterogeneity in symptoms between patients, and a slow decline of mobility and other symptoms over time.

For the mobility question, the EAG notes that amongst [redacted] untreated patients, two [redacted] over ten years, and one [redacted] over ten years. This result is of relevance to the assumption of no improvement in the BSC arm of the model (see Section 3.1.1). Of the remaining [redacted], one gets [redacted], one gets [redacted], and one [redacted].

It was unclear to the EAG whether the patients included in the survey who had been treated with VA are included in other studies, e.g., rhLAMAN-10. The ratings for mobility may therefore be double counting patients already included in other analyses. For completeness, the EAG notes that mobility ratings [redacted]. For example, a [redacted]. This is of relevance to the assumption of no disease progression for 6 years.

The results relating to patient and carer QoL are discussed in Sections 3.1.3 and 3.2.3.

2.1.3 New FDA multicomponent analysis of rhLAMAN-05

The company presents a new multicomponent analysis of rhLAMAN-05, which was conducted for the FDA. The relevance of this analysis to the approach taken in modelling the disease is unclear to the EAG, since the model relies on one outcome only. The relevance of these analyses to the evidence base is also unclear, as is whether they will be used to inform future assessments of response either in efficacy studies or in clinical practice. The EAG notes that the analyses were not pre-planned, and that the selection of the best components to include in a multicomponent analysis based on these analyses may be subject to bias due to overfitting of the data to a single data set.

2.1.4 Correlation between serum oligosaccharides and clinical outcomes at last observation in rhLAMAN-10

In Section 3.1.2, the company present analyses correlating serum oligosaccharides with three of the clinical outcomes using data from rhLAMAN-10 non-adult patients. The EAG notes the analyses show some correlation, but that the plots show no strong correlation between changes in outcome measure with no R^2 values presented. Therefore, the EAG is of the opinion that changes in serum oligosaccharides cannot reliably predict response in clinical outcomes. The EAG also notes that not all outcomes were included in the analyses. Notably, the correlation between serum oligosaccharides and CHAQ-DI and EQ-5D-5L was not reported.

2.1.5 New case reports

The company presents three case reports for children who used VA as a bridging treatment for HSCT, and a 7-year-old in Italy, who experienced improvements in hyperactivity, 6MWT, comprehension, verbal expression, hearing loss, and use of antibiotics.

The EAG notes the same limitations of case reports as stated in Section 3.2.3 of the 2022 EAG report.[9] In summary, the extent to which these can evidence whether disease progression is halted for 6 years for patients who respond to treatment is limited by the non-comparative nature, small numbers and non-standardised reporting of all relevant outcomes. The EAG notes that two case reports on the use of VA as a bridging treatment before HSCT is a small evidence base and that without comparison to patients who were not treated with VA, the efficacy and cost-effectiveness of VA in this context remains unclear.

2.1.6 Clinical evidence relating to age at commencement of treatment with VA

The company's model assumes that all patients will commence treatment at 6 years of age. The EAG has considered the clinical evidence available to support this assumption. The EAG identified two sources of data within the company's evidence submission that report on the age of patients at diagnosis, Etoile Alpha (reported in the 2022 CS)[8] and AllStripes[10] (data Table 3 submitted as part of the clarification response 2023). Since the company has positioned the treatment in non-adult patients, only patients who were diagnosed before 18 years of age are relevant.

In Etoile Alpha, the mean age for all patients is 7.5 years, but this includes some patients who were diagnosed before 6 years of age, and who may have a severe disease course and may therefore be out of scope, and one diagnosed at 43 years. It is also unclear if the participants in the study are representative in terms of age at diagnosis to patients in the UK since the study was performed in France and since the inclusion criteria were a mixture of participation in previous clinical trials that did not

specify severity in their inclusion criteria, or participation in the French conditional market access agreement, the inclusion criteria for which could not be identified by the EAG.

AllStripes[10] reports a mean age of [redacted]

The EAG heard from clinical advisors during the first appraisal that patients diagnosed under 5 years of age generally have a severe disease course (see EAG report 2018, Section 3.1),[12] and would therefore not be eligible for treatment with VA. The committee concluded in its 2022 ECD[5] that the number of children diagnosed under the age of 6 would be small (see ECD[5] Section 4.2). The EAG believes it is likely that a proportion of patients will be diagnosed aged greater than 6 years, especially amongst those with mild to moderate disease, whose disease course may be slow and whose symptoms may not be present or clear enough to indicate AM earlier in their lives. This is evidenced by some older ages at diagnosis amongst the evidence base, and by the diagnosis of some patients into adulthood. It is unclear what the mean age at diagnosis is for mild to moderate patients considering these opposing factors, and the EAG cannot, therefore, conclude what an appropriate age for commencement of treatment in the model should be.

2.2 Uncertainties in the clinical evidence after the last committee meeting and the impact of new data

The ECD[5] noted a number of uncertainties in the clinical evidence base relating to VA. In this section, the EAG considers whether new data can help to resolve any uncertainties.

2.2.1 The clinical effectiveness evidence from the rhLAMAN trials was uncertain

In Section 4.4 of the ECD,[5] the committee concluded that the clinical-effectiveness evidence from the rhLAMAN trials was associated with several uncertainties including the lack of a comparator arm in rhLAMAN-10, the small sample sizes, and the length of follow-up. The uncertainty was again noted in Section 4.7, along with the small effect size in clinical outcomes.

In its 2023 CS,[2] the company provides additional follow-up data for rhLAMAN-10, in the analysis "rhLAMAN-11". This analysis is discussed above in detail in Section 2.1.1. The analysis provides additional follow-up data which increases the length of the follow-up but does not increase the sample

size or address the lack of a comparator arm. The lack of a comparator arm may be addressed by additional data collection (see Section 2.3). The effect sizes remained generally similar or smaller in the rhLAMAN-11 analyses to the rhLAMAN-10 analyses.

2.2.2 It was not possible to infer clinical benefits from serum oligosaccharides

In Section 4.6 of the ECD,[5] the committee considered the serum oligosaccharide outcomes and concluded that the results provided biochemical evidence that VA has an effect, but it was not able to infer the nature or size of the clinical benefits from these results.

In its 2023 CS,[2] the company provides an additional analysis of the correlation between serum oligosaccharides and clinical outcomes. The EAG has reviewed this evidence in Section 2.1.4 and is of the opinion that the correlation demonstrated remains insufficient to reliably predict clinical outcomes.

2.2.3 The committee agreed to consider the longer-term data from Etoile Alpha in its decision making

In Section 4.9 of the ECD[5] the committee acknowledged the limited sample size and uncertainties associated with Etoile Alpha, but recognised that this was influenced by the extreme rarity of the condition. It agreed to consider the long-term follow-up data for VA in its decision making.

The EAG notes that Etoile Alpha contains some of the same patients as rhLAMAN-10 and -11. The company confirmed that only four patients in Etoile Alpha were non-adult patients who were not included in rhLAMAN-10/-11, but declined to integrate these patients into the rhLAMAN-11 analysis (see response to 2023 clarification question 6).[3] The EAG had insufficient time to consider these patients separately, but suggests that to avoid double counting, evidence from rhLAMAN-11 should be considered as a primary source of evidence when assessing long term efficacy.

2.2.4 Evidence on the immunological benefits of velmanase alfa are limited and uncertain

In Section 4.10 of the ECD[5] the committee concluded that VA appears to have immunological benefits, but that the evidence on this is limited and uncertain.

In its 2023 CS,[2] the committee included in the summary tables for rhLAMAN-11 data on serum IgG. The data demonstrated improvements in serum IgG, based on the mean change from baseline. No new evidence demonstrating the link between serum IgG and infections was provided, but a summary of data on infections was provided in 2023 clarification response 8f.[3]

2.2.5 The relevance of the results of the multidomain responder analysis was unclear.

In Section 4.11 of the ECD,[5] the committee concluded that the multidomain responder analysis had several limitations, and the relevance of the results was difficult to interpret.

In its 2023 CS,[2] the company does not focus on the super-responder analysis provided at technical engagement in 2022. Instead, the company now assumes that individual NHS LSD centres will develop their own stopping criteria, and uses the multi-criteria domain analysis provided in the 2018 CS[13] as a source of data for assuming discontinuations in the economic model, which are assumed to be 13.3% in the first year, based on responder analyses from rhLAMAN-05, and 10% in each subsequent year, based on expert clinical opinion. The company notes that using more stringent stopping rules would decrease the ICER (2023 clarification response 5).[3] However, the EAG notes that a lack of definition of stopping rules could equally lead to more patients staying on treatment based on clinical opinion, which could lead to higher ICERs.

The company has provided a new multicomponent analysis that was performed for the FDA. This is critiqued by the EAG in Section 2.1.3. The EAG is unsure of the relevance of this analysis.

2.3 Summary of the company's data collection plan and how this will address key uncertainties

The company states in section E1 of the 2023 CS that the key 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
- HRQoL 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 main data collection during any period of managed access would be through the SPARKLE registry. This is an ongoing European registry with an expected recruitment of 100 patients. An interim report in 2026 is expected to be used to inform a restructured economic model. There is also ongoing data collection in the AllStripes study which accepts patients irrespective of treatment but excludes those with HSCT. However, data submitted with the company's clarification response (clarification question 7)[3] indicate that 15 patients were recruited, [redacted].

The EAG notes that SPARKLE will recruit both those treated with VA and those who remain untreated. The EAG asked the company to clarify (clarification question 7)[3] whether there will be sufficient recruitment and follow-up of patients aged 6-18 years across AllStripes and SPARKLE in order to conduct an indirect/matched comparison to resolve the key uncertainties noted in Table 19 of the May 2023 CS.[2] The company responded that the main source of data would be the SPARKLE registry, and AllStripes would be used to validate model inputs. The company provided an update on recruitment to SPARKLE, which appeared to be going well, but did not state how many of these patients will provide data on non-adults who are untreated with VA, in order to perform a matched analysis to resolve uncertainties relating to the lack of a comparator arm in rhLAMAN-10 and -11. The EAG is concerned that the increasing availability of VA and the focus on treatment in non-adult patients will mean that there will be little long-term data relating to untreated patients. A retrospective analysis could be conducted, but the EAG is unclear on whether this is likely to provide sufficient data on key efficacy outcomes since these may not be routinely collected. It is therefore unclear to the EAG whether data uncertainties associated with the natural history of the disease and outcomes under BSC will be resolved by the data collection plan. Furthermore, the EAG notes that the protocol for SPARKLE[14] does not require participants to attend all assessments, and this may lead to missing data points. The protocol also states, "*Provided that a sufficient number of nontreated patients with adequate data are enrolled, a comparison will be conducted between the velmanase alfa-treated and nontreated groups.*"

3 EAG CRITIQUE OF THE MODELLING IN THE COMPANY'S RESUBMISSION

This section focuses on the modelling undertaken by the company in its latest submission. Section 3.1 details where the company's model does not use the Appraisal Committee's preferred assumptions but uses alternative values. The company has an agreed Patient Access Scheme which takes the form of a simple discount ([redacted]); this has remained unchanged since the previous submission.

3.1 Changes between the Committee's preferred assumptions as expressed in the last ECD1 and the company's base case

A summary of the differences between the Committee's preferred approach and the approach used by the company in its base case are shown in Table 2. These are discussed in more detail in Sections 3.1.1 to 3.1.3.

Table 2: Summary of the differences between the NICE Appraisal Committee's preferred approach and the approach used by the company

Number	EAG Parameter description	Committee's stated preference (ECD paragraph)	Approach used by the company in its base case in the latest model
1	Improvements in mobility for patients receiving velmanase alfa (VA) and best supportive care (BSC)	The improvements should be allowed in both the VA and BSC arms (4.15)	The model allows improvements in the VA arm but not in the BSC arm
2	Benefits of delayed progression associated with VA treatment	3 years of delayed disease progression followed by extension of time in health states (4.16)	6 years of no disease progression but no additional extension of time in health states
3	Chronic utility gains in children above that associated with mobility health states	0.10 utility gain for children (4.17)	0.18 utility gain for children

3.1.1 Improvements in mobility for patients receiving VA and BSC treatment

In rhLAMAN-05, the same proportion of patients improved from the walking with assistance (WWA) health state to the walking unassisted (WU) health state in the VA and the BSC arms, although this population contained adult patients as well as non-adult patients. In previous models, the company assumed that improvement was only possible in the VA arm and not the BSC arm, with the committee stating that "*the likelihood of improving mobility in the model should have been consistent with the observed trial data. It concluded that the model should have allowed for improvements in mobility for people having both velmanase alfa and best supportive care*." In the recent model, the company has not acted on the committee's advice, but has assumed, based on expert clinician opinion, that improvement will only happen in the VA arm, with a 20% improvement in both the wheelchair (WC) and in the WWA health states in the initial two years of treatment, with the probability of improvement falling to 2.5% in these states in every subsequent year. Contrastingly, improvement is not allowed in the BSC arm. Previous scenario analyses have shown that the incremental cost-effectiveness ratio (ICER) expressed in terms of cost per quality-adjusted life year (QALY) would increase if patients were allowed to improve when receiving BSC.

The EAG notes that none of the data related to improvement (or disease progression) in the model has used data from the clinical studies. Instead, these values are all estimated from clinical expert opinion which will carry considerable uncertainty. The EAG further comments that data previously related to the increased time in health states due to VA treatment that has been used in previous base cases has been discarded.

The EAG has been unable to run any robust analyses given that the model uses clinical expert opinion only however, to provide an indication of the impact of the results of allowing there to be some improvement on BSC an analysis has been undertaken where it is assumed that there is 10% chance of improvement in mobility in the first year only for patients receiving BSC. This value is still considerably less than the improvements assumed for patients receiving VA treatment.

3.1.2 Benefits of delayed progression associated with VA treatment in mobility for patients receiving VA and BSC treatment

The Committee concluded that "*assuming 3 years of delayed disease progression followed by an extended time in health states based on the original expert elicitation was acceptable for decision making while accounting for uncertainty in the evidence.*" The company, however, has used a different approach in the latest model, where there is 6 years of assumed no disease deterioration whilst receiving VA treatment, but has removed any benefit of VA, in terms of transition probabilities, compared with BSC subsequently. The benefit of being in a better health state at year 6 due to receiving VA treatment

will impact on costs and QALYs through the patient's lifetime, however, the transition probabilities are the same for all patients after 7 years.

Based on the comments in Section 2.1.1.1.1, the EAG believes that the duration of disease delay associated with VA is uncertain. Therefore, the EAG has run an analysis where the Committee's preference has been reinstated compared with the new approach used by the company.

3.1.3 Chronic utility gains in children above that associated with mobility health states

The Committee "*agreed that a 0.1 utility gain for children and young people, and a 0.05 utility gain for adults should be used for decision making.*" The company, however, has assumed a value of 0.18 utility gain whilst being on treatment. This value, which is associated with respiratory benefit, was included in a previous base case submitted by the company and has already been considered by the Committee. The value of 0.18 was estimated by using the 0.9 litre change in forced vital capacity observed in patients in rhLAMAN-10 in patients aged under 18 years and multiplying this by a utility gain of 0.02 per 0.1 litre gain that was an assumption preferred by the NICE Committee in HST19.[15]

The company comments that in rhLAMAN-10 that the EQ-5D-5L was statistically significantly improved (by 0.083) in children receiving VA, although data from rhLAMAN-11 suggests that the EQ-5D-5L improvement has [redacted]. The EAG notes that caution is needed in interpreting these results as: there may have been selection bias in completing the EQ-5D which was completed by 10 of 19 children; that some of these utility gains may also be accounted for within the model due to improvements in mobility state; and that the gain is non-comparative.

As the committee had seen the majority of the data provided by the company prior to its decision to prefer a value of 0.10, the EAG has run analyses using a utility gain of 0.10.

3.2 Changes in the Company's base case which do not oppose the Appraisal Committee's stated preference

The company made some changes made to the model which did not oppose the Committee's stated preference, largely because there was no stated preference in the ECD. These changes are detailed in

Table ***3*** and are discussed in more detail in Sections 3.2.1 to 3.2.5.

Table 3: Changes in the company's model that do not oppose the NICE Appraisal Committee's stated preferences

Number	EAG Parameter description	Committee's stated preference (ECD paragraph)	Approach used by the company in its base case in the latest model.
1	Starting distributions amongst mobility health states	No comment	The model now uses a starting population combining data from patients under 18 years.
2	Age of patients treated	No comment. Previous model used 6 for the paediatric cohort, 12 for the adolescent arm and 18 for the adult cohort	The model assumes that the non-adult patients are all aged 6 years.
3	Utility loss associated with carers	No comment. Previous model used Gani *et al*. values.	Using values associated with spinal muscular atrophy
4	Correction of model errors	N/A	The EAG identified some model errors which have been amended by the company.
5	Updating of data values	N/A	The most recent values have been used in the model.

3.2.1 Starting distributions amongst mobility health states

In the company's revised model, it is assumed that 75% of non-adult patients start in the WU health state and that 25% of non-adult patients start in the WWA health state. Based on the company's response to clarification question 8,[3] it is believed that the distribution of patients in rhLAMAN-10 were 12 in the WU health state, 2 in the WWA health state and 2 in the WC health state with the company assuming that the patients in the WC health state could be grouped with the patients in the WWA health state. The EAG believes that an alternative plausible scenario is that patients in the WC health state would not be treated and if this are omitted the distribution between health states would be 86% (12/14) in the WU health state and 14% (2/14) in the WWA health state. This alternative distribution has been run in a scenario analysis.

3.2.2 Age of patients treated

In the company's revised model, it is assumed that all patients receive treatment at the age of 6 years with the functionality to use 8 years instead which is implied in the model to be the average age of patients under 18 years in rhLAMAN-10. As detailed in Section 2.1.6, there is uncertainty regarding the average age of people treated with VA were it to receive a positive recommendation. The EAG has run an analysis using 8 years rather than 6 years.

3.2.3 Utility loss associated with carers

In the company's previous models, it is assumed that the carer disutility associated with each health state were: 0.01 for WU; 0.02 for WWA; 0.05 for WC; 0.14 for severe immobility (SI) and 0.14 for short end stage. These values were sourced from consultation with clinical experts and using published carer disutility based on an expanded disability status scale as reported by Gani *et al*.[16]

In the company's revised submission, the source of the carer disutility has been changed. The company states that the new source is based on NICE TA755 which related to types 2 and 3 spinal muscular atrophy (SMA).[17] However, there appears to be a discrepancy in the disutility values detailed in the report and that in the report and the model. Table 9 of the company's submission indicates that the values reported in TA755 would be multiplied by 1.5 to consider multiple caregivers and affected siblings which resulted in carer disutilities of 0.12 for WU and WWA and 0.24 for WC, SI and short end stage. In contrast, Table 10 and the mathematical model state values of 0.08 for WU and WWA and 0.16 for WC, SI and short end stage. The EAG comments that both sets of disutilities are markedly higher than those used previously which had been used following discussions with clinical experts. Furthermore, the EAG noted that it was not clear that the values stated by the company were accepted by the Appraisal Committee in TA755. The committee stated that '*SMA has a substantial effect on the quality of life of patients, caregivers and their families'* it also states that '*Caregiver utility is considered in decision making but is difficult to quantify'* and that '*it should consider carer utility in its decision making but that quantifying caregiver utility was extremely difficult.*' The EAG notes that SMA is a disease with different characteristics to alpha mannosidosis and that utilities from SMA may not be generalisable to alpha mannosidosis. The EAG additionally notes that the previous values had received the backing of clinical experts which may not be the case for the carer disutilities assumed in the latest company model.

The EAG has run analyses using the carer disutilities already seen by the Committee.

3.2.4 Correction of model errors

During the appraisal process the EAG identified what it believed to be errors in the company's model. The company agreed that this was the case and changed the model to remove the errors. The EAG is content with these changes.

3.2.5 Updating of data values

Due to the relatively large period of time since the company's original submission in 2018 some of the data that was appropriate initially has since become dated. At the request of the EAG, the company has updated parameters to the latest available values. The EAG is content with this change.

4 RESULTS PRESENTED BY THE COMPANY AND GENERATED BY THE EAG

This section provides deterministic ICERs. No appropriate probabilistic ICERs could be generated as the functionality in the company's model had not been updated to reflect the new company base case. However, as detailed in the first EAG report[12], the model was relatively linear and thus the deterministic ICER should be a good indicator of the probabilistic one.

4.1 The Company's base case ICER

The company's base case ICER is shown in Table 4 and is £101,073.

Table 4: The company's base case

Treatment	Discounted		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
VA	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	101,073

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; VA: velmanase alfa.

4.2 The EAG's base case ICER

The EAG has made changes to the company's base case where the EAG believed there was not strong evidence that either the committee's stated preference in the ECD[1] or that the company's previous assumption was incorrect. These changes relate to: the delay in disease progression associated with VA treatment; the chronic utility gain due to being on VA treatment and the level of utility loss associated with carers. The impacts of the three changes are shown individually, and in combination, in Table 5. The EAG's base case, which combines all three changes is £148,638.

Table 5: Changes made to the company's base case by the EAG and the EAG's preferred base case

Description	Incremental		ICER (£)
	Costs (£)	QALYs	
Company's base case	[redacted]	[redacted]	101,073
EAG 1: Delay in progression for VA = 3 years with extended time in health states	[redacted]	[redacted]	130,428
EAG 2: Utility gain from VA = 0.10	[redacted]	[redacted]	123,548
EAG 3: Utility loss associated with carers as in previous submissions	[redacted]	[redacted]	93,771
EAG base case (EAG1, EAG2 and EAG3)	[redacted]	[redacted]	148,638

EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; VA: velmanase alfa.

4.3 Exploratory analyses undertaken by the EAG

In addition to the changes that form the EAG's base case, the EAG explored aspects of the modelling which were believed to be associated with significant uncertainty. Three exploratory analyses were undertaken to provide the Appraisal Committee with an indication of the sensitivity of the ICER to these changes. These changes were: to allow an improvement in patients receiving BSC in the first year (SA1); to change the baseline distribution between the WU HS and the WWA HS (SA2); and to increase the average age of patients when receiving VA (SA3). Individually, each change increased the ICER by between £13,000 and £22,000; combining all three of these changes increased the ICER by over £50,000 to £200,555.

Additionally, the EAG explored the impact of assumptions related to the level of delay in disease progression, with scenarios exploring a range in delay of 4 to 6 years, with no extended time in HSs beyond these delay (SA4 to SA6). If the company's assumption of 6 years without disease progression was correct then the EAG's base case ICER would fall to £112,810. A delay of 4 years with no extended time in HSs, produces a slightly lower ICER than the assumption of 3 years' delay with extended times in each HS as assumed in previous submissions. Combining the assumption of a 6-year delay with SA1, SA2 and SA3 generates an ICER of 156,225.

Table 6: Sensitivity analyses undertaken using the EAG's base case

Description	Incremental		ICER (£)
	Costs (£)	QALYs	
EAG base case	[redacted]	[redacted]	148,638
SA1: Improvement allowed for BSC patients for 10% of patients in year 1	[redacted]	[redacted]	161,644
SA2: Baseline distribution across HSs set to 0.86 for the WU HS and 0.14 for WWA HS	[redacted]	[redacted]	167,650
SA3: Baseline age of patients = 8 years	[redacted]	[redacted]	170,996
SA4: Assumed delay in disease progression for 4 years with no extended time in HSs	[redacted]	[redacted]	142,521
SA5: Assumed delay in disease progression for 5 years with no extended time in HSs	[redacted]	[redacted]	125,758
SA6: Assumed delay in disease progression for 6 years with no extended time in HSs	[redacted]	[redacted]	112,810
SA7: (SA1, SA2, SA3)	[redacted]	[redacted]	200,555
SA8: SA6 and SA7	[redacted]	[redacted]	156,225

BSC: best supportive care; EAG: external assessment group; HS: health state; ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; SA: sensitivity analysis; VA: velmanase alfa; WU: walking unassisted; WWA: walking with assistance.

5 CONCLUSIONS

New clinical evidence provided by the company included additional years of follow-up for the single-arm rhLAMAN-10/-11 study, a new patient and caregiver survey, a new multicriteria analysis conducted for the FDA, correlation plots between serum oligosaccharides and selected clinical outcomes, new case reports, and more information about ongoing data collection for those with and without VA treatment.

The EAG has critiqued the evidence with respect to its relevance to key modelling assumptions that were subject to uncertainty, and other areas that the committee felt remained uncertain after the last committee meeting. It has also considered how planned data collection may resolve these uncertainties.

The EAG notes that the new data has provided longer follow-up for some patients. The modelling assumption of no disease progression for 6 years was based on a last-observation analysis of CHAQ-DI, and [redacted] the patients in this analysis had [redacted] follow-up. CHAQ-DI is a composite outcome, whereas the health state it was used to inform relates to only one component of CHAQ-DI (walking). The numbers of patients at later timepoints were small and therefore results were uncertain. There were also uncertainties about which patients would stay on treatment in clinical practice, and results were heterogeneous with some patients demonstrating [redacted]. The long-term data comes from rhLAMAN-10/-11 which remains a single arm study, and it therefore remains unclear what the efficacy of the treatment is compared to BSC. The results of other outcomes were [redacted] between rhLAMAN-10 and -11, but subject to the same limitations as for CHAQ-DI.

The EAG was concerned that some of the VA treated patients in the 2022 patient and caregiver survey may be included in other studies and noted that mobility [redacted] over 10 years in [redacted] untreated patients, suggesting that those receiving BSC in the model may accrue some improvements. Those receiving VA [redacted] over 5 years of treatment.

The EAG noted the new multicriteria analysis but was unsure of its relevance. The EAG also noted the correlation plots for serum oligosaccharides but concluded serum oligosaccharides cannot reliably predict response in clinical outcomes. The EAG also noted the two new case reports relating to bridging treatment, but since these were non-comparative, concluded the efficacy of VA in this context remains unclear.

The EAG also reviewed evidence relating to age at diagnosis from Etoile Alpha and AllStripes but was unable to conclude what the appropriate age in the model should be for when patients would start VA treatment if it were recommended.

The EAG noted the company's move from recommending detailed stopping rules to recommending that these should be defined by centres and clinicians on a patient-by-patient basis. The EAG noted that this could lead to a decrease in patients stopping treatment, which may increase ICERs.

With respect to areas the committee felt remained uncertain after the last committee meeting, the EAG did not feel that any were fully resolved, though some progress has been made in terms of longer-term data. The EAG believed that the data collection plan had the potential to resolve some key uncertainties such as what happens to patients receiving BSC, but that the company were not able to provide assurances that sufficient data in non-adults would be available to conduct a robust comparative analysis.

The company's base case ICER is £101,073. The EAG's base case ICER is higher at £148,638 although the EAG notes that there is considerable uncertainty in this value. Allowing patients receiving BSC to improve, which was a Committee stated preference, would increase the ICER further, as would assuming that more patients started in the WU HS and increasing the average age of patients treated with VA. Indicative analyses indicate that these changes could increase the ICER to over £200,000

Assuming that VA delayed disease for a period of four years or greater would reduce the EAG's base case ICER. When using the company preferred assumption of a delay of 6 years, with no additional time in HSs reduced this ICER to £112,810. However, adding in improvements in BSC in year 1, assuming more people start in the WU HS and increasing the average age at VA commencement indicates that this ICER could be in excess of £150,000.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Velmanase alfa for treating alpha-mannosidosis [ID800]

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this appraisal.

Your comments and feedback on the key issues below are really valued. The EAR 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 EAR that are likely to be discussed by the committee. The key issues in the EAR 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 EAR.

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 EAR 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.

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 [redacted], all information submitted under [redacted], and all information submitted under [redacted] 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 **xxx.** 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.

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
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Disease progression after treatment with velmanase alfa	Yes	The 6-year delay in disease progression used in the updated model is based on new clinical data from rhLAMAN-11: the treatment duration of the 19 patients aged <18 years for the co–primary outcome of 3MSCT was mean (SD) [redacted] years (median [redacted]). There were similar mean (SD) treatment durations for the other outcomes of 6MWT ([redacted] years, n=19) FVC% predicted ([redacted] years, n=18), CHAQ-DI ([redacted] years, n=19) and EQ-5D ([redacted], n=10) as shown in Appendix C. The 3-year delay preferred by the EAG is likely an underestimate, as the median duration is 4.5 years, so over half of patients had >4 years treatment duration. In this specific age-group, patients demonstrated not only long-term stability in these outcomes, but statistically significant improvements from baseline (see Tables 4 and 6 in company 2023 resubmission and full data set in Appendix C). These new long-term data are highly supportive of a delay in disease progression of at least 6 years in patients initiating treatment with VA aged <18 years, and given the observed long-term improvements from baseline, may be conservative. Two patients with stable disease in rhLAMAN-09 had treatment durations of 11.8 years, supporting the clinical plausibility of even longer term disease stabilisation with VA treatment in this age-group.

		The critique of the rhLAMAN-11 results in the EAG report focuses solely on improvements from baseline, instead of also considering stabilisation from baseline, which is important since disease stabilisation and the years of delay in disease progression are key inputs for the modelling. Disease stabilisation is an important treatment effect and an important outcome for patients in a slowly progressing disease such as AM, where early treatment in childhood can prevent accumulation of oligosaccharides and organ damage. Chiesi agree with the EAG that results are heterogeneous between patients, which is reflective of the inherent variability of AM, as well as the challenging nature of performing tests in children/young adults with cognitive impairment. Although individual plots of 3MSCT, 6MWT, FVC %predicted and CHAQ-DI fluctuate over time as expected (see Appendix C), these new long-term data clearly show that on average, patients who initiate treatment <18 years improve or stabilise over time, for up to 12 years. These data also confirm a greater treatment effect in the new optimised population of patients initiating treatment <18 years when compared those initiating VA aged ≥18 years. In addition, the 6-year delay in disease progression (with no extended time in health states) used in the company base-case is **conservative** given the updated model structure. To remove the uncertainty in the transition probabilities between treatment arms, in response to critique by the EAG for potential double counting, the model has been updated so that patients treated with VA and BSC have the same forwards progression through the model after the 6-year delay. This is a conservative approach as it is very unlikely that there would be zero treatment effect after 6 years in treated patients. To account for this underestimated treatment effect in the updated model, there is no improvement (backwards transition) allowed in the BSC arm (see additional issue 1) and the company's preferred on-treatment utility of 0.18 is maintained, based on long-term improvements in lung function observed in rhLAMAN-11 (see key issue 3). The EAG base-case has kept the preferred assumption of 3 years of delayed disease progression (+ extended time in health states) based on the last committee meeting's preferred settings. It should be noted that the committee expressed this preference base on the evidence applied to the full population rather than the <18 years population being

		considered now, and before the new rhLAMAN-11 data were available. The estimates for extended time in health states was based on the original expert elicitation from 2017 that was deemed acceptable for decision-making while accounting for uncertainty in the evidence at the time. However, the 3-year delay likely underestimates the treatment effect of VA in the new optimised population even with the extended time in health states, and does not take into account the new clinical data from rhLAMAN-11 that shows a greater long-term treatment effect in patients initiating VA <18 years compared with those ≥18 years. For these reasons, Chiesi has maintained the 6-year delay with no extended time in health states in the company base-case. As a scenario, Chiesi have provided an additional analysis using a 4-year delay in disease progression + extended time in health states after discussions with the EAG at technical engagement. This increases the ICER to £129,287. As new evidence to support the delay in disease progression with VA, Chiesi have provided the final CSRs for rhLAMAN-07 and rhLAMAN-09 as requested by the EAG.[1, 2] Real-world evidence from the French registry study (Etoile-Alpha) submitted in May 2022 are now published.[3] These data support the long-term treatment effect of VA and provide real-world confirmation of the new results seen in rhLAMAN-11. Patient-level data provided at clarification describe additional cases of those initiating VA in childhood as part of a managed access programme who were not part of rhLAMAN-11 (patients 0101, 0102, 0201 and 0301). These patients also showed disease improvement with long-term treatment. Despite expected heterogeneity in treatment response, patients showed symptom improvements consistent with rhLAMAN-11, many of which are not captured in a mobility based model (improvements in lung function, cognition, dexterity, fatigue, pain). Additional real-world evidence to further support a delay in disease progression with VA is provided by the natural history caregiver survey - the final dataset has been submitted as part of technical engagement.[4] Although final analysis is still ongoing and results are not

		yet available split by age-group, overall descriptive results are available from 51 patients (26 treated with VA; mean age started on VA, 18.9 years, mean duration of treatment, 6 years). These real-world data highlight the heterogeneity in symptoms and disease progression experienced by patients. Not all patients started treatment in childhood, but overall results support a delay in the progression of symptoms in patients treated with VA when compared with untreated patients, including walking ability, requirement for walking aids, breathing ability, pain/discomfort, mental health and self-care. As this study included patients who also initiated VA in adulthood, it may underestimate the treatment effect in the optimised population of patients initiating <18 years, which show a greater treatment effect in rhLAMAN-11.
Key issue 2: Disease progression without velmanase alfa treatment	Yes	To reduce uncertainty and in response to critique from the EAG, Chiesi updated the model in this resubmission so that transition probabilities after the delay in disease progression were the same for untreated and treated patients, as described above. The transition probabilities were based on expert elicitation from 2017. At that time, the experts had experience of disease progression in untreated patients, but no experience of treating patients with VA, so the estimates for the VA arm have greater uncertainty and were elicited before the availability of long-term rhLAMAN data. At previous committee meetings, the transition probabilities were deemed acceptable for decision-making while accounting for uncertainty in the evidence. New real-world evidence describing disease progression in untreated patients over 10 years (children and into adulthood) is provided in the final dataset of the natural history caregiver survey.[4] The results confirm the heterogeneity of symptoms and disease progression experienced by patients but clearly demonstrate that untreated patients experience a slow gradual decline in their mobility, lung function, disability status and quality of life, with significant healthcare and social care needs. These data should also reassure the committee the mobility of untreated patients does not spontaneously improve.

		As evidence comparing treated and untreated patients is limited, Chiesi continue to collect data in an untreated cohort in the SPARKLE registry and have proposed future indirect comparisons with the treated patient cohort from rhLAMAN-11 and SPARKLE.
Key issue: Utility gain associated with velmanase alfa treatment	Yes	At the previous meeting, the committee agreed that a 0.1 utility gain for children and young people should be used for decision making, as the model may not have captured some important within health-state benefits from VA (such as reduced fatigue and pain, and improved cognition) and benefits from VA not captured in EQ-5D. As the updated model has no extended time in health states to prevent double counting, the utility benefit of VA as patients progress through the model is now further underestimated. In addition, the current model still does not take into account any improvements in lung function or minor infections that have been observed with VA treatment in clinical trials and real-world studies. The results of rhLAMAN-11 in the new <18 years population show statistically significant long-term improvements from baseline in lung function (FVC % predicted, n=19) with a +1.28L gain in FVC at last observation. In the 10 patients who completed the EQ-5D, the utility improvements seen at 4 years were maintained at last observation. As the model does not take into account benefits in lung function, and the on-treatment utility benefits are now further underestimated in the updated model structure, Chiesi has kept the 0.18 utility gain in the company base case, calculated from the +0.9L FVC benefit observed in rhLAMAN-10 at 4 years (based on 0.2 utility gain per 1L accepted for HST19). A scenario analysis using the long-term respiratory benefit seen in rhLAMAN-11 (+1.2L) reduces the ICER further to £89,719. New real-world evidence to support improvements in respiratory function, quality of life, mental health and self-care with VA compared with untreated patients is provided in the final dataset of the natural history caregiver survey.[4]

		The utility values for health states used to model ultra-rare disease in children are inherently uncertain due to the nature of AM; however, the uncertainty could be reduced by newer vignette studies that are planned by Chiesi as part of an ongoing evidence generation plan.
Key issue: Utility loss for carers	Yes	After discussions with the EAG at technical engagement, Chiesi have corrected an error with the cost multiplier function so that the calculations for 1.5 carers are now accurate. Chiesi have also accepted the carer utility values that were preferred by the committee for decision-making and have updated this in the new company base case (see Table 4 below). New real-world evidence describing the carer burden experienced by those looking after children with AM is provided in the final dataset of the natural history caregiver survey.[4]
Key issue: Average age at the start of treatment with velmanase alfa (among children and young adults <18 years)	Yes	Chiesi have maintained the starting age of 6 years in the company base-case to reflect the EAG base-case. This age is appropriate for the new population of patients initiating treatment <18 years and also reflects the updated label of velmanase alfa to cover all paediatric patients from birth. As an autosomal recessive disease, there is a 25% chance of siblings being affected, so these patients are likely to be diagnosed at birth. Additional evidence supporting the age of AM diagnosis is provided by the observational study Zielonka et al. 2019 (N=111)[5] which has been submitted as part of technical engagement. This study reported a median age of diagnosis of 7 years (median, 84 months, IQR 47-198 months) but included patients diagnosed from 1967-2014 and from multiple countries. In the UK, the age of diagnosis is now plausibly lower as diagnostic testing is improving rapidly with the advent of next-generation sequencing and newer gene panels, as well as the possibility of newborn screening in the future.

		New evidence has also been submitted describing the use of VA in infants as a bridging therapy for HSCT (see additional issue 2).
Key issue: Expected proportion of children and young adults needing assistance with walking at the start of treatment with velmanase alfa	No	Chiesi have maintained the starting distribution of patients (75% WU, 25% WWA) in the company base-case. The starting distribution is uncertain. As such, Chiesi have also provided a scenario analysis with the EAG's new preferred starting distributions (86% WU, 14% WWA). This increases the ICER to £115,284.

Additional issues

All: Please use the table below to respond to additional issues in the EAR 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 EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: No improvement in BSC arm.	EAG SA1 and section 3.1.1, EAR	No	As discussed in Key issue 1, the company base case does not include the 10% improvement in the BSC arm, because the updated model has a new conservative assumption of no extended time in health states with VA treatment. Although Chiesi accepts this change is an oversimplification and likely underestimates the potential for delayed disease progression with VA after 6 years, it removes the possibility of double-counting in the delay in disease progression which was a key concern of the EAG in previous assessment reports. Because of the likely underestimation of the treatment effect with VA in this updated model, the company base-case does not include the 10% improvement in the BSC arm used in EAG SA1 because this would underestimate the treatment effect further.

Additional issue 2: Bridging therapy for HSCT	Table 1, EAR; Section 2.1.5, EAR	Yes	One the case reports of the use of VA in infants as a bridging therapy for HSCT has now been published as a full journal article and is provided as part of technical engagement (Santoro et al., 2023)[6].
Additional issue 3: Etoile alpha population being out of scope	Page 14, EAR	No	The EAG have described some patients in Etoile Alpha as being out of scope as some were diagnosed before 6 years of age, so may have type 3 severe AM. This is factually inaccurate – all patients in Etoile Alpha were mild or moderate AM and were treated in France according the labelled indication of velmanase alfa. Although some of the patients included in the real-world Etoile Alpha study were more severely impaired than patients in the rhLAMAN trials, patients included in Etoile Alpha were people with mild to moderate AM (type 1 and type 2) and are indicated for VA, so this is not off label use. Severely impaired patients are <u>not</u> the same as patients with the severe phenotype of AM (type 3) who die in early childhood and are not indicated in the label. We are concerned that the EAG may have misunderstood the severity of the symptoms associated with mild-to-moderate AM and the natural history of the disease, and have further concerns that the EAG has misinterpreted the results of the Etoile Alpha study, which were submitted in May 2022.

Additional issue 4: removal of cost multiplier in calculating the number of carers	Page 23, EAR	No	After discussions with the EAG at technical engagement, Chiesi have corrected an error with the cost multiplier function so that the calculations for 1.5 carers are now accurate. This means that the discrepancy in the utility values described by the EAG can now be removed from the assessment report, as agreed.

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 EAR 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)
Key issue: utility loss for carers	New carer disutility values for type 2/3 SMA	EAG and committee's preferred utility values and correction of the cost multiplier for 1.5 carers	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER: see below
Company's base case following technical engagement (or revised base case)	Incremental QALYs: 2.873 (+0.208 vs original base-case [2.666])	Incremental costs: £299,092 (+£29,684 vs original base-case [£269,408])	Please provide company revised base-case ICER: £104,103 (+£3,030 vs original base-case [£101,073])

Sensitivity analyses around revised base case

Table 5 Updated Key Scenario Analyses

Scenario	Scenario detail	ICER	Rationale and impact of new clinical data on plausibility
Base case	-	£104,103	New base case uses a conservative 6-year delay in disease progression (evidenced from the mean [redacted]-year treatment duration in rhLAMAN-11) then the same transition probabilities as BSC
Include personal and caregiver expenditure		£105,895	Including personal and carer expenditure has a negligible impact on the ICER. There are very limited data that report personal expenditure for families caring for a disabled child. The value is likely to be very specific to each family and their own personal circumstances.
Include caregiver productivity loss	Include caregiver productivity losses due to reduced earnings	£152,944	Including caregiver productivity loss increases the ICER. The model includes the functionality for time spent caring for a person with AM to be distributed between professional care (costed as a PSS cost) or personal care (potentially accounted for as reduced productivity. As patients become less mobile, a greater proportion of their caring is provided professionally, so the impact of including caregiver productivity is there is a reduction in the productivity loss as a patient becomes less mobile, which may be a counterintuitive situation. In reality, it may be the case that as a person becomes more disabled, they may require professional care as well as a carer to retire or reduce their working hours to provide care. The provision of personal caregiver and professional care will be a complex case-by-case situation that takes into account the caregiver finances, employer benefits, social care provisions locally, the ability of caregivers to provide significant care etc. As such, caution should be taken when considering this scenario.
Time horizon 50 years	-	£101,003	New AM mortality data show a median age of death of 45 years (range 18-56 years), with 47% of deaths due to pneumonia[7]. Reducing the time horizon of the model from 100 to 50 years reduces the ICER.

No annual withdrawal	No treatment discontinuation for responders until entering 'WC' health state	£220,629	Removing annual discontinuation after year 1 increases treatment costs and the ICER. Clinical trial and real-world data support discontinuation rates in paediatric patients. Clinical advice suggests this scenario is not plausible for a once-weekly IV infusion and stopping rules for ERTs are routine practice in NHS LSD centres.
Permanent delay in progression	A permanent delay in disease progression in VA responders until treatment discontinuation	£62,977	New rhLAMAN-11 data and real-world evidence suggest not only a long-term delay in disease progression of at least 6 years, but trial data in children support disease improvement up to 12 years, which suggests that a permanent delay in disease progression is plausible and that the base case is conservative.
Discontinue if WC dependent	Treatment is discontinued upon entering the 'WC dependent' health state	£97,898	Including a stopping rule upon WC dependence slightly reduces the ICER. Clinical practice suggests this scenario may be plausible for a once-weekly IV infusion and stopping rules for ERTs are routine practice in NHS LSD centres.
UK MPS Society Health State Utilities	MPS Society Survey utility values are used for HSUVs	£82,398	HSUVs for AM are subject to uncertainty due to the small and heterogeneous patient population. Using alternative sources of HSUV collected from a relevant patient population in the UK reduces the ICER.
rhLAMAN-11 utility benefit	Include long-term on-treatment respiratory utility benefit	£89,719	Long-term rhLAMAN-11 results show statistically significantly improved lung function (FVC and FVC % predicted) from baseline – new results show greater improvements in FVC in children at last observation in rhLAMAN-11 (up to 12 years) compared with rhLAMAN-10 (up to 4 years) which show long-term improvements in

	from rhLAMAN-11 **(+0.256)**		respiratory function with VA are sustainable and plausible, which are supported by real-world data.
Exclude carer disutility	Exclude carer disutility	£105,202	Removing carer disutility has a negligible impact on the ICER.
Include 2.2 caregivers		£103,599	Caring for a child(ren) with AM impacts on multiple caregivers, including other parents, grandparents and siblings as shown in the new caregiver survey. In TA755, 2.2 caregivers was accepted for a similar genetic disorder (type 2/3 SMA). As such, the base case with 1.5 caregivers may be conservative and a scenario with 2.2 caregivers is plausible.
Starting age of 7	Based on Zielonka 2019	£112,189	Increasing the stating age to 7 increases the ICER. The Zielonka 2019 study reported a median age of diagnosis of 7 years, however in the UK, the age of diagnosis is now plausibly lower as diagnostic testing is improving rapidly with the advent of next-generation sequencing and newer gene panels, as well as the possibility of newborn screening in the future.
Starting distribution	86% WU, 14% WWA	£115,284	Increasing the proportion of patients starting in the WU state from 75% to 86%, and decreasing the proportion of WWA patients from 25% to 14% increases the ICER.
4-year delay + extended time in health states		£129,287	A 4-year delay in disease progression combined with an extended time in health states increases the ICER.

Abbreviations: BSC, best supportive care; HSUV, Health State Utility Values, ICER = incremental cost-effectiveness ratio; LSD, lysosomal storage disorders; MPS = mucopolysaccharidosis; VA = velmanase alfa; WC, wheelchair dependent

References

1. Chiesi data on file. rhLAMAN-07 clinical study report. 2023.
2. Chiesi data on file. *rhLAMAN-09 clinical study report*. 2023.
3. Guffon, N. ; Gaches, F.; Daridon, C.; Larbi, H.; Heron, B. , *Long-term efficacy of velmanase alfa in patients with AM: retrospective analysis of a French Registry for up to 9.5 years*, in *Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium*. 2022: Freiburg, Germany.
4. RDRP, Rare Disease Research Partners. *Natural history caregiver survey - final dataset*. 2023.
5. Zielonka, M., et al., *Ultra-orphan lysosomal storage diseases: A cross-sectional quantitative analysis of the natural history of alpha-mannosidosis.* J Inherit Metab Dis, 2019. **42**(5): p. 975-983.
6. Santoro, L., et al., *First experience of combined enzyme replacement therapy and hematopoietic stem cell transplantation in alpha-mannosidosis.* Am J Med Genet A, 2023. **191**(7): p. 1948-1952.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Velmanase alfa for treating alpha-mannosidosis [ID800]

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this appraisal.

Your comments and feedback on the key issues below are really valued. The EAR 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 EAR that are likely to be discussed by the committee. The key issues in the EAR 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 EAR.

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 EAR 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.

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 9am on Monday 31 July 2023**.** 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.

About you

Table 1 About you

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

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue: Disease progression after treatment with velmanase alfa	Yes/No	Clinical trial data and patient outcomes have shown that velmanase alfa has the potential to significantly halt disease progression over a prolonged period of time offering patients stability, enhanced life expectancy and a life with minimal health related burden. Due to the highly heterogeneous nature of alpha mannosidosis, it is hard to predict disease progression after treatment as patients respond differently. Age and presentation of symptoms at diagnosis could have an impact on treatment outcomes, with patients responding differently, even if they have the same mutation or are within the same family. Outcomes are also predicted by Clinical severity of symptoms at time treatment commenced. We know that starting

		treatment before onset of clinical disease has the potential to prevent or reduce rate of progression giving a better prognosis of outcomes 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). Harmatz et al (2018) concluded "Thus, velmanase alfa appears to improve outcomes across multiple variables compared with placebo in both pediatric and adult patients".
Key issue: Disease progression without velmanase alfa treatment	Yes/No	Natural history studies show that alpha mannosidosis is a very heterogeneous condition and can vary from patient to patient. Please see previous patient organisations submissions for overview of disease progression and natural history. In summary without treatments individuals all accessed a broad range of services, including clinical support, speech and language therapy, audiology, occupational therapy, social care, MH services, financial support, educational support and

		wheelchair services. Multiple surgical procedures were required due to hearing problems, skeletal issues, adenoid and tonsillectomy. Mobility varies considerably, with some remaining mobile well into adulthood and others becoming immobile. Please see Adam et al (2018) Disease progression of alpha mannosidosis and impact on patients and caers – A UK natural history survey https://doi.org/10.1016/j.ymgmr.2019.100480 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'.
Key issue: Utility gain associated with velmanase alfa treatment	Yes/No	Utility benefits of velmanase alfa have been observed in L Borgwardt's paper, 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 https://doi.org/10.1007/s10545-018-0185-0) Disease stabilization is also a relevant end point, especially for adult patients The committee have already recognised that velmanase alfa is a promising and innovative treatment. Further global studies and registries as presented by the company should hopefully show the ongoing benefit of velmanase alfa for patients, recognizing that disease stabilization is also a relevant end point, especially for adult patients.

		Any ongoing uncertainties could potentially be monitored through a MAA.
Key issue: Utility loss for carers	Yes/No	For utility loss of carers supporting untreated individuals, Please see Adam et al (2018) Disease progression of alpha mannosidosis and impact on patients and caers – A UK natural history survey https://doi.org/10.1016/j.ymgmr.2019.100480
Key issue: Average age at the start of treatment with velmanase alfa (among children and young adults <18 years)	Yes/No	Based on UK MPS Society figures; The mean age of diagnosis of under 18 year olds known to the MPS Society was 4 years (range 2-5years). We would expect all children who met the eligibility criteria, to be started on treatment, as soon as possible following diagnosis. This aligns with the age of patients (mean age 4.5ys) who were enrolled on the long term safety and efficacy of velmanase alfa treatment in children under 6 years of age with alpha mannosidosis. Guffon et al (2023) https://doi.org/10.1002/jimd.12602
Key issue: Expected proportion of children and young adults needing assistance with walking at the start of treatment with velmanase alfa	Yes/No	Reviewing children under 18 years known to the MPS Society and assuming all would be started on treatment soon after diagnosis, we can conclude the following; Whilst some children at diagnosis had some balance and co-ordination issues, all were mobile and required no assistance with walking. Based on UK figures our assumption is that 0% of children and young adults starting treatment would require assistance with walking.

Additional issues

All: Please use the table below to respond to additional issues in the EAR 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 EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

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.

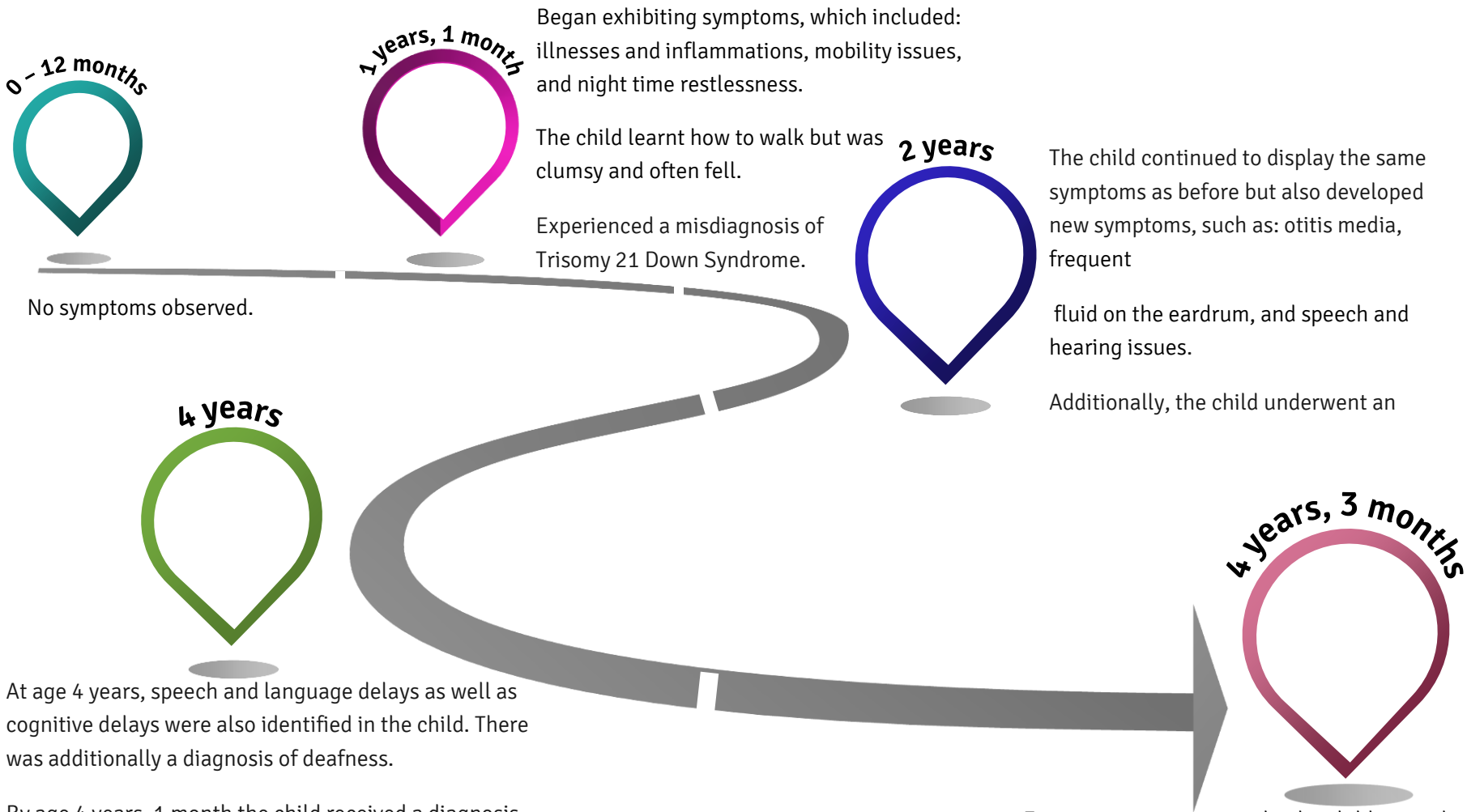
Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR 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)
Insert key issue as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Patient A – Case Study

Timeline overview



Patient A – Case Study

Demographics

Age now: 5 years, 5 months

Sex: Male

Age first symptoms appeared: 1 year, 1 month

Age of diagnosis: 4 years, 1 month

Age first started treatment: 4 years, 3 months

Diagnostic pathway

Patient A developed infections and inflammations from the age of 1 year and 1 month. This included fevers and common colds. He would often cry a lot when they had a fever. The child's immune system couldn't manage infections, so whenever he had a fever, he would need to immediately take medication (exact medication unspecified). His parents felt it wasn't obvious that the child had any underlying condition at that time.

The child learnt how to walk at the age of 14 months but was said to be clumsy and often fell over. Other symptoms the child experienced was a frequent runny nose, restlessness at night time, and issues with toileting unaided. Around this age, the family went to their Ears, Nose and Throat (ENT) specialist who misdiagnosed the child with Trisomy 21, Down Syndrome. This diagnosis was refuted by their paediatrician.

The child continued to exhibit the same symptoms at age 2, but also developed additional symptoms, such as otitis media, speech and hearing impairments, and experienced three instances of fluid on the eardrum. The otitis media, or middle ear infection, had caused the inflammation and build-up of fluid behind the eardrum. To assist with this, the child underwent an unknown number of surgeries to have tubes implanted in his ears.

At age 4 years, following the conclusion of the brainstem evoked response audiometry (BERA) test, the child received a diagnosis of deafness. The child's speech at this point was unclear and strangers had difficulty understanding him. Despite attending speech therapy, there was continued issues with speech and language and so he was subsequently diagnosed, by a specialist, with speech and language delay. The child was then seen by a new paediatrician who noticed that he had a developmental delay. The child was referred to a specialist paediatric centre for testing and was diagnosed with slight cognitive delay. The family were advised that hearing aids would improve the deafness, cognitive delay, and speech and language delay.

An ENT specialist referred the family to a human genetics practice as they had an inclination that the child may have a genetic defect. The child was diagnosed with alpha-mannosidosis at the end of February 2022, when he was 4 years and 1 month old.

Patient A – Case Study

Experience with treatment

The parents had a discussion with a specialist about a Bone Marrow Transplant but were advised not to go through with this procedure.

The ENT specialist then advised the family of the available ERT treatment and, approximately two months after diagnosis the child received his first treatment of ERT on the 19th of April 2022 through local regulatory health authority.

To avoid having a permanent infusion area, nurses switch the location of the cannula every time they administer an infusion to the child.

The child has been said to have been doing well on ERT and symptoms have improved.

Illnesses and inflammations:	• The number of illnesses have been significantly fewer • Less reliant on medication to eliminate fevers • May occasionally require medicine at night to help the fever subside
Hearing difficulties and infections:	• Hasn't had a middle ear infection since starting ERT • Currently has permanent tubes fitted in his ears which will be removed between February and March 2024
Speech and language:	• Since starting ERT, speech and language have improved • Currently attending speech therapy which is working well, has improved his ability to communicate with his peers • By 5 years of age, his vocabulary had significantly expanded, had developed a passion for learning, and was able to talk to his peers about common interests • Despite his speech improvement, he is reportedly less clear than his younger sibling. He sometimes attempts to say too much at once and has difficulty finding the right words.
Toileting:	• Is now able to go to the toilet on his own and doesn't require support
Sleep:	• Doesn't require as much support with sleeping • Is less restless at night time
Mobility:	• There are no more restrictions to his mobility. He can now climb the playgroup equipment a lot more quickly and with considerably more confidence. His teachers occasionally find themselves unable to keep up with the child as his mobility had greatly improved. • Currently attends occupational therapy

Patient A – Case Study

Impact of treatment on patient and family

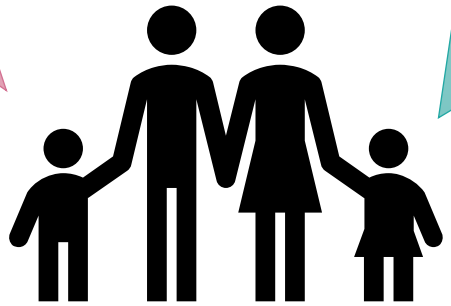
Impact on the child	Impact on the family
Health Owing to the treatment, the child's health continues to be managed and kept steady. The child presents good mental health as he is typically joyful and happy. Hobbies The child learnt how to independently ride a bike by the time he was 4 years old. His parents describe him as courageous, often active, and partakes in regular exercise. **On Mondays, the child attends gymnastics with their sibling. They also attend a football club where he is described as not being fearful and very involved in the sport.** Kindergarten The child currently attends kindergarten every day and is within a class of 16, with 4 children who also receive additional support. He has an array of kindergarten friends who are able to comprehend him when he communicates. Additionally, the child takes part in all of the kindergarten activities and likes to sing the songs he learns in kindergarten. He is said to greatly enjoy kindergarten and is eager to attend every day.	Health Since alpha-mannosidosis is a life-limiting condition, the family initially found it difficult as they were worried about their child's future. The family now feel happier knowing that the treatment is keeping their child's health stable and that they can now enjoy observing how happy and joyous their child is. Travel Home therapy worked considerably better for the child's family due to less travel required. The parents affirm that treatment is typically uninterrupted and that nurses are able to administer even while they are abroad, acknowledging the value of uninterrupted access to care. Treatment is only interrupted when the child is sick with a fever. Socialisation The parents feel the only disadvantage of ERT is that they find it difficult to balance a social life due to their busy schedule with infusions and the child's extracurricular activities. The diagnosis and treatment has since brought the family closer together and they enjoy spending time together as a family.

Patient A – Case Study

Family statement

"Really, we have a lot of trust and we're supported very well by the MPS Society, but also by the doctors. And we know that there are lots of offers as well that we're very grateful for. Unfortunately sometimes we can't take them up because of time restrictions."

"It's maybe hard to say in one sentence, but really we're just very glad that the disease can be treated. And as a family, we are very hopeful that medicine just keeps advancing in the field and that we can protect the brain and the bones and everything. So we're just hopeful, really, for medical advances. And we are very glad that patients can be supported. And we hope that patients can be supported even more in future."



"We were very happy that we were able to start his treatment so quickly and so soon, because there was only really the check-up."

"And also, thanks to one of our nurses, we're in a WhatsApp group with other families with the same situation. And we really like that exchange with those families. And other families are always really astounded and surprised by how quickly we got the diagnosis and the treatment and the home therapy. They always say that we're kind of the example for how quickly things can go in Germany as well. That it can be very fast to get support and treatment for the kid as well."

Velmanase alfa for treating alpha-mannosidosis (ID800)

EAG additional analyses following the company's response to Technical Engagement (August 2023)

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
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Date completed	7th August 2023

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Declared competing interests of the author
No author has a conflict of interest to declare.

CONTENTS

TABLES

FIGURES

1 INTRODUCTION

This document summarises the latest company submission relating to the clinical and cost-effectiveness of velmanase alfa (VA) for treating alpha-mannosidosis (AM). This highly specialised technology appraisal has been long-running with the initial committee meeting taking place on the 25th of April 2018 with a fourth committee meeting being undertaken on the 8th of June 2022. During this time, the company have made multiple changes including the population within the decision problem, the estimates of clinical gain for patients within the model and within the evidence base, which has been updated when new data became available. In July 2023, the EAG produced a report that critiqued the company's submission in May 2023 and included an EAG base case and exploratory analyses.[1]

The company responded to the EAG report in Technical Engagement.[2] The EAG has reviewed this document and has produced this report in response. This document should be read in conjunction with the last EAG report.[1] For brevity, in the clinical section the EAG has not reproduced text from its earlier report but has focussed on new data provided by the company and some additional commentary on previous evidence. In contrast, the text relating to the cost-effectiveness analyses has been largely replicated as these are not lengthy pieces of text and are considered important in providing context for the analyses undertaken.

Following a phone call between NICE, the EAG and the company, the company acknowledged a mistake in its model which has been rectified to the satisfaction of the EAG. One further change is that in writing this document the EAG could not justify excluding a different starting distribution between health states (HS) in its base case (See Section 3.2.1 for further details). Accordingly, this change has become part of the EAG base case rather than a sensitivity analysis.

Section 2 focuses on the critique of new data provided by the company. Section 3 provides the EAG's critique of the modelling undertaken by the company. Section 4 provides cost-effectiveness results reported as incremental cost-effectiveness ratios (ICERs) expressed in terms of cost per quality-adjusted life year (QALY). Section 5 provides the EAG's conclusions.

2 CRITIQUE OF CLINICAL EFFECTIVENESS DATA IN RESPONSE TO TECHNICAL ENGAGEMENT

This section of the report should be read in conjunction with the EAG's last report.[1] The views expressed there should be considered the EAG's current view, unless an update has been provided here.

2.1 Response to company's comments titled "Key issue 1: Disease progression after treatment with velmanase alfa"

2.1.1 rhLAMAN-11

The company initially supported its assumption of a 6-year delay in disease progression using data on CHAQ-DI (see Table 10 of company CS 2023, where it is stated "*rhLAMAN-11: mean treatment duration of* [redacted] *years in 19 children treated with VA – see Section* ***Error! Reference source not found.***" where Section 3.2.3 refers exclusively to CHAQ-DI results.)

In its Technical Engagement response,[2] the company now supports the 6-year delay using multiple outcomes from rh-LAMAN-11, including the 3-minute stair climb test (3MSCT), 6-minute walk test (6MWT), forced vital capacity as a percent of age-standardised predicted values (FVC% predicted), CHAQ-DI and EQ-5D. The mean duration of treatment for these outcomes ranged from [redacted] years for the EQ-5D to [redacted] years for FVC% predicted. The EAG notes that median is likely to be a better measure than the mean where data are skewed because the median is less prone to bias by outliers. Therefore, the use of the mean may not be appropriate here given that the treatment duration data of the 19 patients aged <18 years are not symmetric. Median durations are [redacted] years for 3MSCT, 6MWT and CHAQ-DI, [redacted] years for FVC% predicted, and [redacted] years for EQ-5D. This reflects the point made previously by the EAG that there are few patients at later time points, since more than 50% of patients were not follow-up for 6 or more years.

The company highlights "*long-term stability*" and "*statistically significant improvements from baseline*" for these outcomes. The EAG provided a critique of these results in Section 2.1.1.1.2 of its last report,[1] noting the small number of patients at time points beyond 4 years, data missing for some patients without an explanation and lack of response or stabilisation in some patients based on the plots provided in the company's appendix C. The EAG focusses here on the two outcomes of greatest relevance to the model's mobility health state, the 3MSCT and 6MWT, and this should be considered alongside the existing critique of the CHAQ-DI data, which remains of equally high relevance to the model's mobility health states.

3MSCT

The 3MSCT data shown indicates that at least [redacted] Others seem to fluctuate over time, with consistently [redacted] in total below 0 at any given time point. The majority, however,

have an improvement or stabilisation. It should also be noted that children with AM grow, albeit often at a slower rate, and the impact of growth on the improvements and stabilisations observed cannot be determined from the data provided. Furthermore, it cannot be assumed that the patient who does not respond would be taken off treatment, as they may stay on treatment if they have responded in other domains.

Figure 1 rhLAMAN-11: Individual plots of 3MSCT over time. Reproduction of Figure 3 in the company's 2023 appendix C.

6MWT

[redacted]

Again, growth may impact on these results. An analysis of 6MWT% predicted was conducted, but the individual plots were not supplied by the company. The values for the 6MWT and the 6MWT% predicted have been collated by the EAG in Table 1 for 4 and 6 years. 6MWT% predicted showed [redacted] overall, with the lower end of the range [redacted]

Table 1 rh-LAMAN-11: 6MWT and 6MWT % predicated data at two selected timepoints

Timepoint	6MWT not adjusted for age				6MWT% predicted			
	Change from baseline		% change from baseline		Change from baseline		% change from baseline	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
48 months	[redacted]							

72 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CHAQ-DI

For ease of comparison, the individual plots for CHAQ-DI are again reproduced here (Figure 3). Please note, that in these plots values above zero indicate worsening from baseline. The EAG's previous critique included: that CHAQ-DI is a composite outcome that may not be representative of walking states; the last observation is [redacted] in the analysis, and responses are heterogeneous; it is unclear which patients in the analysis would stay on treatment in clinical practice; [redacted] are in the analysis at 6 years to provide certainty in the estimated effect; and that there was no comparator arm.

Figure 2 rhLAMAN-11: Individual plots of 6MWT over time. Reproduction of Figure 4 in the company's 2023 appendix C.

Figure 3: Individual plots of CHAQ-DI over time. (Reproduction of Figure 6 in the 2023 company appendices)

2.1.2 Natural history caregiver survey

The company has submitted a new natural history caregiver survey. The EAG are unsure if this is the same patient and caregiver survey that was provided in the May 2023 CS. In the new analysis, patients and/or caregivers were asked about health states 10 years ago, 5 years ago, and 0 years ago (presumed to be when the questionnaire was completed). The company states that these data "*further support a delay in disease progression with VA*" but do not state what length of delay is supported by the data. The company notes some patients in the analysis started treatment in adulthood and may therefore underestimate treatment effects in children.

The EAG notes that it is unclear how many of these patients are also in rhLAMAN-11. It also notes that this survey relies on patient/carer recall, which is less reliable than prospectively collected data, and may be at greater risk of recall bias. Furthermore, the mean time on treatment was 6.0 ±4.4 years, (median 5.3, range 0.3-12.5 years), and therefore half the patients have 5.3 years or less follow-up, meaning comparisons to 5 or 10 years ago are not 5 or 10 years on-treatment for many patients. It is also not clear how many of these patients are non-adults, and what the outcomes for non-adults would be. Notably, slide 33 indicates that there are [redacted] patients treated with VA who are <18 years of age in the analysis, but [redacted] who are ≥18 years. The results, which show that patients on enzyme replacement therapy (ERT), although it was unclear if all had received VA) have [redacted] (see slide 9), are therefore difficult to interpret, may double count rhLAMAN-11 patients, and are at high risk of recall bias.

Other outcomes include [redacted]. These outcomes are subject to the same overall uncertainties regarding the number who were non-adults, the time on treatment, the amount of double counting with rhLAMAN-11 and the risk of recall bias.

The slide deck suggests a number of additional analyses that could be done within the patient and caregiver survey, which include taking into account time on treatment and age (slide 34). The EAG agrees these analyses would be useful but notes that to avoid double counting of patients in any overall consideration of the evidence base, it would be useful for these analyses to be conducted for those who are not already considered in rhLAMAN-11 separately.

2.1.3 Other points made by the company

The company states that the EAG did not consider stabilisation, only improvement. The EAG are not able to comment on what may considered "*stabilisation*" in the context of these outcomes in these patients, but note that for CHAQ-DI, the [redacted].

The company stated that the additional patients from Etoile Alpha showed symptom improvement. The EAG had insufficient time to consider these patients separately and had asked the company to integrate

them into their analysis, which they did not do. The EAG suggests that to avoid double counting of patients who appear in both Etoile Alpha and rh-LAMAN-11, and in the absence of an integrated analysis, evidence from rhLAMAN-11 should be considered as the primary source of evidence when assessing long term efficacy.

The EAG does not think they requested the CSRs for rhLAMAN-07 and -09. These documents have not been critiqued as rh-LAMAN-11 includes patients from these studies.

2.2 Response to company's comments titled "*Key issue 2: Disease progression without velmanase alfa treatment*"

The company has submitted a new natural history caregiver survey.[3] In this survey, it is unclear how many untreated patients provide data relating to disease course prior to age 18 years, though the EAG notes that in the excel database supplied, if the correct filters have been applied by the EAG, this number may be as little as [redacted]. [redacted] Further evidence from the rhLAMAN-05 randomised controlled trial showed some patients in the placebo arm improved (see Section 3.1.1).

The [redacted] in the patient and caregiver survey who have not had treatment may not be sufficient to facilitate a matched analysis with long-term data for patients on treatment from rhLAMAN-11 and nor has the study recorded the same outcomes as rhLAMAN-11. The company notes that SPARKLE continues to recruit untreated patients. This study is critiqued in Section 2.3 of the EAG's 2023 report.[1]

2.3 Response to company's comment titled "*Key issue: Utility gain associated with velmanase alfa treatment*"

The EAG notes that the FVC% predicted data referred to by the company are not new. The use of an absolute gain in lung volume may be confounded by the growth of children with AM. The EAG's reading of Tables 5 and 6 in the 2023 CS[4] indicates that the company's claim that the EQ-5D was maintained cannot be verified, as values [redacted].

The EAG has critiqued the natural history caregiver survey in Section 2.1.2. The EAG cannot comment on the usefulness of the planned vignette studies since these are not described in sufficient detail.

2.4 Response to company's comment titled "Key issue: Average age at the start of treatment with velmanase alfa (among children and young adults <18 years)"

The company provides additional evidence on the age at diagnosis of patients with AM from a published study.[5] The study was a review of evidence in the published literature, which included case descriptions or case series, and found 111 cases across 72 publications. The use of published articles to estimate age at diagnosis may not result in a representative sample compared to clinical practice in England.

The company's patient and caregiver survey[3] reports the following mean and median ages at diagnosis: [redacted]. It is not clear how representative these samples are of patients in clinical practice in England, or whether mean age at diagnosis may change with greater diagnosis of siblings and/or de novo presentations if a treatment becomes available. The EAG remains unclear what the appropriate age at presentation in the model should be.

2.5 Additional issues raised in the technical engagement

Etoile alpha population out of scope: The EAG did not state that these patients were out of scope, only that they may be (see Section 2.1.6 of EAG's 2023 report[1]). The EAG acknowledged the uncertainty in age at diagnosis partly in response to this uncertainty about which patients were eligible for inclusion. The new evidence from the patient and caregiver survey has not resolved the issue of age at diagnosis (see Section 2.4) and since in this study the [redacted], the EAG remains uncertain what the appropriate age at diagnosis should be in the model.

The EAG is fully aware that severe impairment is different from severe disease course and believe that it has at no point indicated otherwise. The EAG made efforts to ascertain the inclusion criteria of Etoile Alpha and the rhLAMAN early trials (because Etoile Alpha drew some of its population from these trials) by referring to the CSRs provided by the company and to the protocols published on clinical trial online registries. The EAG could not find any mention of a restriction to mild to moderate disease and considers it reasonable to note that there was uncertainty about the severity of disease course of some of the participants in Etoile Alpha. The company have now explicitly stated that the patients were all mild to moderate, and the EAG is satisfied with this statement. The generalisability of the age at diagnosis of this cohort remains unclear, however.

3 EAG CRITIQUE OF THE MODELLING IN THE COMPANY'S RESUBMISSION

This section focuses on the modelling undertaken by the company in its latest submission. Section 3.1 details where the company's model does not use the Appraisal Committee's preferred assumptions but uses alternative values. The company has an agreed Patient Access Scheme which takes the form of a simple discount ([redacted]); this has remained unchanged since the previous submission.

3.1 Changes between the Committee's preferred assumptions as expressed in the last ECD[6] and the company's base case

A summary of the differences between the Committee's preferred approach and the approach used by the company in its base case are shown in Table 2. These are discussed in more detail in Sections 3.1.1 to 3.1.3.

Table 2: Summary of the differences between the NICE Appraisal Committee's preferred approach and the approach used by the company

Number	EAG Parameter description	Committee's stated preference (ECD paragraph)	Approach used by the company in its base case in the latest model
1	Improvements in mobility for patients receiving velmanase alfa (VA) and best supportive care (BSC)	The improvements should be allowed in both the VA and BSC arms (4.15)	The model allows improvements in the VA arm but not in the BSC arm
2	Benefits of delayed progression associated with VA treatment	3 years of delayed disease progression followed by extension of time in health states (4.16)	6 years of no disease progression but no additional extension of time in health states
3	Chronic utility gains in children above that associated with mobility health states	0.10 utility gain for children (4.17)	0.18 utility gain for children

3.1.1 Improvements in mobility for patients receiving VA and BSC treatment

In rhLAMAN-05, the same proportion of patients improved from the walking with assistance (WWA) health state to the walking unassisted (WU) health state in the VA and the BSC arms, although this population contained adult patients as well as non-adult patients. In previous models, the company assumed that improvement was only possible in the VA arm and not the BSC arm, with the committee stating that "*the likelihood of improving mobility in the model should have been consistent with the observed trial data. It concluded that the model should have allowed for improvements in mobility for people having both velmanase alfa and best supportive care*." In the recent model, the company has not acted on the committee's advice, but has assumed, based on expert clinician opinion, that improvement will only happen in the VA arm, with a 20% improvement in both the wheelchair (WC) and in the WWA health states in the initial two years of treatment, with the probability of improvement falling to 2.5% in these states in every subsequent year. Contrastingly, improvement is not allowed in the BSC arm. Previous scenario analyses have shown that the incremental cost-effectiveness ratio (ICER) expressed in terms of cost per quality-adjusted life year (QALY) would increase if patients were allowed to improve when receiving BSC.

The EAG notes that none of the data related to improvement (or disease progression) in the model has used data from the clinical studies. Instead, these values are all estimated from clinical expert opinion which will carry considerable uncertainty. The EAG further comments that data previously related to the increased time in health states due to VA treatment that has been used in previous base cases has been discarded.

The EAG has been unable to run any robust analyses given that the model uses clinical expert opinion only however, to provide an indication of the impact of the results of allowing there to be some improvement on BSC an analysis has been undertaken where it is assumed that there is 10% chance of improvement in mobility in the first year only for patients receiving BSC. This value is still considerably less than the improvements assumed for patients receiving VA treatment.

3.1.2 Benefits of delayed progression associated with VA treatment in mobility for patients receiving VA and BSC treatment

The Committee concluded that "*assuming 3 years of delayed disease progression followed by an extended time in health states based on the original expert elicitation was acceptable for decision making while accounting for uncertainty in the evidence.*" The company, however, has used a different approach in the latest model, where there is 6 years of assumed no disease deterioration whilst receiving VA treatment, but has removed any benefit of VA, in terms of transition probabilities, compared with BSC subsequently. The benefit of being in a better health state at year 6 due to receiving VA treatment

will impact on costs and QALYs through the patient's lifetime, however, the transition probabilities are the same for all patients after 7 years.

Based on the comments in Section 2.1., the EAG believes that the duration of disease delay associated with VA is uncertain. Therefore, the EAG has run an analysis where the Committee's preference has been reinstated compared with the new approach used by the company.

3.1.3 Chronic utility gains in children above that associated with mobility health states

The Committee "*agreed that a 0.1 utility gain for children and young people, and a 0.05 utility gain for adults should be used for decision making.*" The company, however, has assumed a value of 0.18 utility gain whilst being on treatment. This value, which is associated with respiratory benefit, was included in a previous base case submitted by the company and has already been considered by the Committee. The value of 0.18 was estimated by using the 0.9 litre change in forced vital capacity observed in patients in rhLAMAN-10 in patients aged under 18 years and multiplying this by a utility gain of 0.02 per 0.1 litre gain that was an assumption preferred by the NICE Committee in HST19.[7]

The company comments that in rhLAMAN-10 that the EQ-5D-5L was statistically significantly improved (by 0.083) in children receiving VA, although data from rhLAMAN-11 suggests that the EQ-5D-5L improvement has [redacted]. The EAG notes that caution is needed in interpreting these results as: there may have been selection bias in completing the EQ-5D which was completed by 10 of 19 children; that some of these utility gains may also be accounted for within the model due to improvements in mobility state; and that the gain is non-comparative.

As the committee had seen the majority of the data provided by the company prior to its decision to prefer a value of 0.10, the EAG has run analyses using a utility gain of 0.10.

3.2 Changes in the Company's base case which do not oppose the Appraisal Committee's stated preference

The company made some changes made to the model which did not oppose the Committee's stated preference, largely because there was no stated preference in the ECD. These changes are detailed in

Table ***3*** and are discussed in more detail in Sections 3.2.1 to 3.2.5.

Between the company's submission in May 2023 and the submission in August 2023 the company has changed its preference in relation to the disutility associated with carers, reverting to the values used in the model discussed at the last committee meeting. It is unclear whether the company was persuaded by the arguments put forward by the EAG or whether the impact on the ICER (the company's assumption in May 2023 increased the ICER) was considered when reversing the decision on carer utility. The change in the disutility for carers has resulted in increased QALYs for all analyses.

The EAG's comments in its previous document[1] about there being a mismatch between the text and the model was incorrect and is retracted. The reason for the erroneous statement was that there was an additional change in the model that was not highlighted by the company, which when investigated resulted in the identification of an error relating to the costs of professional care. The company has amended this error, which has resulted in the costs being reduced in all analyses.

Table 3: Changes in the company's model that do not oppose the NICE Appraisal Committee's stated preferences

Number	EAG Parameter description	Committee's stated preference (ECD paragraph)	Approach used by the company in its base case in the latest model.
1	Starting distributions amongst mobility health states	No comment	The model now uses a starting population combining data from patients under 18 years.
2	Age of patients treated	No comment. Previous model used 6 for the paediatric cohort, 12 for the adolescent arm and 18 for the adult cohort	The model assumes that the non-adult patients are all aged 6 years.
3	Correction of model errors	N/A	The EAG identified some model errors which have been amended by the company.
4	Updating of data values	N/A	The most recent values have been used in the model.

3.2.1 Starting distributions amongst mobility health states

In the company's revised model, it is assumed that 75% of non-adult patients start in the WU health state and that 25% of non-adult patients start in the WWA health state. Based on the company's response to clarification question 8,[8] it is believed that the distribution of patients in rhLAMAN-10 were 12 in the WU health state, 2 in the WWA health state and 2 in the WC health state with the company assuming that the patients in the WC health state could be grouped with the patients in the WWA health state. The EAG believes that an alternative plausible scenario is that patients in the WC health state would not be treated and if these are omitted the distribution between health states would be 86% (12/14) in the WU health state and 14% (2/14) in the WWA health state. The higher proportion of patients in the WU state would also be consistent with patients being diagnosed at an earlier age as assumed by the company. This alternative distribution has been added into the EAG's base case, although previously this was a sensitivity analysis.

3.2.2 Age of patients treated

In the company's revised model, it is assumed that all patients receive treatment at the age of 6 years with the functionality to use 8 years instead which is implied in the model to be the average age of patients under 18 years in rhLAMAN-10. As detailed in Section 2.1.6, there is uncertainty regarding the average age of people treated with VA were it to receive a positive recommendation. The EAG has run a sensitivity analysis using 8 years rather than 6 years.

3.2.3 Correction of model errors

During the appraisal process the EAG identified what it believed to be errors in the company's model. The company agreed that this was the case and changed the model to remove the errors. The EAG is content with these changes.

3.2.4 Updating of data values

Due to the relatively large period of time since the company's original submission in 2018 some of the data that was appropriate initially has since become dated. At the request of the EAG, the company has updated parameters to the latest available values. The EAG is content with this change.

4 RESULTS PRESENTED BY THE COMPANY AND GENERATED BY THE EAG

This section provides deterministic ICERs. No appropriate probabilistic ICERs could be generated as the functionality in the company's model had not been updated to reflect the new company base case. However, as detailed in the first EAG report,[9] the model was relatively linear and thus the deterministic ICER should be a good indicator of the probabilistic one.

4.1 The Company's base case ICER

The company's base case ICER is shown in Table 4 and is £104,103.

Table 4: The company's base case

Treatment	Discounted		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
VA	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	104,103

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; VA: velmanase alfa.

4.2 The EAG's base case ICER

The EAG has made changes to the company's base case where the EAG believed there was not compelling evidence that the committee's stated preference in the ECD was no longer correct.[6] These changes relate to the delay in disease progression associated with VA treatment and the chronic utility gain due to being on VA treatment. Additionally, the baseline distribution amongst HSs has been changed.

The impacts of these changes are shown individually, and in combination, in Table 5. The EAG's base case ICER, which combines all changes is £174,369 although the EAG cautions that there is still considerable uncertainty in this value. If the company's preferred assumption regarding the delay in disease progression was used the ICER falls to £139,862, see Table 6.

Table 5: Changes made to the company's base case by the EAG and the EAG's preferred base case

Description	Incremental		ICER (£)
	Costs (£)	QALYs	
Company's base case	[redacted]	[redacted]	104,103
EAG 1: Delay in progression for VA = 3 years with extended time in health states	[redacted]	[redacted]	127,434
EAG 2: Utility gain from VA = 0.10	[redacted]	[redacted]	125,240
EAG 3: Baseline distribution across HSs set to 0.86 for the WU HS and 0.14 for WWA HS	[redacted]	[redacted]	114,974

EAG base case (EAG1, EAG2 and EAG3)	[redacted]	[redacted]	174,369

EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; VA: velmanase alfa.

4.3 Exploratory analyses undertaken by the EAG

In addition to the changes that form the EAG's base case, the EAG explored aspects of the modelling which were believed to be associated with significant uncertainty. Two exploratory analyses were undertaken to provide the Appraisal Committee with an indication of the sensitivity of the ICER to these changes. These changes were to allow an improvement in patients receiving BSC in the first year (SA1); and to increase the average age of patients when receiving VA (SA2). Individually, each change increased the ICER by between £7,000 and £24,000; combining both changes increased the ICER by £32,000 to £206,418.

Additionally, the EAG explored the impact of assumptions related to the level of delay in disease progression, with scenarios exploring a range in delay of 4 to 6 years, with no extended time in HSs beyond these delays (SA3 to SA5). If the company's assumption of 6 years without disease progression was correct, then the EAG's base case ICER falls to £139,862. A delay of 4 years with no extended time in HSs, produces a slightly lower ICER (£169,044) than the assumption of 3 years' delay with extended times in each HS. Combining the assumption of a 6-year delay in disease progression with SA1 and SA2 generates an ICER of £167,228.

Table 6: Sensitivity analyses undertaken using the EAG's base case

Description	Incremental		ICER (£)
	Costs (£)	QALYs	
EAG base case	[redacted]	[redacted]	174,369
SA1: Improvement allowed for BSC patients for 10% of patients in year 1	[redacted]	[redacted]	181,853
SA2: Baseline age of patients = 8 years	[redacted]	[redacted]	198,320
SA3: Assumed delay in disease progression for 4 years with no extended time in HSs	[redacted]	[redacted]	169,044
SA4: Assumed delay in disease progression for 5 years with no extended time in HSs	[redacted]	[redacted]	152,553
SA5: Assumed in disease progression for 6 years with no extended time in HSs	[redacted]	[redacted]	139,862
SA6: (SA1 and SA2)	[redacted]	[redacted]	206,418
SA7: SA5 and SA6	[redacted]	[redacted]	167,228

BSC: best supportive care; EAG: external assessment group; HS: health state; ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; SA: sensitivity analysis; VA: velmanase alfa; WU: walking unassisted; WWA: walking with assistance.

5 CONCLUSIONS

The conclusions from the EAG report 2023[1] should be considered alongside this section. Only conclusions that have been affected by the company's technical engagement response[2] are included here.

"Key issue 1: Disease progression after treatment with velmanase alfa": The company's technical engagement[2] supported the assumption of a 6-year delay in disease progression with reference to additional outcomes from rhLAMAN-11, where previously only results form CHAQ-DI had been used, and reference to a new patient and caregiver survey. The EAG concludes that although the rhLAMAN-11 plots for the 3MSCT and 6MWT [redacted], the lack of adjustments for growth in the 3MSCT and 6MWT individual plots makes it difficult to interpret to what extent [redacted] for the results seen. A comparison of 6MWT and 6MWT%predicted mean and median values at 48 and 72 months suggests using 6MWT without accounting for age favours VA. CHAQ-DI, whilst imperfect as it includes other aspects of disability alongside walking state, may remain the most relevant outcome to inform the mobility health states in the model as it may not be affected by growth to the same extent, and includes a question about walking with assistance (though an analysis of this portion of the questionnaire was not made available to the EAG, see EAG report 2023,[1] Section 2.1.1.1.1). The small number of patients at later time points reduces the EAG's confidence in the results for all outcomes, though the EAG notes that greater numbers are available up to 48 months. It remains unclear which patients included in the analyses would stay on treatment in clinical practice. Additional data from the patient and caregivers survey does not provide more certainty as the amount of double counting of rhLAMAN-11 patients is unclear, analyses have not been provided for non-adult patients which account for their time on treatment, and results are at high risk of recall bias.

The EAG therefore does not believe that sufficient evidence has been submitted to robustly demonstrate a delay to treatment progression of 6 years for those who would stay on treatment in clinical practice. The EAG is not stating that this is implausible but highlights the considerable uncertainty and has provided scenario analyses within the cost-effectiveness modelling which covers the committee's preferred assumption following the last committee meeting and delays in disease deterioration between 4 and 6 years.

"*Key issue 2: Disease progression without velmanase alfa treatment*": The company's patient and caregiver survey included patients who have not had ERT or HSCT/BMT treatment for AM. The EAG notes that the [redacted] in the patient and caregiver survey who have not had treatment may not be sufficient to facilitate a matched analysis with long-term data for patients on treatment from rhLAMAN-11 and notes that the outcomes that are measured are not the same as in rhLAMAN-11. The

company notes that SPARKLE continues to recruit untreated patients. This study is critiqued in Section 2.3 of the EAG's 2023 report.[1]

"Key issue: Utility gain associated with velmanase alfa treatment": The EAG noted that the use of absolute gain in lung volume in non-adult patients may be confounded by growth, and that the company's claim that the EQ-5D was maintained over time could not be verified, as values [redacted]. The EAG could not comment on the usefulness of planned vignette studies since these are not described in sufficient detail.

"Key issue: Average age at the start of treatment with velmanase alfa (among children and young adults <18 years)": The EAG concluded that the published study provided by the company was of unknown representativeness to the clinical practice in England, and that the patient and caregiver survey reported [redacted] mean ages at diagnosis in the ERT and untreated arms, but these were also of unknown representativeness to clinical practice in England. The EAG remains unclear what the appropriate age at presentation in the model should be.

Etoile Alpha population out of scope: The EAG are satisfied with the company's statement that all patients in Etoile Alpha were mild to moderate patients. The generalisability of the age at diagnosis of this cohort also remains unclear, however.

The company's base case ICER is £104,103. The EAG's base case ICER is significantly higher at £174,369 although the EAG notes that there is considerable uncertainty in this value. Allowing patients receiving BSC to improve, which was a Committee stated preference, would increase the ICER further, as would increasing the average age of patients treated with VA. Indicative analyses indicate that these changes combined could increase the ICER to over £200,000, although this would fall to £167,228 if the company's preference regarding delay in disease progression was assumed.

If VA delayed disease for a period of four years or greater this would reduce the EAG's base case ICER (£169,044). Using the company preferred assumption of a delay of 6 years, with no additional time in HSs reduced this ICER to £139,862. However, adding in improvements in BSC in year 1 and increasing the average age at VA commencement would increase the ICER of £139,862 to £167,228. Whilst there is uncertainty in the ICER and the Committee's deliberations may reach a different value to that of the EAG, the EAG believes that the ICER is likely to be more than £150,000.

6 REFERENCES

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This short addendum to the EAG's response to the company's response to Technical Engagement has been undertaken at the request of NICE. It its base case, the company had excluded people within wheelchairs from those receiving VA; both the company's base case and the EAG's base case have been rerun allowing patients starting in the wheelchair (WC) health state (HS) to receive VA. The distributions between the walking unassisted (WU), walking with assistance (WWA) and WC HS are contained in for the company's base case, the EAG's base case and the requested analysis. In this analysis, the distribution across HSs was 75% WU, 12.5% WWA and 12.5% WC based on an assumed 12, 2 and 2 patients in each group. (Table 1)

Table 1: The distribution of patients amongst health states used in selected analyses

	WU	WWA	WC
Company base case	75%	25%	0.0%
EAG base case	85.7%	14.3%	0.0%
Requested analysis	75%	12.5%	12.5%

The results from the company's base case and the EAG's base case are shown in Table 2 which also contains results when the distribution from the requestion analyses was used.

Table 2: Change in results when the new distribution across HSs was used

Description	Incremental		ICER (£)
	Costs (£)	QALYs	
Company's base case	[redacted]	[redacted]	104,103
EAG base case	[redacted]	[redacted]	174,369
Company's base case with a new distribution amongst HSs	[redacted]	[redacted]	112,432
EAG base case with a new distribution amongst HSs	[redacted]	[redacted]	167,771

It is seen that the ICER increases by approximately £8000 in the company's base case and decreases by approximately £8000 in the EAG's base case when the distribution includes patients in wheelchairs.

Matt Stevenson / Andrew Rawdin

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Chiesi Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Abigail Stevenson

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Comment number	Comments

1	**Question 1. Has all of the relevant evidence been taken into account?**
	
	No – Chiesi do not believe NICE has taken into account all the clinical evidence included in the company resubmission, as the following evidence was not taken into account as part of the committee's decision-making, nor was it discussed at the committee meeting:
	
	• Long-term data from rhLAMAN-10 in 33 adults and children treated for 48 months:
	  ○ Long-term mobility status data from Borgwardt et al., 2018 (1) that showed 3 patients using a wheelchair at baseline no longer required mobility assistance at 48 months
	  ○ <18 and ≥18 years subgroup data for mobility, lung function, quality of life outcomes published in Lund et al., 2018 (2) and Borgwardt et al., 2018 (1) show differences in observed treatment effect in children and adults, and the importance of disease stabilisation and reduction in pain in adults that are not adequately captured in EQ-5D or the model
	  ○ BOT-2 analysis published in Phillips et al., 2020 (3) that showed statistically significant improvements in upper limb extremity function, fine motor deficits and running speed that are not adequately captured in EQ-5D or the model
	  ○ Caregiver feedback of 33 patients published as a poster by Lund et al., 2021 (4) that report improvements in clinical problems and substantial reduction in minor infections after long-term treatment that are not adequately captured in EQ-5D or the model
	  ○ Infection data from rhLAMAN-05 and rhLAMAN-10 published as a poster by Borgwardt et al., 2018 (5) to show rate of infection per infected patient was 1.5 under placebo vs. 0 with velmanase alfa and substantiates the long-term reduction in minor infections that is not adequately captured in EQ-5D or the model
	  ○ Super-responder analysis of rhLAMAN-05 and -10 published by Harmatz et al., 2018 (6) reporting patients who respond in all 3 domains used to estimate the proportion of patients who would discontinue treatment according to proposed 'super responder' stopping rules that were not considered by the committee
	• Real-world evidence in the Etoile Alpha retrospective registry in [redacted] adults and children (7):
	  ○ Patient-level data provided at technical engagement to show long-term clinical and functional improvements in [redacted] patients treated for >5 years, for up to 9 years
	  ○ Patient-level age-adjusted FVC (% predicted) data provided at technical engagement to show that lung function improvements seen in children were not due to growth
	  ○ Infection data that showed [redacted] infections during the entire study period – when compared with natural history data showing lifelong recurrent infections
	  ○ Individual case reports from the study describing improvements in activities of daily living, reduced pain and fatigue, and ability to return to school after treatment show improvements in quality of life and impact beyond direct health benefits that are not adequately captured by EQ-5D or in the model – these were highlighted in the ERG report as "*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"* but does not appear to have been considered in decision-making
	• Real-world case studies in 5 adults treated with velmanase alfa published in Garcia-Navarrete et al., 2021 (8) that showed disease stabilisation, reduced infections and fatigue
	  ○ 2 siblings on treatment for >7 years who can still walk unaided in their 3rd decade of life: had treatment discontinued for ~70 days during the COVID-19 pandemic and experienced worsening of gait and mobility during that time, that improved on treatment re-initiation
	  ○ 1 patient initiated with velmanase alfa at 19 years old had improved speech and no longer required a wheelchair to walk after treatment

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	○ 1 patient initiated with velmanase alfa at 21 years old whose disease stabilised after 18 months of treatment, and fatigue was reduced, with EQ-5D VAS score improvement from 70 to 80 and increased ability to work fulltime due to improved energy levels • A published case report of a UK patient initiated at 32 years old and treated for >7 years (Cole et al., 2021 (9)), supported by the clinical expert statement submitted at technical engagement and the patient expert testimony at the 4th committee meeting ○ Showed improvements in mobility, reductions in pain and analgesia requirements, no infections since treatment, improved cognition, social skills and independence so is now able to work in a shop ○ Despite mobility improvements, this patient did not change health state in the model as orthopaedic boots were classed as 'walking with assistance'. Post-treatment, this person's EQ-5D-5L utility value was 0.758 vs. 0.378 for patients on BSC in the MPS Society utility survey (Adams et al. 2019 (10)). When compared with 0.577, the committee's preferred baseline utility health state for 'walking with assistance', this equates to a 0.18 utility gain in an adult patient that is not captured in the model. • Caregiver burden and carer quality of life data published in Adam et al., 2019 (10) , Verrechia et al., 2021 (11) and case reports in Garcia-Navarrete et al., 2021 (8) report lifelong caregiver burden as patients with AM cannot live independently. Caregiver disutility and burden is not adequately captured in the model and was not taken into consideration in decision-making. ○ Verrachia et al., (11) reports long-term residential care needs of an adult patient ○ Case reports describe siblings affected by AM where the caregiver burden is greater • A published study (Hennermann et al., 2022 (12)) reported a median age of death of 45 years with 47% primary causes of death due to pneumonia, providing new evidence on the natural history of untreated patients that was not considered by the committee regarding the impact of reduced infections with velmanase alfa • All the cost-effectiveness scenarios that were provided in the submission and updated at technical engagement were not considered, or the clinical plausibility discussed with clinical experts at the 4th committee meeting, including time horizon, a permanent delay in responders/super-responders and discontinuation on wheelchair dependency • The proposed data collection plan was not fully considered, including proposed statistical analyses using data from ongoing studies rhLAMAN-07 and -09 that will report in 2023, the AllStripes study that will report in 2023, and the SPARKLE registry that reports yearly. ○ Statistical analyses (Table 66, p104 of the company submission) addressing the clinical uncertainty on the lack of control arm will estimate the treatment effect compared with untreated patients using long-term data ○ The AllStripes retrospective study will include ~25 untreated patients in the US and UK – interim data from [redacted] untreated patients have been provided during consultation that show patient mobility journeys and age when ability to walk unassisted was lost (range [redacted] years, n=[redacted]) which will inform the transition probabilities in future modelling (Chiesi data on file, 2022 (13)) ○ The SPARKLE registry (protocol published in Hennerman et al. 2020 (14)) includes untreated and treated patients in Europe: 2-year interim baseline data provided at technical engagement for 40 patients recruited from 21 sites, including baseline EQ-5D-5L data (n=16) and CHAQ-DI (n=14) patients. Recruitment is ongoing with an expected 70 patients at 40 sites: 5 sites have been confirmed in the UK. ○ Additional data collection will start in Scotland from Q4 2022 after velmanase alfa was accepted for the SMC's ultra-orphan framework (SMC 2022 (15)) Taken together, these results provide long-term evidence of delayed disease progression in adults and children treated with velmanase alfa, with clinically relevant improvements or stabilisation in measures of mobility, lung function, physical functioning, activities of daily living, reduced infections and improved quality of life when compared with baseline measurements. A substantial

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	proportion of patients have been treated long-term for over 5 years, with [redacted] patients for up to 9 years in Etoile Alpha, and 3 patients reported in case studies treated for over 7 years. The clinical validity of these results has been confirmed by two clinicians working in the UK NHS who manage patients with AM in England and Wales (16). In not considering all the above evidence in its decision-making processes, it is possible that the committee have not fully understood the natural history of the disease, underestimated the long-term clinical, quality of life benefits as well as the impact of treatment beyond direct health benefits for patient and carers, and overestimated the cost per QALY in their preferred ICERs. The ultra-rare and heterogeneous nature of AM means that the exact length of the delay in disease progression and exact utility values are unclear and have some inherent uncertainty. This uncertainty means it is especially important for the committee to consider all available evidence, including real-world evidence. However, there is no evidence during the appraisal and in the ECD that the committee has substantively engaged with the company's resubmission or examined the totality of the evidence. The evidence provided in the re-submission is quite clearly relevant and it is also quite clear the committee has not taken all of it into account. The totality of the current evidence submitted supports a consistent long-term delay in disease progression, reductions in infections and pain, and improvements in clinical and quality of life parameters that are clinically plausible in adults and children, in a substantial proportion of the diagnosed AM population. If after considering all the current evidence, the committee remain unsatisfied with the degree of uncertainty, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the specific clinical uncertainties highlighted by the ERG through a managed access agreement. In Section 4.31, the committee have not explained why the proposed data collection plan and analyses cannot address the clinical uncertainties, only that the data would not provide robust estimates, but not the reasons for this: "*This was because the ongoing trial and registry data would not provide more robust estimates for quality of life or long-term clinical effectiveness."* This statement appears contradictory to the evidence, as the ongoing SPARKLE registry and AllStripes study have already reported interim mobility data and utility data in untreated patients, and the rhLAMAN-07/-09 studies will provide 10-year clinical trial data in treated patients in 2023. In Section 4.31 it states "*Also, there are substantial challenges in collecting any robust evidence from the small number of people with alpha-mannosidosis*". This statement appears to be discriminatory to patients with ultra-rare diseases in that it suggests that the managed access process is not appropriate for assessing treatments for ultra-rare conditions with small populations as the robustness of data required by the HST process cannot to be collected in ultra-rare populations, which would not be fair or equitable for people with AM. In Section 4.31, "*the committee noted that the company's latest submission contained several years of additional evidence that was not available when it first considered velmanase alfa. But it agreed that this had not substantially resolved the uncertainties discussed at previous evaluations.*" Since the original draft guidance in 2018, long-term rhLAMAN-10 and real-world data in patients treated for up to 9 years has reduced the uncertainty on long-term disease stabilisation and improvements in mobility, lung function and quality of life, with subsequent improvements in cost-effectiveness estimates. New natural history data are available on the mortality and morbidity of untreated patients and natural history studies, such as Hennerman et al., 2022 (12) and the AllStripes study (13). This contradicts the conclusions of the committee that further data collection could not reduce uncertainty and indicates that all the relevant evidence has not been considered in its decision-making. Indeed, the committee have changes its assumptions during this time and increased the length of delay in disease progression from zero to 3 years, and increased the utility benefit in children and adolescents from 0.05 to 0.1, based on new rhLAMAN-10 analyses and real-world evidence.

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	In Section 4.31, "*It concluded that it was highly unlikely that evidence collected within an MAA of a reasonable duration would resolve the key uncertainties enough for it to re-evaluate velmanase alfa with a greater degree of certainty at the end of the managed access period*." This statement shows that the committee have misunderstood or have not considered the proposed data collection plan appropriately, as the statistical analyses described in Table 66, p104 of the company submission can address the clinical uncertainties and use data that will report in 2023, supplemented by the yearly SPARKLE interim analyses that already has 40 patients recruited and will report its first efficacy results in 2023. Chiesi provided information on outcomes being measured in the ongoing European SPARKLE registry and rhLAMAN-07 and -09 trials that will provide these data within a reasonable timeframe (up to a maximum of five years), as specified by the Innovative Medicines Fund. In Section 4.32, the ECD states that the current proposed MAA with its starting rules contradicts principle 1 of the Innovative Medicines Fund. As the Innovative Medicines Fund Principles were published in June 2022 (17) after the submission of the proposed draft MAA and five years after the start of this appraisal, Chiesi is committed to working with NICE and NHS England to ensure that the principles guiding any agreed MAA are appropriate for the assessment of velmanase alfa. Immediately dismissing the proposed MAA as incompatible with the IMF without taking into account the company's commitment to working within the IMF is incorrect and fails to respect proper process and the company's approach and submissions. In Section 4.1, the committee recognised that AM severely affects the quality of life of families and carers, and noted that people need a high level of care the professional life of patients, families and carers can be compromised. However, the committee have failed to consider the true carer disutility and impact beyond direct health benefits for carers provided by the new real-world evidence, with no discussion of carer disutility in section 4.18. Patient case reports from Etoile Alpha and published case studies shows increased independence, and return to school or full-time work for some patients treated with velmanase alfa that has not been taken into account by the committee when considering the impact of beyond direct health benefits in section 4.28. In addition, as AM is an autosomal recessive disease, there is a 25% chance that any siblings will be affected by AM. In families with multiple affected siblings, caregiver burden is greater, so discussion of the use of multiple caregivers in the economic model may be justified. The implications of the committee not fully considering carer disutility or the impact beyond direct health benefits for carers means that the long-term benefits for carers has been underestimated and their preferred ICERs have overestimated the cost per QALY. In Section 4.30, the committee also stated it had considered patient testimony of people treated with velmanase alfa, but the only specific information included was in section 4.10 on infections. Other aspects of the patient expert testimony were not included in the guidance which implies this has not been considered in committee decision-making. In particular, the testimony from the UK patient treated with velmanase alfa for over 7 years that was highlighted by the patient expert representative from the MPS Society at the 4th committee meeting has not been included in the draft guidance. As such, this testimony was not considered in a fair and equitable manner during the decision-making process, and the long-term patient benefit of velmanase alfa in real-world clinical practice has been underestimated. In addition, no questions were asked of the patient expert with AM who attended the 4th committee meeting to explore potential patient benefits of a treatment for AM that could delay disease progression and reduce pain and fatigue. The committee's failure to take all of the relevant evidence into account would clearly have a material impact upon the cost-effectiveness assessment. In Section 1, the committee states that the preferred cost-effectiveness estimates are higher than those considered value for money. However, the committee have not fully considered the clinical plausibility of all the scenarios provided by the company because they were not discussed with clinical experts at the 4th committee meeting, and were not published in the guidance. The decision on the preferred scenario appears arbitrary and was not agreed with clinical experts. Some scenarios were

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	plausibly cost-effective under the £100K per QALY threshold, including a discontinuation scenario if patients become wheelchair dependent, discontinuation based on non-"super-responders" from a published responder analysis, and a scenario with a permanent delay in disease progression in those "super-responders". This was especially true for children and adolescents. In Section 4.23 the committee "*agreed that applying stopping rules would imply that people who continue treatment would gain greater long-term benefits than the averages seen in clinical trials*". The committee should fully explore these scenarios in consultation with clinical experts. In particular, the committee should take into consideration the proposed starting and stopping criteria, which are similar to those used for other ERTs in current clinical practice according to a UK clinical expert consulted as part of our submission. If the committee remain unsatisfied with the degree of uncertainty after full consideration of the clinical plausibility of the scenarios in consultation with clinical experts, the plausibility of these scenarios can be assessed during a period of managed access and addressed by the proposed data collection plan and statistical analyses.
2	**Question 2 - Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** **No** – as well as not taking into account all the evidence (as detailed in comment 1), the committee has not made reasonable interpretations of the evidence in the draft guidance, including: • a misunderstanding and/or lack of consideration of the natural history of alpha mannosidosis as a slowly progressive, heterogeneous ultra-rare disease and the clinical and patient relevance of disease stabilisation as a treatment effect • a lack of consideration of NICE's real-world evidence framework (18) and the challenges in performing studies in AM in its interpretations of Etoile Alpha, case series and case reports • its preferred assumption for a 3-year delay in disease progression is not evidence-based, and does not take into account the delay in disease progression observed in real-life clinical practice in 10 patients treated long-term for between 7-9 years • its preferred assumptions for the on-treatment utility benefit of 0.05 for adults and 0.01 for children based on EQ-5D-5L trial measurements may underestimate the benefit for an ultra-rare heterogeneous disease such as AM, and may not be appropriate, in line with the new NICE methods guide (19). It also does not take into account improved functioning, activities of daily living and independence observed in the real-world evidence. The company's preferred use of clinical-trial observed FVC and 6MWT surrogate utility values were accepted by the committee in HST19 for MPSIVa (20), an MPS-like condition deemed similar to AM by a clinical expert at the 4th committee meeting. As such, the committee's interpretation that these values lack face validity appears unfair and inequitable. • the reasons for its preferred scenario for the most plausible ICERs were unclear, contradict the committee conclusions that strict starting and stopping rules could reduce the ICER, and how the ultra-rare nature of the condition and the low budget impact were included in its estimation of the most plausible ICERs was not explained in the guidance. The guidance is also unclear how the committee had considered expert opinion in its interpretations of the most plausible ICER or its preferred scenario, as these scenarios were not discussed at the 4th committee meeting. As such, the decision-making on the preferred scenario appeared arbitrary and it would appear that only those scenarios above the threshold, or increased the ICER were preferred. As such, the committee's interpretation of the preferred scenario and ICERs appears unreasonable.

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	• insufficient flexibility on the degree of uncertainty that is acceptable for the only treatment available for an ultra-rare disease, for use in population that includes children (under 18 years old) and for an innovative technology, in line with the new NICE methods guide (19). As such, the committee's interpretation of the preferred scenario and ICERs appears unreasonable, and inequitable. • a lack of clarity, contradiction and inconsistency in the reasons for rejecting the draft MAA and proposed data collection plan and statistical analyses • the descriptions of the evidence and its interpretation throughout the guidance are inconsistent, contradictory and unclear, and have not been updated accurately to reflect the new submitted evidence, nor includes all the clinical expert and patient testimony at the 4th committee meeting. This suggests that the process and interpretations used in the committee decision-making has not developed over the time that has passed since the publication of the first ECD, so the maturing evidence base has not been considered in a fair and equitable process using new and more appropriate methodology for assessing real-world evidence in ultra-rare disease Taken together, a misunderstanding or lack of consideration of these issues means that the committee have not interpreted the clinical and economic evidence reasonably, and the clinical and quality of life benefits of velmanase alfa have been underestimated, and therefore the committee prefer ICERs that overestimate the cost per QALY. If after considering all these issues reasonably in consultation with clinical and patient experts, the committee remain unsatisfied with the degree of uncertainty, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the specific clinical uncertainties highlighted by the ERG through a managed access agreement. As noted above, the committee appears to have dismissed he company's proposed MAA without providing proper reasons or justifications. Alpha mannosidosis is an ultra-rare, slowly degenerative, heterogeneous condition. Throughout the guidance and the interpretation of the clinical evidence, there are examples that demonstrate that the committee have failed to give appropriate consideration to the natural history of the condition, or the clinical and patient-relevance of long-term disease stabilisation that has been observed in studies of velmanase alfa conducted for nearly 10 years. In Section 1 and 2, the description of AM as 'rare' and as 'people surviving into adulthood' is not a fair representation of the severity of the condition. New data on the natural history and the severity of the symptoms experienced by untreated patients has been provided by the company (see comment 1) but has either simply not been considered and/or interpreted reasonably. Throughout the guidance, the committee refer to the '*size of the benefits'* and that '*the size of the benefit was small'.* Although clinically-relevant improvements were observed in rhLAMAN-10 and the real-world studies, the committee have not taken into account disease stabilisation in their interpretations of the evidence, which is especially relevant for adult patients who are likely to have irreversible cellular damage from oligosaccharide accumulation. In Section 4.8, the guidance also refers to Etoile Alpha as 'off-label use' which is factually inaccurate and represents a misunderstanding of the indicated population for velmanase alfa. If after reasonable consideration of the natural history, the severity of the condition and the importance of disease stabilisation, the committee remain unsatisfied with the uncertainty in delayed disease progression and clinical benefits with velmanase alfa compared with untreated patients, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address this specific issue through a managed access agreement within the time period specified by the IMF. The committee's preferred assumption of 3 years of delayed disease progression followed by the extended time in health states in patients who respond to treatment seems arbitrary, not evidence-based and the reasons for choosing 3 years and rejecting the company's estimate of 5 years (which was based on clinical trial and real-world evidence) is not explained clearly in the guidance.

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	The consideration of a clinically-plausible longer delay or permanent delay in disease progression in 'super-responders' was also not included in the guidance or discussed with clinical experts. This is despite of its conclusions in 4.23 that the committee "*accepted that it was plausible that using a more stringent definition of response might have further increased the delay in disease progression*". The long-term clinical trial and real-world evidence shows disease stabilisation or improvement with velmanase alfa compared with baseline in 10 patients treated long-term for between 7-9 years. The committee has also not interpreted the real-world Etoile Alpha and the case studies reasonably in line with the NICE real-world evidence framework (18), which demonstrates how committees can accept real-world evidence in their decision-making. Given the challenges in performing clinical studies in AM, there is inherent uncertainty in the precise size and nature of the long-term clinical and quality of life benefits. And given this uncertainty, it is imperative that the committee takes into account all available evidence in its totality. In particular, it is important that results observed in clinical trials are confirmed with real-world data. The real-world evidence for velmanase alfa strongly supports the plausibility of the long-term clinically-relevant improvements in mobility, functioning and quality of life observed in clinical trials. The challenges with AM trials should be considered reasonably when the robustness of the results are interpreted by the committee in line with NICE's real-world evidence framework. The real-world evidence includes data from adults and children treated with velmanase alfa who have a wide range of symptoms and at different disease stages, including those in the later stages of disease progression, who have cognitive impairment and/or who use a wheelchair. The different nature of the treatment effect seen in adults and children provided in subgroup analyses from the clinical trials has not been considered by the committee in light of the new real-world evidence. Adults with AM are more likely to be in a wheelchair and experience greater levels of pain than children. As such, although substantial improvements in walking status may not have been seen in adults treated with velmanase alfa, other clinically relevant treatment benefits, such as reduced levels of pain and fatigue were seen in clinical trials and supported by real-world evidence. The committee's preferred assumption of an additional on-treatment utility benefit of 0.05 for adults and 0.1 for children using EQ-5D-5L utility gains from rhLAMAN-10 underestimates the true utility benefit. This is because the committee has not reasonably interpreted the limitations of EQ-5D in measuring utility values in AM, as this is a generic instrument that does not capture all the clinical manifestations of the disease, and is not appropriate for children. The limitations of EQ-5D was highlighted by a paediatric metabolic clinical expert at the 4th committee meeting. EQ-5D-5L measurements cannot be appropriately crosswalked to the 3L in children as no appropriate UK value set exists in children, and the Hernandez-Alava algorithm recommended by NICE only applies from age 16 years. For these reasons, the EQ-5D is not recommended by NICE when assessing quality of life in children in its new NICE manual (19). As such, the committee has not reasonably interpreted the utility benefit in children in line with its own guidance. In addition, the committee have not considered the challenges in measuring quality of life in AM as a heterogeneous ultra-rare condition affecting multiple organ systems, in adults and children, and those with cognitive impairment. Despite these significant challenges, rhLAMAN-10 showed long-term improvements in EQ-5D-5L and real-world evidence from the patient reports showing clinically relevant improvements in activities of daily living, independence, levels of pain and fatigue, which together strongly support the robustness of the quality-of-life improvements and the long-term on-treatment utility benefit with velmanase alfa used in the model. We do not believe the committee has taken into account these limitations and significant challenges when interpreting the quality-of-life results of the clinical trials and the real-world evidence in section 4.7, 4.9 and 4.17. Because of these limitations and the utility benefit underestimation with EQ-5D, the company preferred to use clinical-trial observed FVC and 6MWT surrogate utility values, in line with the new NICE methods guide. These were accepted by the HST committee in HST19 for MPSIVa (20), a condition deemed similar to AM by a clinical expert at the 4th committee meeting. As such, the committee's rejection of these values and their interpretation that they lack face validity appears unfair and inequitable. The implications of the committee not considering the limitations in measuring utility with EQ-5D in adults and children with AM, and not considering the use of

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	surrogate utility measures appropriately means that the long-term quality of life benefits for patients has been underestimated and their preferred ICERs overestimate the cost per QALY. The interpretations of the most plausible ICER and preferred scenario for the cost-effectiveness estimates are unclear in the guidance and have not been decided in consultation with clinical experts. The company provided scenarios with stopping rules based on 'responders' and 'super-responders' but these were not discussed with clinical experts at the committee meeting. In Section 4.23 the committee "*agreed that applying stopping rules would imply that people who continue treatment would gain greater long-term benefits than the averages seen in clinical trials*", and in 4.26, "*the committee recalled that strict starting and stopping rules could reduce the ICER*" but these were not included in the preferred scenario nor the most plausible ICERs, and the reasons and clinical validity of excluding them was not given. The guidance does not include results of the scenarios with the starting and stopping rules applied, so the quantitative effect on the plausible ICERs is not known. In 4.33, "*the committee also considered that it was appropriate to take into account the very small population size and the size of the impact on the NHS in its decision making. It also took into account the other factors affecting its decision, including the substantial uncertainty in the clinical and economic evidence*". Given the acceptance of the committee that starting and stopping rules could reduce the ICER and the consideration of the small population size and the budget impact, and the importance of these to the overall assessment, it is wholly unclear how the committee took these into account in its interpretations of the most plausible ICER (if at all). In NICE's new manual (19) in section 6.2.34 it states in specific circumstances (in treatments for a rare disease, or for use in a population that is predominately children, or for innovative and complex technologies), the committee may be able to make recommendations accepting a higher degree of uncertainty. Given that velmanase alfa fulfils all 3 of these criteria, and the ultra-orphan nature of AM, the committee's interpretation that the clinical and economic evidence was too uncertain for them to accept seems to contradict the new manual and appears to be unreasonable. If after reasonable consideration of the clinical plausibility of the scenarios in consultation with clinical experts and in line with the new NICE methods guide, the committee are still unwilling to accept the levels of uncertainty, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the clinical uncertainties through a managed access agreement within the time period specified by the IMF.
3	**Question 3. Are the provisional recommendations sound and a suitable basis for guidance on the use of velmanase alfa in the context of national commissioning by NHS England?** **No** - as well as the committee not taking into account all the evidence (as detailed in comment 1), and not making reasonable interpretations of the evidence (as detailed in comment 2), the provisional recommendations are not sound or suitable for guidance for the use of velmanase alfa in the context of a national highly specialised service, because: • The wording in the section 1 of the recommendations describing AM inappropriately as 'rare' suggests that the committee have misunderstood or not considered important aspects of AM as an ultra-rare, progressive heterogeneous disease and thus are not sound or suitable for recommendations for the only licensed disease-modifying treatment for AM. • The process followed by the HST committee in assessing the current evidence base at the 4th committee meeting does not align with the latest NICE methods guide and real-world evidence framework in assessing ultra-rare diseases, utility values in children or real-world studies. This has led to unreasonable interpretations of the evidence and flawed decision-making, so that the recommendations are not sound or suitable in the context of national highly specialised commissioning by NHS England. • The interpretations regarding the degree of uncertainty in the evidence base for commissioning the only treatment option for patients with AM in England and Wales are

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	not sound or suitable and contradict NICE's own methods guides for considering flexibility in the degree of acceptable uncertainty for treatments for rare diseases, for children, and for innovative therapies. As AM is an ultra-rare disease, indicated for children, and velmanase alfa is the only disease-modifying treatment for AM without which patients have no other therapy, the recommendations are not sound or suitable. • The proposed starting and stopping rules have not been included in the most plausible cost-effectiveness estimates, (see comment 2 above) which are similar to those often used by NHS England in commissioning ERTs as part of a highly specialised service. When considered alongside the small patient numbers and low budget impact, the decision-making on the grounds of cost-effectiveness using an ICER without these starting and stopping rules applied is not sound or suitable in the context of national highly specialised commissioning. • As noted under comments 1 and 2, the committee's dismissal of the company's proposal for an MAA lacks appropriate justification, and in any event is inconsistent, contradictory and improper.
4	**Question 4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** **Yes** – the processes followed by the HST committee in its decision-making and by NICE during the public consultation period appear to discriminate against people with AM on the grounds of disability due to the ultra-rare, disabling nature of AM. The processes used also discriminate against children with AM on the grounds of age and disability. • The process used by the HST committee appears to be discriminatory to patients with AM on the grounds of disability due to the ultra-rare, disabling nature of AM. The population with AM is small, even for a HST; however, the committee has failed to give due consideration to this in a fair and equitable way when considering the levels of uncertainty in the context of an ultra-rare, disabling disease. Some uncertainties in clinical trials in AM can never be addressed due to the inherently small size of the population; however, the HST process was designed to overcome this issue and further guidance in the new NICE methods guide also allows for flexibility in accepting uncertainty for rare diseases and innovative treatments. If there is clinical uncertainty that can be addressed by further data collection, then managed access is an option for the committee. Chiesi have proposed a data collection plan and statistical analyses including 10-year data in treated patients compared with retrospective and registry data in untreated patients that will provide additional data on utility estimates and the comparative treatment benefit. However, in 4.31 the guidance states "*But it was not convinced that the proposed MAA would resolve the key uncertainties in the evidence. This was because the ongoing trial and registry data would not provide more robust estimates for quality of life or long-term clinical effectiveness. Also, there are substantial challenges in collecting any robust evidence from the small number of people with alpha-mannosidosis who would be eligible to have velmanase alfa in clinical practice*." This statement appears to discriminate against people with AM due to the ultra-rare nature of their disability as the committee are dismissing the data collection plan on the grounds of the size of the population, and the process that the committee has taken in making its decision shows an unwillingness to use appropriate HTA methodologies for data related to very small populations. • The process used by the HST committee appears to be discriminatory to patients with AM on the grounds of disability due to the ultra-rare, disabling nature of AM without a current treatment. As there is no recommended treatment for AM, the comparator for velmanase

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	alfa is best supportive care. In other ultra-rare diseases assessed via the NICE process, such as Pompe disease and Fabry disease, other treatments are available, so new treatments can be recommended if they can show clinical equivalence and are similarly priced. As there are no treatments for velmanase alfa, proving cost effectiveness for a high cost, innovative treatment compared with best supportive is challenging in the NICE HST process. For these reasons, the new NICE methods guide allows for flexibility in accepting uncertainty for rare diseases and innovative treatments. As velmanase alfa has been accepted by the committee as an innovative treatment with a significant unmet need in section 4.29, velmanase alfa fulfils these criteria. As such, the committee has failed to give due consideration to this population in a fair and equitable way and the process that the committee has taken in making its decision appears to discriminate against people with AM on the grounds of disability due to its unwillingness to use appropriate HTA methodologies for the data related to very small populations without a current treatment, leading to inequity in access to treatments for people with AM, due the inherent ultra-rare nature of their disability and their lack of a current treatment option. • The discrimination also appears to be on the grounds of age and disability with regards to children with AM. The company submitted rhLAMAN-10 data that included subgroup data for children and adults <18 and ≥18 years for efficacy, quality of life and pain published in Lund et al. 2018 and Borgwardt et al. 2018 that showed differences in observed treatment effects, and the importance of disease stabilisation and reduction in pain in adults. It also submitted patient-level data for Etoile Alpha at technical engagement and Etoile Alpha data by age was summarised in Table 3 of the ERG report. Despite this, the guidance does not include a section discussing the difference in overall treatment effect between adults and children in the context of the new long-term rhLAMAN-10 or Etoile Alpha data. The new NICE methods guide allows for flexibility in accepting uncertainty for rare diseases, innovative treatments and children; as velmanase alfa fulfils all 3 of these criteria for the <18 years subpopulation, the process that the committee has taken in making its decision appears to discriminate against very small populations that include children in its failure to use appropriate HTA methodologies. • Where the potential treatment population comprises vulnerable patients with an ultra-rate and severely debilitating illness, and with protected characteristics, it is especially important for the committee to take into account all available evidence in its totality. The clear failure to give proper consideration to the company's resubmission, and dismiss certain evidence outright means the committee has fallen short of its legal obligations and has discriminated against patients. • The online consultation process involved multiple, ongoing problems with the website during the consultation period which has excluded people, especially those with the protected characteristic of disability from fully contributing to this consultation, and as such the process would be discriminatory if the negative recommendation was published as final guidance. The online public consultation ran from 8 July – 16 August 2022. Examples of poor consultation practice via the NICE website that have hindered access include: o Up until 16 July, the public consultation link to contribute to the consultation was omitted from the website. This was communicated to NICE by the company on the 18 July and was corrected on the afternoon of the 19 July – however the inability to comment up until this time will have led to confusion and inability to comment during the early stage of the consultation by members of the public and individual clinical experts and patients. o The link to the PDF version of the ECD was incorrect on the 19 July and did not link to the velmanase alfa ECD. This was communicated to NICE by the company on the 19 July. The inability to download a PDF of the ECD during the early

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	stages of the consultation will have led to confusion and inability to comment by members of the public and individual clinical experts and patients. o On Thursday the 28 July the link to the PDF version of the ECD was broken and linked to a page that stated "*We can't find this page within Velmanase alfa for treating alpha mannosidosis [ID800]. It's probably been moved, updated or deleted*." This was reported to NICE by the company on Thursday 28 July but it is unclear how long the ECD was unavailable for, or when the PDF was available during the consultation. The inability to download a PDF company of the ECD during this time will have led to confusion and inability to comment by members of the public and individual clinical experts and patients. o On Sunday 14 August Chiesi were contacted by a clinical expert stating they were having problems with opening links to the consultation and had contacted the NICE team. o Incorrect and conflicting deadline dates were published on the initial documentation and consultation pages and project information pages (4 August, 11 August, 12 August) that may have led to confusion on the deadline date o The timeline on the topic page is incomplete and does not include the date for the 4th committee meeting nor the dates for evaluation consultation 2, which could mislead members of the public, especially those with the protected characteristic of disability that there was no public consultation, or that the 4th committee meeting had occurred. As the 4th committee meeting was not stated on the website, it would have been difficult for members of the public to know to register for the meeting as a public observer.
5	**Section 1 and throughout the ECD: "Alpha mannosidosis is a rare and serious condition…"** Alpha-mannosidosis (AM) is an **ultra-rare** condition. Currently the wording describing the rarity of the disease throughout the draft guidance is inconsistent and confused, being referred to as 'rare' in section 1, 'ultra-rare' in section 2.1, 'rare' in section 4.1 and 'exceptionally rare' in section 4.33. Given that there are an estimated 25 patients with AM in England according to the MPS society, and the exceptional rarity and low patient numbers are taken into consideration in committee decision-making as stated in section 4.33, it is important that this is consistent throughout the document for clarity. The inconsistency and lack of clarity describing the ultra-rare nature of AM during the process demonstrates the lack of understanding of the condition by the committee and underplays the severity and exceptional rarity of the condition, which may have contributed to its inappropriate interpretation of the evidence and lack of consideration of the ultra-rarity of the condition and low budget impact in its preferred cost-effectiveness estimates.
6	**Section 1: "But, because of important limitations in the available evidence, the exact size and nature of the clinical benefits (both in the short- and longer-term) are highly uncertain.…"** Given the challenges in performing clinical studies in a heterogenous and ultra-rare progressive disease, there is inherent uncertainty in the precise size and nature of the long-term benefits with treatments for AM. However, as specified in comments 1 and 2, the committee have failed to use new NICE methodology to appropriately consider uncertainty in an ultra-rare disease, that affects

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	children, and for an innovative treatment, so that the decision-making process does not appear be fair or equitable to patients with AM. The committee have failed to specify what are the exact limitations of the clinical trial and real-world evidence, and if they are (a) inherent due to the nature of AM, or (b) due to the robustness of the clinical trial evidence. If the committee still believe that the short and long-term benefits are too uncertain for routine commissioning due to (b), Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the clinical uncertainties through a managed access agreement within the time period specified by the IMF. The committee and the ERG should consider the proposed data collection plan fully at the next committee meeting, as the proposed new statistical analyses were not reviewed by the ERG in its assessment report and were not discussed at the 4th committee meeting.
7	**Section 1: "there is very little observed evidence to inform the model, and most of the data used in the model is based on expert opinion rather than clinical trial evidence…."** This statement does not reflect the increased use of clinical data that was used to update the model at resubmission and as stated in comment 1 shows that the committee have not taken all the evidence into account in its decision making. In the resubmission, more clinical data have been used to inform the model, including: • rates of discontinuation using rates of non-responders in the published responder analysis (Harmatz et al., 2018 (6)) • a scenario analysis with an increased rate of discontinuation using rates of non-super responders in the published responder analysis (Harmatz et al., 2018 (6)) • the on-treatment utility benefit based on improvements in EQ-5D-5L, lung function and mobility from rhLAMAN-10 (1), and lung function and mobility improvements from Etoile Alpha (7) • a 5-year delay in disease progression, supported by improvements or stabilisation observed in rhLAMAN-10 (up to 48 months), Etoile Alpha (up to 9.5 years), and case reports (up to 7.5 years) Despite these improvements in the resubmission, should the committee still believe that the model inputs are too uncertain for routine commissioning, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the clinical uncertainties through a managed access agreement within the time period specified by the IMF. These would include data on specific economic uncertainties such as transition probabilities between health states and utility data in both untreated and treated patients from SPARKLE and AllStripes which will be used to update the model so that more clinical data can be used instead of expert opinion. Interim EQ-5D-5L data and age at mobility status change are already available, with full data sets that will be available by end of 2023. The committee and the ERG should consider the proposed data collection plan fully at the next committee meeting, as the proposed statistical analyses were not reviewed by the ERG in its assessment report and was not discussed at the 4th committee meeting. If there are observed data that the committee would prefer to be included in the model, this could be addressed as part of a managed access agreement.
8	**Section 1: "The cost-effectiveness estimates for velmanase alfa are higher than those considered value for money in the context of a highly specialised service. Taking into account all the evidence and the factors affecting the decision, including the extremely rare and disabling nature of alpha-mannosidosis, velmanase alfa is not recommended for use in the NHS"**

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	As stated in comments 1, 2 and 3, this statement demonstrates that the committee did not fully consider all the scenarios provided by the company that may be clinically plausible in consultation with clinical experts at the 4th committee meeting. Some scenarios were plausibly cost-effective under the £100K per QALY threshold, including a discontinuation scenario if patients become wheelchair dependent, discontinuation based on non-'super responders' from a published responder analysis, and a scenario of a permanent delay in disease progression in those 'super-responders' who are more likely to benefit from treatment. This was especially true for children and adolescents. The committee should fully explore these scenarios in consultation with clinical experts. In particular, the committee should take into consideration the proposed starting and stopping criteria in its preferred ICERs, which are similar to those used for other ERTs in current clinical practice according to a UK clinical expert consulted as part of our submission (16). If the committee remain unsatisfied with the levels of uncertainty after full consideration of the clinical plausibility of the scenarios in consultation with clinical experts, the plausibility of these scenarios can be assessed during a period of managed access and addressed by the proposed data collection plan and statistical analyses.
9	**Section 2, 2,2: "More moderate forms are characterised by slower disease progression with people surviving into adulthood"** As highlighted in comment 1 and 2, this statement demonstrates that the committee have misunderstood or have not considered the severity of the morbidity and mortality of patients with AM who are eligible for velmanase alfa. The description of patients as 'surviving into adulthood' is not a fair representation of the severity of the condition and understates and misrepresents the severity of the morbidity and mortality of AM. New data on the natural history and the severity of the symptoms experienced by untreated patients has been provided by the company (see comment 1) but has not been considered and/or interpreted reasonably by the committee. In the resubmission, Chiesi included new natural history data reporting life expectancy and cause of death in untreated patients with AM. These data have now been published and report a median age of death of 45 years (mean, 40.3 ± 13.2; range 18-56; n = 15) and pneumonia being the primary cause of death in people with AM (Hennermann et al., 2022 (12)). These natural history data should be considered by the committee in its considerations of the clinical and economic evidence. Long-term mortality data in patients treated with velmanase alfa are not yet known. Data for up to 10 years will be available from rhLAMAN-07/-09 in 2023 and the SPARKLE registry will collect data for up to 15 years reporting in 2035 with yearly interim reports. This misunderstanding or lack of consideration of the natural progression of the disease in untreated patients means that the committee have not reasonably interpreted the clinical and economic evidence, and the clinical and quality of life benefits of velmanase alfa have been underestimated, especially with respect to disease stabilisation and maintenance of the ability to walk.
10	**Section 2, 2.2: "These more moderate forms are associated with a very wide range of impairments, complications and comorbidities that increase with time. The impairments include…"** As highlighted in comments 1, 2 and 9, this statement demonstrates that the committee has not considered all the evidence and have misunderstood or not considered appropriately the severity

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	and range of the comorbidities of AM, its slow and progressive nature, or that long-term disease stabilisation is a clinical and patient-relevant outcome in its interpretation of the evidence. The list of complications stated in the guidance does not include: hearing impairment from early childhood, growth decline, psychiatric disorders, mobility issues or cognitive impairment. The description of the slow progressive heterogeneous nature of AM and the fact that most adults lose the ability to walk unassisted, become wheelchair dependent and reliant on third-party assistance in all aspects of their lives is also not reflected in section 2.2. A new natural history publication and case reports included in the company submission show hearing impairment at an early age as one of the first symptoms, as well as growth decline, cognitive impairment and psychiatric problems in patients with AM (Lipinski et al., 2022 (21)). Interim data from the AllStripes study (n=[redacted]) provided by the company during this consultation show all untreated patients have mobility difficulties and the [redacted] patients who lost the ability to walk unassisted did so between the ages of [redacted] years (13). This misunderstanding or lack of consideration of the natural history of the disease means that the committee have not interpreted the clinical and economic evidence reasonably, and the clinical and quality of life benefits of velmanase alfa have been underestimated, especially with respect to disease stabilisation and maintenance of the ability to walk.
11	**Section 2, 2.4: "An allogeneic haematopoietic stem cell transplant from a matched sibling or matched umbilical cord donor is an option for some people when clinically indicated, but is associated with significant risks."** As highlighted in comment 1, 2, 9 and 10, this statement demonstrates that the committee has misunderstood the disease and potential existing treatment approaches, and demonstrates inconsistency in the wording of the guidance and its decision-making. This statement does not reflect current clinical practice and does not reflect the advice from a paediatric metabolic specialist at the 4th committee meeting that stem cell transplant is only appropriate when clinically indicated for young children, usually under 5 years.
12	**Section 4, 4.2 "It was also aware that the clinical and economic evidence available for velmanase alfa did not include people with advanced disease, for example, people dependent on a wheelchair. So, the committee was uncertain whether velmanase alfa would be considered for this group. It stated that it would be helpful to clearly define how velmanase alfa treatment would be considered for more advanced forms of mild to moderate alpha-mannosidosis in clinical practice."** This statement is factually inaccurate and shows that the committee have not considered all the evidence from clinical trials and real-world evidence in their decision-making, as highlighted in comments 1 and 2. Three patients in rhLAMAN-10 (3 of 33; 2 children and 1 adult) used a wheelchair at baseline, as reported in Table 3 in Borgwardt et al., 2018 (1). At last observation, all 3 patients who had originally required the wheelchair at baseline no longer required mobility assistance. Participants in the Etoile Alpha study included those with advanced disease, including those using a wheelchair, as described in the Etoile Alpha case reports (7) and in Table 20, page 53-57 of the company submission. [redacted]. These data were also described in the ERG report: *" in general the*

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	accounts of the improvements experienced by patients are extremely positive and indicate that the treatment has made tangible improvements to their lives." Both rhLAMAN-10 and Etoile Alpha show that patients with advanced disease still experience clinical and quality of life benefits with velmanase alfa, with improvements in mobility and reductions in levels of pain and fatigue. However, due to the severity of their impairment and the irreversibility of some of their symptoms due to lifelong oligosaccharide accumulation, it may be difficult to accurately quantify the benefits as part of a QALY calculation, in addition to the difficulties in measuring quality of life in patients with cognitive impairment. To help with committee decision-making in the treatment of patients with advanced disease, the company provided updated scenario analyses with different starting and stopping criteria that reduces the uncertainty and improves the cost-effectiveness estimates (page 23, technical engagement), which included discontinuation if the patient became wheelchair dependent. The company base case did not include any patients who were already in a wheelchair – a scenario analysis with baseline distributions including patients in a wheelchair at baseline (rhLAMAN-10 distributions) was included which was preferred by the ERG that marginally increased the ICERs. In not considering all the above evidence in its decision-making processes, the implications are that the committee have misunderstood and underestimated the long-term clinical and quality of life benefits for patients who were in a wheelchair at baseline, as well as the impact of treatment beyond direct health benefits for patient and carers, and overestimated the cost per QALY in their preferred ICERs.
13	**Section 4.4 "The committee discussed in detail the clinical evidence most relevant to the decision problem submitted by the company"** This statement suggests that only the most relevant clinical evidence was discussed by the committee, and suggests that some of the clinical evidence submitted by the company was not considered, as highlighted in comment 1. In the context of an ultra-rare disease with limited evidence, excluding evidence would not be considered reasonable. If all the evidence detailed in comment 1 was not discussed or excluded by the committee, the reasons for doing so should be justified in the context of an ultra-rare disease. In not considering all the evidence in its decision-making processes, the implications are that the committee have misunderstood and underestimated the long-term clinical and quality of life benefits of velmanase alfa, as well as the impact of treatment beyond direct health benefits for patient and carers, and overestimated the cost per QALY in their preferred ICERs
14	**Section 4, 4.4 "rhLAMAN-10 (n=33) was a single-arm open-label study that provided data on people who had treatment with velmanase alfa for up to 48 months."** This statement does not clarify that rhLAMAN-10 was an extension study of rhLAMAN-05 and provides comparative data with baseline measurements, to show a delay in disease progression, as well as any improvements from baseline. This shows that the committee may not have understood all the evidence or interpreted it appropriately, as highlighted in comments 1 and 2.
15	**Section 4, 4.4 "The outcomes measured in the clinical trials covered serum oligosaccharide levels, mobility and functional capacity, lung function, quality of life, cognition and hearing."**

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	This statement does not include all the rhLAMAN-10 data that were provided to the committee and shows that the committee have not considered all the evidence in its decision-making, as highlighted in comments 1 and 2. The outcomes listed do not include **motor proficiency and levels of disability and pain** so does not reflect all the clinical outcomes that were reported in the publications of rhLAMAN-10 and in the real-world evidence. In particular, the rhLAMAN-10 analysis of Bruininks-Oseretsky test of motor proficiency (BOT-2) that was provided in the company resubmission and published by Phillips et al., 2020 (3) has not been included in the guidance and has not been considered by the committee or the ERG. This BOT-2 analysis of rhLAMAN-10 showed improvements in upper limb extremity function, fine motor deficits and running speed with velmanase alfa. For the combined adult and paediatric group there was a statistically significant improvement in BOT-2 total score of 13% (p =0.035, 95% CI 1.0, 25.0) from baseline to last observation. A survey of patients and carers with a similar condition (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 dressing, eating and drinking, ability to use a computer, use a pen/pencil and participate in sports (Leiro et al., 2021 (22)). 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 by the EQ-5D-5L or the model. Details of the levels of disability are reported up to 4 years post-treatment in rhLAMAN-10 from Borgwardt et al., 2018 (1). 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. rhLAMAN-10, Etoile Alpha and case reports show reductions in pain and fatigue with velmanase alfa, although CHAQ-VAS data are limited. CHAQ-VAS Pain scores were reported in rhLAMAN-10 in Borgwardt et al., 2018 (1). 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., 2002 (23). In not considering all the above evidence in its decision-making processes, the implications are that the committee have misunderstood the natural history of the disease, underestimated the long-term clinical, quality of life benefits as well as the impact of treatment beyond direct health benefits for patient and carers, and overestimated the cost per QALY in their preferred ICERs.
16	**Section 4, 4.4 "The ERG highlighted that there were uncertainties associated with the trials. It noted the lack of a control arm in rhLAMAN-10."** The statement lacks clarity regarding the uncertainties and appears to show that the ERG have misunderstood the rhLAMAN-10 study and integrated analysis. Chiesi have provided all the

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	protocols for the clinical trials and real-world studies so there should be no outstanding uncertainties regarding the trials or their design that were not resolved at technical engagement. The lack of a control arm in rhLAMAN-10 is inherent in its study design as an extension trial of rhLAMAN-05, and the design comparing the outcomes with baseline measurements is well described in the protocol and publications. If after considering all the current evidence and the appropriateness of the clinical trial design for an ultra-rare disease associated with slow disease progression, the committee remain unsatisfied with the levels of uncertainty, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the specific clinical uncertainties highlighted by the ERG through a managed access agreement. This would include performing an indirect comparison of treated patients from an updated rhLAMAN-10 analysis with 10-year data from rhLAMAN-07 and rhLAMAN-09 which will complete in 2023, and comparing with data from untreated patients collected in the SPARKLE registry and the AllStripes Study. The committee and the ERG should consider the proposed data collection plan fully at the next committee meeting, as these proposed statistical analyses were not reviewed by the ERG in its assessment report and was not discussed at the 4th committee meeting.
17	**Section 4, 4.4 "The committee considered the amount of evidence to be fairly small, and that it would have been better if the trials had run for longer. But it recognised that this was influenced by the extreme rarity of the condition."** This statement on the amount of evidence is subjective and demonstrates that the committee have not considered AM as an ultra-rare disease reasonably in its interpretations of the evidence base and the inherent levels of uncertainty. The rhLAMAN-10 integrated analysis included 33 patients, which is a substantial proportion of the diagnosed population with AM in Europe. The committee should consider the ultra-rare nature of the condition, and compare it with clinical data for other similar ultra-rare conditions. The committee also state that it would have been better if the trials had run for longer. This contradicts its decision in section 4.31 that the data collection plan proposed by Chiesi would not provide robust enough evidence or resolve further uncertainty, since the plan will provide rhLAMAN-07/-09 data for up to 10 years, with an updated integrated rhLAMAN-10 analysis, and an indirect comparison with untreated patients from SPARKLE and AllStripes. This demonstrates that the committee has not considered all the evidence or the data collection plan appropriately in its decision-making.
18	**Section 4, 4.5 "People included in the rhLAMAN trials were likely to have been younger (between 5 years and 35 years) than people seen in clinical practice in England."** This statement shows that the committee have not updated the guidance or considered the new evidence in their decision-making and have misunderstood the mortality of AM. Chiesi provided new natural history data in untreated patients with AM with new mortality data. These data report a median age of death of 45 years (mean, 40.3 ± 13.2; range 18-56; n = 15) (Hennermann et al., 2022 (12)). As such, untreated patients in England are unlikely to live beyond their 6th decade, so the people in the rhLAMAN trials are likely to be similar ages to those in clinical practice. In not considering all the above evidence in its decision-making processes, the implications are that the committee have misunderstood the natural history of the disease, and not considered the mortality estimates in their assessment of the economic evidence, including the time horizon of the model.

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19	**Section 4, 4.5 "The ERG noted that, in rhLAMAN-05, people in the velmanase alfa arm were more compromised at baseline than people in the placebo arm. This could have affected some outcomes, but the ERG was uncertain about whether it would favour velmanase alfa or placebo."** This statement shows that the committee have not fully considered or reasonably interpreted all the evidence in its decision-making. It demonstrates that the rhLAMAN-05 data has not been properly explored by the ERG in light of the new clinical evidence and the statement that it is uncertain whether it would favour velmanase alfa or placebo is not useful for committee decision-making. Chiesi request that the opinion of clinical experts is consulted on this issue as the treatment effect for velmanase alfa may have been underestimated.
20	**Section 4, 4.5 "Alpha-mannosidosis progresses faster in younger people, so it is easier to detect clinically significant differences in younger people."** This statement is confusing and may be factually inaccurate. In AM, faster disease progression is seen in patients who develop symptoms at an earlier age as they are likely to have a more severe phenotype than those who develop symptoms later in life, but there is no evidence to suggest that progression slows with age; disease progression is a factor of disease severity (and likely residual enzyme activity), similar to other MPS disorders. This statement demonstrates that the committee have not understood the natural history of AM or considered all the new evidence or interpreted it reasonably as highlighted in comments 1 and 2, 9 and 10. This statement does not reflect the slow, progressive nature of AM and does not reflect that the clinical and patient-relevance of disease stabilisation in older patients has been considered in committee decision-making. The clinically-relevant stabilisation observed for many clinical outcomes in rhLAMAN-10 and in real-world studies of patients treated with velmanase alfa for nearly 10 years has not been considered by the committee in its decision-making, nor has the committee properly recognised the importance of disease stabilisation for patients and carers, or the opinion of clinical experts. In not considering all the above evidence in its decision-making processes, the implications are that the committee have misunderstood and underestimated the long-term clinical, quality of life benefits as well as the impact of treatment beyond direct health benefits for patient and carers, and overestimated the cost per QALY in their preferred ICERs
21	**Section 4, 4.7 Mobility, functional capacity and quality of life** The inaccurate descriptions of the clinical trial design and results in this section show that the committee have misunderstood, or not considered the rhLAMAN-05 and rhLAMAN-10 data appropriately in their interpretations of the evidence in the context of AM as a slowly progressive, ultra-rare, heterogeneous disease that affects adults and children. The omission of the 12-month timescale when describing the rhLAMAN-05 results in section 4.7 does not accurately reflect the trial design and is an important detail that should be included to explain the clinical relevance of the results. As AM is a slowly progressing disease, changes in functional outcomes are unlikely to be detectable over 12 months, which is why long-term extension studies were performed (rhLAMAN-10 and -07/-09). The statement that the ERG was unclear whether the rhLAMAN-05 trial (24) met its objective of showing clinical efficacy shows a misunderstanding of rhLAMAN-05 and shows a lacks clarity and confusion in the committee decision-making. The co-primary endpoints were change from baseline to week 52 in serum oligosaccharides and the 3-min stair climb test (3MSCT). rhLAMAN-05 met the primary endpoint of change in oligosaccharides after 12 months vs. placebo, but not in the

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	functional primary endpoint of 3MSCT, which is explained by the 12-month timeframe which was not included in section 4.7, which shows a misinterpretation of the rhLAMAN-05 trial results. rhLAMAN-10 showed substantial long-term improvements in mobility, lung function, quality of life levels of disability and pain, and upper limb strength and dexterity when treated with velmanase alfa when compared with baseline measurements over 48 months (1, 2), but this is not accurately described in section 4.7, which shows that the committee may not have interpreted the results appropriately in their decision-making. As detailed in comment 1, rhLAMAN-10 results for lung function (forced vital capacity), levels of disability and pain (Childhood Health Assessment Questionnaire VAS pain and disability index), the BOT-2 data and quality of life (EQ-5D-5L) in rhLAMAN-10 after 48 months (1-3) were not included in the guidance and were not interpreted by the committee appropriately. In not considering all the above evidence in its decision-making processes, the implications are that the committee may have misunderstood and underestimated the long-term clinical, quality of life benefits as well as the impact of treatment beyond direct health benefits for patient and carers, and overestimated the cost per QALY in their preferred ICERs.
22	**Section 4, 4.7 "The committee highlighted that, without a comparison with placebo, it was unclear how much of the changes could be attributed to velmanase alfa. It particularly noted that some of the changes may be explained by expected physiological changes with age. The committee discussed how to interpret the clinical-effectiveness results. It noted, in particular, that the size of the observed benefits was small. It also noted that it was unclear whether the benefits would translate into substantially meaningful improvements for people with alpha-mannosidosis."** "**The committee recognised that the small population size may have influenced the uncertainty of the evidence (for example, statistical significance), but would not necessarily be expected to have affected the size of the benefits."** These statements show that the committee has not considered all the evidence and has not interpreted the evidence reasonably with regards to the importance of disease stabilisation in an ultra-rare, slowly progressive heterogeneous disease. With regards to the small population not affecting the size of the benefits, the committee have failed to recognise both the heterogeneous nature of the condition and the fact that similar to other MPS disorders, AM is a slowly degenerative condition. The clinically-relevant stabilisation observed for many clinical outcomes in rhLAMAN-10 and in real-world studies of patients treated with velmanase alfa for nearly 10 years has not been considered by the committee in its decision-making, nor has it recognised the importance of disease stabilisation for patients and carers, or the opinion of clinical experts. Although the size of the observed additional benefits in rhLAMAN-10 was small, these improvements were clinically relevant, and shows evidence of definitive disease stabilisation with velmanase alfa. The statement that 'it particularly noted that some of the changes may be explained by expected physiological changes with age' shows that the evidence provided in age subgroup analyses from the clinical trials has not been considered by the committee in its guidance, or reconsidered in light of the new real-world evidence. Age-adjusted %predicted FVC results by age were provided in rhLAMAN-10 (2) which show the statistically significant improvements in lung function were not due to age. Age-adjusted %predicted FVC were also provided for Etoile Alpha. Adults with AM are more likely than children to have more severe mobility problems and/or use a wheelchair, as well as experiencing greater levels of pain. As such, although substantial improvements in walking status may not have been seen in adults treated with velmanase alfa, other clinically relevant treatment benefits, such as reduced levels of pain and fatigue were seen in clinical trials and is supported by the new real-world evidence submitted by the company.

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	In rhLAMAN-10, not all clinical differences reached statistical significance from baseline, but the improvements observed were clinically-relevant, based on minimally importance differences, or resulted in changes in walking status, levels of disability and pain, published in Borgwardt et al. 2018 (1). The improvements observed in rhLAMAN-10 were confirmed with substantial improvements seen in Etoile Alpha and case reports. In not considering all the above evidence in its decision-making processes, the committee may have misunderstood and underestimated the long-term clinical, quality of life benefits as well as the impact of treatment beyond direct health benefits for patient and carers, and overestimated the cost per QALY in their preferred ICERs.
23	**Section 4, 4.7 Quality of Life** Improvements in quality of life and functioning are highly relevant to a NICE assessment and are a key parameter of the economic modelling, but the lack of consideration of all the quality-of-life evidence in Section 4 including EQ-5D-5L, pain and disability observed in rhLAMAN-10 with velmanase alfa shows that the committee have not considered all the evidence in its decision-making, or interpreted it appropriately in line with NICE methods. Chiesi provided quality of life data from Borgwardt et al. 2018 (1) for EQ-5D-5L, CHAQ-DI and CHAQ VAS pain, as well as improvements in levels of mobility presented for both adults and children. However these data split by age were not included in the guidance or discussed at the 4th committee meeting. Chiesi also provided the Adam et al., 2019 (10) publication that reported patient and carer quality of life EQ-5D-5L and HUI-3 data in 8 untreated and 1 treated patient(s) in the UK, and interim EQ-5D-5L data for 16 patients in the SPARKLE registry has also been provided at consultation (25). The difficulties in measuring quality of life in patients was discussed with clinical experts at the 4th committee meeting who confirmed that EQ-5D as a generic tool could not capture all aspects of AM and would be difficult to perform in children and those with cognitive impairment. As described in comment 2, EQ-5D is not recommended by NICE when assessing quality of life in children in its new manual (19). EQ-5D-5L measurements cannot be appropriately crosswalked to the 3L in children as no appropriate UK value set exists in children, and the Hernandez-Alava algorithm (26) recommended by NICE only applies from age 16 years. As such the EQ-5D-5L utility gains from rhLAMAN-10 likely underestimates the true utility benefit due to the limitations of the EQ-5D in capturing aspects of ultra-rare heterogenous diseases such as AM, especially in children and those with cognitive impairment. In addition, NICE's own task and finish report on HRQoL (NICE, 2020 (27)) stated that EQ-5D was inappropriate for use in people with hearing impairment – this will apply to AM as this is one of the first symptoms to appear in childhood and natural history studies show that all people with AM have hearing impairment. Taken together, this shows that the committee has not reasonably interpreted the utility benefit in children in line with its own guidance, and the quality-of-life benefits of velmanase alfa have been underestimated, and therefore the committee prefer ICERs that will overestimate the cost per QALY. If after considering all these issues reasonably, the committee remain unsatisfied with the levels of uncertainty with the utility and quality-of-life data, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address these specific uncertainties through a managed access agreement.
24	**Section 4, 4.9 Long-term benefits of velmanase alfa**

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	The statement that velmanase alfa was used off label in France is factually inaccurate. Although the patients included in the study were more severely impaired than patient in the rhLAMAN clinical trials, the patients included in Etoile Alpha were people with mild to moderate alpha mannosidosis (type 1 and type 2) and are indicated for velmanase alfa, so this is not off label use. Severely impaired patients are not the same as patients with the severe phenotype of AM (type 3) who die in early childhood which is not indicated in the label. This statement shows that the committee have misunderstood the severity of the symptoms associated with mild-to-moderate AM and the natural history of the disease, which has implications that the committee have misinterpreted the results of the Etoile Alpha study. The long-term nature of Etoile Alpha was not clear in section 4.9, or that both adults and children were treated for up to 9.5 years, so it is unclear if this has been considered appropriately by the committee.
	
	As an important real-world evidence study, the Etoile Alpha should be interpreted by the ERG and committee in line with NICE's real-world evidence framework (18). As shown in the detailed points below, the committee have not fully considered the clinical evidence provided by Etoile Alpha appropriately and have misinterpreted the results and the opinions of the ERG and clinical experts. The statements in section 4.9 are not an accurate representation of the Etoile Alpha results, the critique of the study in the ERG report, or an accurate representation of the discussion at the 4th committee meeting.
	
	The limitations of Etoile Alpha highlighted by the ERG in the ECD can be addressed as follows:
	
	• the population in the study was likely more severe than that expected in clinical practice
	  ○ as included patients were more severely impaired than expected, the improvements and stabilisation observed in Etoile Alpha may underestimate the effect of velmanase alfa in patients in clinical practice
	  ○ rhLAMAN-10 was considered by the committee to have patients younger than expected in clinical practice, so these data in a real-world setting are supportive of a treatment benefit with velmanase alfa in older, more severely affected patients
	• it was a single-arm study comparing results with baseline rather than best supportive care
	  ○ as a long-term study up to 9.5 years, comparing results with baseline shows a delay in disease progression in a slowly progressive disease such as AM
	  ○ an indirect comparison with best supportive care is proposed as part of a data collection plan during a period of managed access as described in comment 2
	• there were many missing data points, which may not have been missing at random
	  ○ % predicted FVC results by patient were provided to the ERG at technical engagement
	  ○ the 2MWT is only performed in very young children and is superseded by the 6MWT so the missing 2MWT is not relevant for this population – most patients provided 6MWT instead (unless lack of mobility prevented measurements being taken)
	• there was a lack of adjustment for age for outcomes in which childhood growth could lead to improvement
	  ○ **lung function**: % predicted FVC results adjusted for age by patient were provided to the ERG at technical engagement, along with supportive published natural history evidence to show reduced lung function by age in untreated patients (Beck et al., 2013 (28)), which provided evidence to show childhood growth could not account for the substantial lung function improvement shown in Etoile Alpha. After technical engagement, the ERG concluded "*these data are supportive of the FVC improvements seen in the Etoile Alpha study not being due to growth"*.
	  ○ **mobility:** Chiesi accept the ERG's criticism that that growth could account for some improvements in the 6MWT and the 3MSCT but in the paediatric subgroup only as these results were not age-adjusted. Discussions at the 4th committee

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	meeting with the paediatric clinical expert stated that improvements in mobility tests are expected due to growth up to around 10 years of age. ○ As only [redacted] patients in Etoile Alpha started treatment below 10 years, and the youngest being [redacted] years old at velmanase alfa initiation, the criticism that the improvements are due to growth is unlikely to account for the substantial improvements in clinical parameters observed versus baseline in patients treated for up to 9.5 years • data were not collected on all outcomes used to assess response to velmanase alfa in the company's proposed starting and stopping criteria ○ The protocol for Etoile Alpha was designed to collect data in France as part of a managed access process by the French reimbursement authorities, and as such does not align exactly to the starting and stopping criteria in the MAA proposed for NICE by Chiesi UK so this is not a relevant criticism ○ The proposed stopping and starting criteria were drafted in 2018. Should the committee agree that starting and stopping criteria are appropriate, these can be refined as part of the final discussions at the 5th committee in consultation with clinical experts and patient groups Taken together, a misunderstanding or lack of consideration of the Etoile Alpha results means that the committee have not interpreted the real-world evidence reasonably, and the clinical and quality of life benefits of velmanase alfa have been underestimated, and therefore the committee prefer ICERs that will overestimate the cost per QALY. If after considering all these issues reasonably, the committee remain unsatisfied with the levels of uncertainty with the real-world evidence, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address clinical uncertainties through a managed access agreement.
25	**Section 4, 4.9 Long-term benefits of velmanase alfa** As highlighted in comments 1 and 2, this section demonstrates that the committee have not considered all the long-term real-world evidence or considered it appropriately in the context of an ultra-rare heterogeneous disease. The company submitted patient-level data of all participants in Etoile Alpha (n=[redacted]) (29), as well as additional published case series of adults treated with velmanase alfa (n=5) (8), and a UK case report of a patient treated for over 7 years (9). The case report of the treated UK patient was highlighted by the patient group at the 4th committee meeting and the case series were summarised as follows in the ERG report: *" 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."* It is unclear if the committee considered this evidence of tangible improvements to support the uncertainty in the appropriateness of the EQ-5D-5L data in their decision-making, and the 'tangible improvements' is a contradiction of committee's interpretations of the evidence in section 4.9. Although considered a low level of evidence, these studies provide real-world data on adults treated long-term with velmanase alfa for 7-9 years. This constitutes a substantial level of evidence in the context of an ultra-rare condition and should be considered in line with NICE's real world evidence framework in committee decision-making. As there is no reference to these data in section 4.9 it is unclear if the committee considered them in their decision-making, or if they interpreted them reasonably in the context of an ultra-rare disease. If after considering all these issues reasonably, the committee remain unsatisfied with the levels of uncertainty with the long-term real-world evidence, Chiesi have proposed a data collection plan

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	and pre-planned statistical analyses that can address long-term clinical uncertainties through a managed access agreement.
26	**Section 4, 4.10 Infections** The statement in 4.10 that infection rates were not collected as an efficacy outcome in the trials is factually inaccurate and shows that the committee have not considered all the infection data in their decision-making, and have underestimated the reduction in infection rates with velmanase alfa, and have not considered the clinical benefit of this appropriately in the context of an ultra-rare disease. As the cost and disutility of minor infections are not included in the model, this additional evidence suggests that the committee have overestimated the most plausible ICERs in their interpretations of the evidence. • Data from rhLAMAN-10, Etoile Alpha and case reports all show a 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 studies; a statistically significant increase in serum IgG occurs rapidly within 1 year, as shown in rhLAMAN-05 (24). • Infection events after 1 month of treatment were recorded in rhLAMAN-05 and presented as a poster by Borgwardt in 2018 (5): after 1 month, the rate of infection per infected patient was 1.5 under placebo vs. 0 with velmanase alfa. An infection burden questionnaire in rhLAMAN-10 (4) showed a total of 21 of 32 caregivers in the pre-treatment period reported frequent infections as an important morbidity of AM that impacted patients' social interactions and quality of life. 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. • The reduction in infections suggested in rhLAMAN-10 was confirmed in real-world studies that showed a substantial reduction in infections with velmanase alfa. [redacted] respiratory infections were observed in the Etoile Alpha review period (up to 9.5 years), with some patients reporting no longer needing to be on prophylactic antibiotics (supported by interviews with 2 UK clinical experts). This is in stark contrast to new natural history data in a cohort of 12 untreated Polish patients with alpha mannosidosis over 14 years showed all untreated patients had recurrent infections (Lipinski et al, 2022 (21)). It is unclear why the totality of the infection data from clinical trials and the real-world data are not sufficient evidence for the committee in the context of an ultra-rare disease, as all the evidence shows no infections post-treatment in studies up to 9.5 years. Data on infection rates are also being collected in ongoing registry studies (SPARKLE and AllStripes). If after considering all the substantive infection data from the clinical trials and real-world evidence, the committee remain unsatisfied with the levels of uncertainty with the reduction in infection rates, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address long-term clinical uncertainties through a managed access agreement.
27	**Section 4, 4.11 Multidomain responder analysis** The multidomain responder analysis was criticised by the ERG for the variation in treatment response between domains as well as the individual domains. In response to technical engagement to address this concern, the company provided a "super-responder" scenario analysis when patients only continue treatment if they respond in all 3 domains (pharmacodynamic, functional and quality of life). However, the results were not included in the considerations and the committee concluded that the multidomain responder analysis had several limitations, and the relevance of the results was difficult to interpret. The wording of this section shows that the committee have not considered the super-responder analysis or interpreted it

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	appropriately in its decision-making, as the specific limitations or the difficulties in interpretation mentioned in the guidance were not explained. The super-responder analysis was presented by the company as a new scenario analysis at technical engagement increasing the rate for discontinuation using a 'super-responder' stopping rule. As highlighted in comment 3, the committee should reasonably consider the proposed stopping criteria, as they are similar to those used for other ERTs in current NHS clinical practice. However, this scenario analysis is not included in the guidance and was not discussed at the 4th committee meeting with clinical experts. If the committee remain unsatisfied with the levels of uncertainty after full consideration of the clinical plausibility of the super responder scenario in consultation with clinical experts, the plausibility of these scenarios can be assessed during a period of managed access and addressed by the proposed data collection plan and statistical analyses.
28	**Section 4, 4.13 Company's economic model** The description of the model does not describe the tunnel states accurately – the tunnel states includes major surgery only (defined as those requiring hospital admission including ventriculoperitoneal shunts, cervical spine decompression and joint replacement). Minor surgical procedures such as day-cases are not included so will not be captured by the model. The statement that 'mobility would be expected to capture most of the important aspects of AM for people' shows that the committee have misunderstood or not considered all aspects of AM as discussed in comments 9 and 10. It demonstrates that committee have not considered other important aspects of AM that would not have been captured by the walking state model, 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 health (anxiety and depression), cognitive function, psychiatric events and increased independence in activities of daily living. As such, the model underestimates the treatment benefit of velmanase alfa because of the multiorgan manifestations of AM and their preferred ICERs have overestimated the cost per QALY. The committee also suggested that lung function might have been considered an option for defining the model structure. This contradicts the committee's decision in section 4.17 that linking utility values to lung function lacks face validity. Should the committee wish to explore a model linked to lung function after a period of managed access this could be discussed with regard to future analyses agreed as part of the data collection plan.
29	**Section 4, 4.14 Sources of data in the model** The statement that the committee was concerned that so few parameters were informed by data from the clinical trials does not reflect the updated model that used additional parameters, as explained in comment 7, which shows that the committee have not taken all the evidence into account in its decision-making. Despite these improvements in the resubmission, should the committee still believe that the model inputs are too uncertain for routine commissioning, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the clinical uncertainties through a managed access agreement within the time period specified by the IMF. The committee understood that parameters informed by expert opinion increased the uncertainty of the model assumptions, but did not take into account that the current model assumptions of

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	extended time in health states is likely to underestimate the treatment effect, since the expert elicitation panel was performed in 2017 prior to the availability of long-term data. The statement that validation of the previous estimates of extended time in health states was validated by a single clinical expert is also factually inaccurate – two clinical experts who manage patients with AM in England and Wales were consulted and the summaries of these expert interviews were provided as part of the consultation (16). Taken together, this description of the model inputs in this section shows that the committee have misinterpreted the certainty of the inputs of the model, underestimated the treatment benefit of velmanase alfa and their preferred ICERs have overestimated the cost per QALY.
30	**Section 4, 4.15 Benefits of velmanase alfa in the model** The section does not reflect all the clinical evidence included in the model and shows that the committee have not considered all the evidence, or made reasonable interpretations of this evidence, as detailed in comment 1 and 2. • The period of complete stability followed by delayed disease progression in responders is not only informed by Etoile Alpha, but rhLAMAN-10, ongoing rhLAMAN-07 data from Etoile Alpha and the case reports – omission of the case reports shows that the committee have not considered them in their decision making on the delay in disease progression • Improvements in mobility from baseline were also informed by rhLAMAN-10, Etoile Alpha and case reports • Reductions in mortality, complications and recovery time associated with severe infections and mortality by 50% is informed by rhLAMAN-10, Etoile Alpha and case reports – as [redacted] infections were reported in these studies, a 50% reduction may be an underestimate As such, the statement that 'the benefits of velmanase alfa in the model were based on assumptions rather than expert opinions rather than directly informed by evidence' does not seem a reasonable interpretation of the evidence. The mobility gains over 12 months in rhLAMAN-05 are the only mobility data included in this section of the guidance and has not been updated to reflect all the clinical evidence. As the 12-month timeframe may not be clinically relevant for changes in mobility status in AM (see comment 21), the omission of any discussion of the rhLAMAN-10 mobility data from Borgwardt et al., 2018 (1) seems unreasonable, and shows that the committee may not have considered this evidence in their decision-making. Details of mobility status up to 4 years post-treatment in rhLAMAN-10 from Borgwardt et al., 2018 (1). 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.

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	The statement that 'this assumption reflected clinical experts' views that it was not plausible that people having best supportive care would improve' does not align with the clinical expert opinion sought during the resubmission that people treated with best supportive care could temporarily improve, but only due to surgery – this also reflects the rhLAMAN-10 data that describes patients changing mobility status due to orthopaedic surgery. Taken together, this section shows that the committee have not considered all the mobility data or interpreted it reasonably, or considered the importance of the timeframes of the rhLAMAN trials or the clinical relevance of disease stabilisation, as highlighted in comments 1 and 2. This misunderstanding or lack of consideration of these issues means that the committee have not interpreted the clinical and economic evidence reasonably, and the clinical and quality of life benefits of velmanase alfa have been underestimated, and therefore the committee prefer ICERs that will overestimate the cost per QALY. If after considering all these issues reasonably in consultation with clinical and patient experts, the committee remain unsatisfied with the levels of uncertainty, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the specific clinical uncertainties highlighted by the ERG through a managed access agreement.
31	**Section 4, 4.16 Progression through the model for people having velmanase alfa** This section shows that the committee have not considered all the evidence (such as the super responder analysis) and has not interpreted the real-world Etoile Alpha and case series in its consideration of the delay in disease progression, as explained in comments 1 and 2. The section discusses 'responders' who have a delay in disease progression but does not include the 'super responder' analysis that addressed some of the ERG's criticisms of the analysis. The stopping criteria of a 'super responder' aligned with the published data in Harmatz et al., 2018 (6) which was published after the draft stopping criteria were developed with clinical experts at an advisory board. Any stopping criteria can be agreed in consultation with NICE, NHS England and clinical experts to align with outcomes collected in clinical trials to reduce the uncertainty. In 4.23, the committee accepted that it was plausible that using a more stringent definition of response might have further increased the delay in disease progression, but this was not included in its preferred scenario and the clinical validity of this was not explored with clinical experts. The company assumption in the delay for disease progression of 5 years followed by an extended time in health states in responders aligns with longer-term data available from Etoile Alpha for up to 9.5 years and case studies for up to 7.5 years. In super-responders, the certainty of this is increased and may even be longer in these patients that respond in all 3 domains, and a scenario analysis of a permanent delay in disease progression was submitted. For these reasons, the committee's preferred assumption of only 3 years does not align with the evidence base and seems arbitrary and shows an unreasonable interpretation of the evidence. The committee's omission of any discussion of the super responder analysis also shows that not all the evidence was taken into account in its decision-making, and contradicts its conclusions in 4.23 that a more stringent definition of response might have further increased the delay in disease progression. The statement that '*the size of velmanase alfa's benefits suggested by the model appeared large in the context of the benefits seen in the trials*' does not take into account the real-world evidence appropriately in line with NICE's real world evidence framework and '*whether there was sufficient evidence to support the benefits*' seems unreasonable in the context of an ultra-rare disease and in line with the flexibility NICE suggests in its own new methods guide. If the committee remain unsatisfied with the levels of uncertainty, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the clinical uncertainty through a managed access agreement.

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32	**Section 4, 4.17 Quality of life and additional utility gain associated with velmanase alfa** This section shows that the committee have not considered all the evidence (such as the rhLAMAN EQ-5D and CHAQ data or the Etoile Alpha and case series) and has not interpreted the EQ-5D data appropriately for use in AM or children according to NICE's own guidance and has underestimated the utility benefit, as explained in comments 1 and 2. The list of utility benefits not included in the model in this section does not include improving lung function – as the committee considered lung function an option for defining the model structure, and as the company uses utility values mapped to FVC, this appears to be an important omission and shows that the committee have not understood the importance of the additional utility benefit with velmanase alfa, given the statistically significant improvements in % predicted FVC seen in rhLAMAN-10 and the lung function improvements seen in Etoile Alpha. The EQ-5D-5L results in rhLAMAN-10 have not been considered appropriately by the committee – EQ-5D-5L improvements observed in the clinical trial justify the additional on-treatment utility benefit used in the model; however the limitations of EQ-5D-5L in measuring quality of life in a heterogeneous disease such as AM means that not all the benefits are captured, so the utility benefit is likely underestimated by the EQ-5D-5L results. Also, the EQ-5D-5L is also not recommended for use in children or in those with hearing impairment in NICE's own guidance, and cannot be mapped to the 3L UK value set. For these reasons, the company used utility values mapped to FVC benefits, as accepted by the committee in HST19 for a similar MPS condition, MPSIVa (20). The committee understood that the results were relatively aligned for adults, but there was a large difference for children, which reflects the inappropriateness of EQ-5D-5L for use in children with AM. As such, it seems an unreasonable and contradictory interpretation by the committee that the FVC mapped values lack face validity, given they are age-adjusted for growth, were accepted for a similar MPS-like condition, and improvements in lung function were important enough by the committee to be considered as an option for the model structure. This statement in the guidance also contradicts the HST's previous acceptance of utility values for HST19 for MPSIVa "*In addition when adding a 0.254 utility gain to the existing value for the walking with assistance state people whose disease responded to velmanase alfa had a similar utility to the general population*". When the FVC and 6MWT-mapped utility gain of 0.254 is added to 0.577, the value for walking with assistance, this results in 0.831, which is not similar to the general population. When this is added to 0.652, the value for walking without assistance, this results in 0.906 – although this is similar to the general population, a value of 1.0 was accepted by the HST for asymptomatic MPSIVa health state, so this interpretation seems unreasonable. For velmanase alfa, when only the FVC-mapped utility gain is added (0.18) to the walking with assistance and walking without assistance health states, this results in 0.757 and 0.832, respectively, which should be more acceptable to the committee. Taken together, the committee interpretations of an on-treatment utility gain of 0.05 in adults and 0.1 in children based on the EQ-5D-5L results of rhLAMAN-10 seem unreasonable and an underestimate of the on-treatment utility gain with velmanase alfa, especially for children. For the reasons stated above, the company prefer the FVC-mapped utility gains which justify an on-treatment utility gain of 0.1 in adults and 0.25 in children. If after considering all these issues reasonably, the committee remain unsatisfied with the levels of uncertainty with the utility and quality-of-life data, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address these specific uncertainties through a managed access agreement.
33	**Section 4, 4.18 Health state utility values and carer disutility**

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	The discussion of the health state utility values shows that the committee have not considered all the evidence in its decision-making and has not updated the guidance based on the updated model. The UK MPS Society utility survey data includes EQ-5D-5L and HUI-3 data from 8 UK patients are now published in Adam et al., 2019 (10). These values were used in the original company base case but in the resubmission the company used the committee's preferred utility values from the rhLAMAN-10 trial in its updated base case, with the MPS Society utilities as a scenario, and this should be reflected in the guidance to show that the committee have taken this into account. No discussion of the appropriateness of EQ-5D as a utility measure in AM or in children with AM has been included. Chiesi have provided interim EQ-5D-5L from baseline measurements from 16 patients in the SPARKLE registry, which can inform on the appropriateness of which health state utility values to use. Updated EQ-5D-5L data from the SPARKLE registry will be included in any data collection plan agreed as part of a managed access agreement to reduce uncertainty with the health state utility values. The omission of the discussion of carer disutility values in this section show that the committee have not considered all the evidence on carer disutility appropriately, and that carer disutility and burden is not adequately captured in the model. The values for carer disutility used in the model were not based on clinical trial data, but are surrogate EDSS values from multiple sclerosis, so may underestimate the carer burden in AM. The published MPS Society survey provided carer HADS and CSI data in Adam et al., 2019 (10). New publications on carer burden were provided by the company that report lifelong caregiver burden as patients with AM cannot live independently. Verrechia et al., 2021 (11) reports the long-term residential care needed for an adult patient. Case reports also describe siblings affected by AM where the caregiver burden is greater (8). As AM is an autosomal recessive disease, there is a 25% chance that any siblings will be affected by AM. In families with multiple affected siblings, caregiver burden is greater, so discussion of the use of multiple caregivers in the economic model may be justified and a scenario with 2 caregivers based on the current carer disutility has been provided at consultation – this reduces the ICER. The implications of the committee not considering carer disutility means that the long-term benefits for carers has been underestimated and their preferred ICERs have overestimated the cost per QALY.
34	**Section 4, 4.19 Ventilation costs** This section shows that the committee has not updated the guidance based on the updated model. The continued ventilation benefit was used in the original company base case but in the resubmission the company used the committee's preferred assumption of no ventilation benefits in its base case, and this should be reflected in the guidance to show that the committee have taken this into account in its decision-making.
35	**Section 4, 4.21 Starting and stopping rules** This section is confusing as it is unclear which stopping rules the committee included in its preferred scenario, and makes no reference to starting rules, the super-responder stopping scenarios, or a stopping rule on wheelchair dependency, showing that committee have not considered all the evidence, and not interpreted it reasonably in the context of a specialised service. The company's base case uses a starting baseline distribution that does not include any patients in a wheelchair, so that no people in a wheelchair start velmanase alfa. However, the ERG preferred the baseline distribution of rhLAMAN-10 that included people who used a wheelchair which increased the ICER. As there was no discussion in section 4.21 of the guidance and there was no discussion at the committee meeting on starting rules regarding people in a wheelchair, it

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	is unclear if the committee do not accept this starting rule as reasonable, as it was not included its preferred scenario. It was also not discussed with clinical experts so the clinical plausibility of this starting rule is unknown. The committee included discussion of some, but not all stopping rules in this section of the guidance, so it unclear which rules are included in its preferred scenario. The 'responder scenario' was accepted by the committee as reasonable; however, the 'super responder scenario' submitted by the company at technical engagement was not included in section 4.21 of the guidance or discussed at the committee with the clinical experts to validate its clinical plausibility. As the 'responder' scenario was accepted as reasonable it is unclear if this would also apply to the 'super-responder' analysis, and if not, the reasons why. Section 4.23 stated that the committee "*agreed that applying stopping rules would imply that people who continue treatment would gain greater long-term benefits than the averages seen in clinical trials*", however, the even greater benefit in the 'super responder' analysis was not recognised or discussed by the committee. The clinical plausibility of a stopping rule if patients became wheelchair dependent was also not discussed at the committee. This scenario was submitted by the company and reduced the ICER but was not discussed with clinical experts. Taken together, it appears that the choice of preferred stopping rule without starting rules seems arbitrary and confused, and has not been agreed in consultation with clinical experts. Given that similar starting and stopping rules are used in commissioning ERTs by NHS England, it seems unreasonable that the committee have not considered all the starting and stopping rules appropriately with clinical experts. In 4.22, the committee conclude that the most plausible ICER associated with velmanase alfa could be lower than the company's base case if strict starting and stopping rules are applied, so it is very important that these rules are included in any preferred ICERs and it is clear how the decisions on these rules have been made, in agreement with clinical experts.
36	**Section 4, 4.22 Starting and stopping rules in the proposed managed access agreement** This section describing the proposed starting and stopping rules are confusing, contradictory to section 4.21 above and 4.23 below, is contradictory to a separate section 4.32 also on stopping rules in a managed access agreement, and reflects the fact there was no adequate discussion of starting and stopping rules with the committee or with clinical experts at the 4th committee meeting. The inclusion of 2 sections on starting and stopping rules in the guidance in section 4.22 and 4.32 is confusing and demonstrates the lack of consistent interpretation in the committee's decision-making. It is unclear which interpretation of the stopping rules the committee used in its decision-making on the MAA. In its resubmission and at the committee meeting, the company highlighted that the previously proposed starting and stopping rules were provisional and had been agreed at an advisory board in 2018 before the availability of long-term rhLAMAN and real-world data and before the publication of the IMF principles. The company submitted a scenario using a 'super responder' stopping rule based on clinical data (a published rhLAMAN-10 analysis by Harmatz et al., 2018 (6)) which addressed the ERG's critique that a formal economic analysis incorporating the refined rules was not possible. There was no discussion of the super-responder analysis in section 4.22. Should the committee agree that velmanase alfa is appropriate for managed access, Chiesi will work with NICE and NHS England to ensure that the principles guiding any agreed MAA are appropriate for the assessment of velmanase alfa and these sections rewritten so that they are up to date and an accurate representation of any agreed stopping rules and data collection agreements.

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37	**4.23 Defining response in the stopping rule** This section describing response rates in the stopping rules are confusing, contradictory to the committee's conclusions in section 4.21, and reflects the fact there was no adequate discussion of stopping rules with the committee or with clinical experts at the 4th committee meeting. It is unclear if the responder rates discussed in this section apply to the stopping rules relating to section 4.21, or only the stopping rules in a managed access agreement in section 4.22, or both. This section does not appear to accurately reflect the new scenario analyses involving super-responders submitted by the company. In the resubmission, the company explored 2 super-responder stopping rule scenarios, one with the existing 5-year delay in disease progression and a scenario with a permanent delay in disease progression in super-responders. These scenarios may be clinically plausible, as the committee agreed in 4.21 that "*applying stopping rules would imply that people who continue treatment would gain greater long-term benefits than the averages seen in clinical trials";* however, these scenarios were not discussed at the committee meeting with clinical experts and in 4.23 the committee has disregarded them as 'uncertain' and 'not directly informative to decision-making', with no reasons given for these interpretations. The ERG highlighted that the super-responder analysis may overestimate the number of patients that stay on velmanase alfa as the definition of a super-responder was less strict than the draft proposed stopping criteria, as it did not include cardiac or infection outcomes. This statement suggests that in clinical practice using even stricter stopping rules, the ICERs could be plausibly lower than the super-responder analysis, but this was not explained clearly in the guidance and it is unclear if the committee understood the implications of this. The final stopping rules will be agreed with NICE, clinical experts and NHS England, and are subject to change, but it should be clear that the ERG concluded that the super-responder analysis alone could underestimate the discontinuation in clinical practice and the plausible ICER could be even lower. It was unclear why in 4.23 the committee were not convinced that the super-responder analysis captured the efficacy of velmanase alfa appropriately, as this contradicts its conclusions on the responder analysis in 4.21 that '*the committee accepted that it was reasonable, in principle, to consider potential stopping rules and to include them in the economic model'* and the 'super-responder' scenario came from the same analysis. Taken together, this section of the guidance shows that the committee have not considered all the evidence, have not interpreted the evidence correctly and their decision-making appears flawed and contradictory. As stated in comment 35 above, since similar starting and stopping rules are used in commissioning ERTs by NHS England, it seems unreasonable that the committee have not considered all the starting and stopping rules appropriately with clinical experts. In 4.22, the committee conclude that the most plausible ICER associated with velmanase alfa could be lower than the company's base case if strict starting and stopping rules are applied, so it is very important that these rules are included in any preferred ICERs and it is clear how the decisions on these rules have been made, in agreement with clinical experts.
38	**Section 4, 4.25 Other assumptions** The inclusion of the baseline walking-state distribution in this section with no reference to starting rules based on wheelchair status shows that the committee have misunderstood the reasoning for the starting distribution and the scenario used by the company in its base case (no patients in a wheelchair). The committee's preferred scenario using the rhLAMAN-10 distributions without reference to the starting rule demonstrate a lack of understanding behind the reasoning for this decision and it appears that the decision for this was arbitrarily chosen as it increases the ICER.
39	**Section 4, 4.26 Cost-effectiveness results**

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	The results of this section do not reflect the updated company base case to account for the committee's preferred assumptions and do not reflect all the scenarios presented by the company that should be considered by the committee in their decision-making on the most preferred ICER, including starting and stopping rules. This shows that the committee decision-making on the preferred ICER has not accounted for the latest economic evidence and the company's updated modelling results, and has not included clinically-relevant starting and stopping rules. The decision-making on the preferred ICER is contradictory on previous conclusions, is not clear on the scenarios that were included and was not decided in consultation with clinical experts. The committee's list of preferred assumptions in section 4.26 include scenarios that are already accounted for in the company's updated base-case – by listing them with no acknowledgement that the company has included them implies that they are not already accepted in the company base-case. The company has already included: • utilities for walking unassisted and walking with assistance taken from the clinical trial • a discount rate of 3.5% • the amended ventilation cost • the cost of home infusion included • the corrected transition probabilities. The company also included scenario analyses for the possibility for people having best supportive care to improve health state and the baseline walking health-state distribution from the final analysis of rhLAMAN-10, as well as a time horizon of 50 years, but these were also not acknowledged and the results not provided. In Section 4.26, the inclusion of starting and stopping rules was acknowledged by the committee to reduce the ICER, but it was unclear whether the preferred ICER included any starting and stopping rules – and if they were included, what rules were applied. This contradicts its conclusions in 4.21 that it was reasonable, in principle, to consider potential stopping rules and to include them in the economic model. It also concluded that the most plausible ICER associated with velmanase alfa could be lower than the company's base case if strict starting and stopping rules were applied. As the committee's most plausible ICERs do not include starting and stopping rules, the choice of the preferred ICER in 4.26 appears confusing and contradictory to 4.21. If after considering all the current clinical and economic evidence, the committee remain unsatisfied with the levels of uncertainty, Chiesi have proposed a data collection plan and pre-planned statistical analyses that can address the specific clinical uncertainties highlighted by the ERG through a managed access agreement.
40	**Section 4, 4.28 Impact of the technology beyond direct health benefits and on the delivery of the specialised service** This lack of detail in this section shows that the committee have misunderstood the severity of the condition, have not taken into account the new evidence on carer burden, or the real-world evidence showing increased social functioning of patients after treatment with velmanase alfa, with improved ability to attend school and work evidenced from Etoile Alpha and case reports. As detailed in comment 1 and 2, this is further evidence that that the committee have not fully considered the impact beyond direct health benefits for patients and carers, meaning that the long-

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	term benefits has been underestimated and their preferred ICERs have overestimated the cost per QALY.
41	**Section 4, 4.30 Equalities** As detailed in comments 1, 2, 3 and 4, the committee have not considered all the evidence, interpreted the evidence reasonably in the context of an innovative treatment for an ultra-rare disease, that affect children, who have no other treatment options. The process that the committee has used in its decision-making appears discriminatory against people with AM on the grounds of the ultra-rare nature of their disability, and on the grounds of age with respect to patients under 18 years. This is because the process that the committee has taken in making its decision shows an unwillingness to use appropriate HTA methodologies for data related to very small populations, for children, or for innovative technologies. In section 4.30, it stated that the committee had taken into account the nature of the population, including the fact that it included children. But in contradiction to this, it stated that no further considerations or adjustments were needed, so it is unclear how the committee had taken the population into account in its decision-making. This shows that the committee has failed to give due consideration to the population in a fair and equitable way when considering the levels of uncertainty in the context of an ultra-rare, disabling disease that affects children with no available therapy, in line with the new NICE methods guide. If the committee were still unsatisfied by the levels of uncertainty, the committee should consider the option of managed access in a fair and equitable way, using all the available evidence and proposed data collection plan. In section 4.30, the committee states that the benefits of the technology has been fully captured in the evidence, modelling and considerations; however, this contradicts its conclusions in 4.17 "*that beyond the modelled health states for mobility and infection, there may be additional benefits from velmanase alfa not captured in the model",* and that *"the committee recognised that the model may not have captured within health-state benefits from velmanase alfa (such as reduced fatigue and pain, and improved cognition) and benefits from velmanase alfa not captured in EQ 5D measurements".* It also did not include starting and stopping rules, despite agreeing it was reasonable to include them, and that "*applying them would imply that people who continue treatment would gain greater long-term benefits than the averages seen in the clinical trials".* In section 4.30 it also states it has considered patient testimony, and all the available evidence – but this is not the case, as demonstrated by the evidence that has not been considered in comment 1. It also stated that it was appropriate to take into account the very small population size, and the size of the impact on the NHS in its decision making; however as the most plausible ICERs were approaching the threshold, and the plausible ICER could be lower when starting and stopping rules were applied, it is unclear how the low budget impact has been accounted for in its decision-making. In section 4.30, the committee agreed that it had considered patients with cognitive impairment in its preferred utility benefit for velmanase alfa, which was above that recorded using EQ-5D questionnaires in rhLAMAN 10. However, as discussed in comment 2 and comment 23, the committee has not used NICE's own guidance on the use of EQ-5D in children and those with hearing impairment (19, 27), and has not reasonably interpreted the use of FVC-based utility measures, in contradiction to its acceptance of them in HST19 (20). Taken together, this suggests that the processes that the HST committee has used in its interpretation of the evidence for velmanase alfa has discriminated against people with AM, in not using appropriate HTA methodology for people with an ultra-rare disability that affects children.

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42	**Section 4, 4.31 Managed access** As detailed in comment 1 and 2, the committee have not appropriately considered all the evidence or the proposed data collection in the ongoing SPARKLE and AllStripes registry or the proposed statistical analyses that can address the clinical uncertainties within the period specified by the IMF. In Section 4.31, the committee have not explained why the proposed data collection plan and analyses cannot address the clinical uncertainties, only that the data would not provide robust estimates, but not the reasons for this: "*This was because the ongoing trial and registry data would not provide more robust estimates for quality of life or long-term clinical effectiveness."* This statement appears contradictory to the evidence, as the ongoing SPARKLE registry and AllStripes study have already reported interim utility and mobility data in untreated patients (13, 25), and the rhLAMAN-07/-09 studies will provide 10-year clinical trial data in treated patients in 2023. In Section 4.31 it states "*Also, there are substantial challenges in collecting any robust evidence from the small number of people with alpha-mannosidosis*". This statement appears to be discriminatory to patients with ultra-rare diseases in that it suggests that the managed access process is not appropriate for assessing treatments for ultra-rare conditions with small populations as the robustness of data required by the HST process is not possible to be collected in ultra-rare populations, which would not be fair or equitable for people with AM. In Section 4.31, "*the committee noted that the company's latest submission contained several years of additional evidence that was not available when it first considered velmanase alfa. But it agreed that this had not substantially resolved the uncertainties discussed at previous evaluations.*" Since the original draft guidance in 2018, long-term rhLAMAN and real-world data in patients treated for up to 9 years has reduced the uncertainty on long-term disease stabilisation and improvements in functioning and quality of life, with subsequent improvements in cost-effectiveness estimates. New natural history data are available on the mortality and morbidity of untreated patients and natural history studies, such as Hennerman et al., 2022 (12) and interim data from AllStripes (13). This contradicts the conclusions of the committee that further data collection could not reduce uncertainty and indicates that all the relevant evidence has not been considered in its decision-making. Indeed, the committee have improved its assumptions on the length of delay in disease progression from zero to 3 years, and increased the utility benefit in children and adolescents from 0.05 to 0.1, based on new rhLAMAN-10 analyses and real-world evidence. In Section 4.31, "*It concluded that it was highly unlikely that evidence collected within an MAA of a reasonable duration would resolve the key uncertainties enough for it to re-evaluate velmanase alfa with a greater degree of certainty at the end of the managed access period*." This statement shows that the committee have misunderstood or have not considered the proposed data collection plan appropriately, as the statistical analyses described in Table 66, p 104 of the company submission can address the clinical uncertainties and use data that will report in 2023, supplemented by the yearly SPARKLE interim analyses that already has 40 patients recruited and will report its first efficacy results in 2023. Chiesi provided information on outcomes being measured in the ongoing European SPARKLE registry and rhLAMAN-07 and -09 trials that will provide these data within a reasonable timeframe (up to a maximum of five years), as specified by the Innovative Medicines Fund.
43	**Section 4, 4.32 Starting and stopping rules in the MAA** This section describing the proposed starting and stopping rules are confusing and is contradictory to the preceding separate section 4.22 also on stopping rules in a managed access agreement,

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	which reflects the fact there was no adequate discussion of starting and stopping rules with the committee or with clinical experts at the 4th committee meeting. The inclusion of 2 sections on starting and stopping rules in the guidance in section 4.22 and 4.32 is confusing and demonstrates the lack of consistent interpretation in the committee's decision-making. It is unclear which interpretation of the stopping rules the committee used in its decision-making on the MAA and the reasons for its decision-making. In section 4.32, the committee recalled that stopping rules based on non-response were included in the model, but does not acknowledge other proposed stopping rules, such as the super-responder analysis that was not discussed with clinical experts. In Section 4.32, the ECD states that the current proposed MAA with its starting rules contradicts principle 1 of the Innovative Medicines Fund. As the Innovative Medicines Fund Principles were published in June 2022 (17) after the submission of the proposed draft MAA and 5 years after the start of this appraisal, Chiesi will work with NICE and NHS England to ensure that the principles guiding any agreed MAA are appropriate for the assessment of velmanase alfa. Moreover, we do not consider that the company's proposed MAA is necessarily inconsistent with the Innovative Medicines Fund Principles. While the Principles state that medicines recommended with managed access will be made available to the entire eligible patient population, the realities of NHS clinical practice are that only patients likely to benefit from velmanase alfa treatment will receive the product and only those whose condition improves and/or who tolerate the treatment will continue to receive treatment. In Section 4.32, the committee concluded that velmanase alfa does not have plausible potential to be cost effective, yet as described in comments 1, 2, and 35-37 not all the evidence was taken into account, including the super-responder analysis. It also thought that a period of further data collection through an MAA would be unlikely to resolve the key uncertainties in the evaluation, however, as describe in comments 1, 2 and 42 not all the statistical analysis and data collection plan were considered by the committee appropriately. As such, the decision-making does not reflect all the evidence or reasonable interpretations of the evidence, and does not appear to be sound or suitable in the context of highly specialised commissioning for the only treatment for patients with AM.
44	**Section 4, 4.33 Conclusions** The section of the guidance is contradictory and shows that the interpretations of the evidence in the committee decision-making is not reasonable and summarised the inconsistency and inequitable nature of the process used to consider the evidence. In section 4.33, the committee highlighted that "*it was aware that small increases in clinical outcomes can translate to substantial improvements for people with AM"*; however, this has not been taken into consideration in its interpretation of the evidence and is contradictory to the next sentence that states "*important limitations in the nature and extent of the evidence, and the size of the improvements seen in the clinical trials*". This statement also disregards the importance of disease stabilisation, as highlighted in comments 1 and 2 and represents a misunderstanding of the natural history of a slow progressive, heterogeneous disease such as AM. In section 4.33, the committee accepted that "*it was appropriate to take into account the low budget impact and exceptional rarity of the condition in its decision making";* however, how it was taken into account in its considerations of cost-effectiveness were not explained in the cost-effectiveness results section. It also stated that "*it also took into account the other factors affecting its decision, including the substantial uncertainty in the clinical and economic evidence";* however, how it did so in its consideration of cost-effectiveness is not stated, and it is unclear if NICE's own

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	guidance has been followed on the flexibility in accepting greater uncertainty for innovative treatments, for rare diseases, and for those that affect children. In Section 4.33, the committee concluded that "*data collection would be unlikely to resolve the key clinical uncertainties*". As highlighted in comments 1, 2, 42 and 43, the guidance shows that the committee have not considered the proposed data collection plan and statistical analyses appropriately, or in consultation with clinical experts. As such, the process used by the committee in making this conclusion is not sound or suitable in the context of highly specialised commissioning for the only treatment for patients with AM.
45	**Reference list** 1. Borgwardt L, Guffon N, Amraoui Y, Jones SA, De Meirleir L, Lund AM, et al. 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). Journal of Inborn Errors of Metabolism and Screening. 2018;6:2326409818796854. 2. Lund AM, Borgwardt L, Cattaneo F, Ardigò D, Geraci S, Gil-Campos M, et al. Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis. J Inherit Metab Dis. 2018;41(6):1225-33. 3. Phillips D, Hennermann JB, Tylki-Szymanska A, Borgwardt L, Gil-Campos M, Guffon N, et al. Use of the Bruininks-Oseretsky test of motor proficiency (BOT-2) to assess efficacy of velmanase alfa as enzyme therapy for alpha-mannosidosis. Mol Genet Metab Rep. 2020;23:100586. 4. Lund A, Guffon N, Gil-Campos M, Cattaneo F, Heron B, Tylki-Szymanska A, et al. Effect of velmanase alfa (human recombinant alpha-mannosidase) enzyme-replacement therapy on quality of life and disease burden of patients with alpha-mannosidosis: Results from caregiver feedback. Molecular Genetics and Metabolism. 2021;132(2):S67. 5. Borgwardt LG, N.; Amraoui, Y; Gil-Campos, M; Heron, B; Tylki-Szymanska, A., editor The burden of infections for alpha-mannosidosis patients participating in velmanase alfa clinical trials and the impact of treatment. SSIEM Annual Symposium; 2018 4-7 September; Athens, Greece. 6. Harmatz P, Cattaneo F, Ardigò D, Geraci S, Hennermann JB, Guffon N, et al. Enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase): Novel global treatment response model and outcomes in patients with alpha-mannosidosis. Mol Genet Metab. 2018;124(2):152-60. 7. Chiesi FSpA. Clinical study report - Etoile Alpha Multi-center, non-comparative, retrospective registry for patients receiving or having received a LAMZEDE therapy in France. 2021 29 June 2021. 8. Garcia-Navarretea SG-C, M; Cerkauskaite, A; Cerkauskiene, R; Gál, T; Lopez-Rodriguez, MA; Gonzalez-Garcia, A; Suarez Carantoña, C; Manzano Espinosa, L; Bruno, I; Elefante, P; Magnolato, A. Use of velmanase alfa in adult patients with alpha-mannosidosis – Case reports: Springer Healthcare Italia; 2021. 9. Cole DS, Maw KJ. Clinical outcomes in an adult patient with alpha-mannosidosis treated with velmanase alfa for 5 years. Molecular Genetics and Metabolism. 2021;132(2):S27. 10. Adam J, Malone R, Lloyd S, Lee J, Hendriksz CJ, Ramaswami U. Disease progression of alpha-mannosidosis and impact on patients and carers - A UK natural history survey. Mol Genet Metab Rep. 2019;20:100480. 11. Verrecchia E, Sicignano LL, Massaro MG, Rocco R, Silvestri G, Rossi S, et al. Caregivers' and Physicians' Perspectives on Alpha-Mannosidosis: A Report from Italy. Adv Ther. 2021;38(1):1-10. 12. Hennermann JB, Raebel EM, Donà F, Jacquemont ML, Cefalo G, Ballabeni A, et al. Mortality in patients with alpha-mannosidosis: a review of patients' data and the literature. Orphanet J Rare Dis. 2022;17(1):287.

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	13. Chiesi data on file. AllStripes: Chiesi interim data delivery; summary of key data. 2022 27/01/22. 14. Hennermann JB, Guffon N, Cattaneo F, Ceravolo F, Borgwardt L, Lund AM, et al. The SPARKLE registry: protocol for an international prospective cohort study in patients with alpha-mannosidosis. Orphanet J Rare Dis. 2020;15(1):271. 15. SMC SMC. SMC2466: UMAR velmanase alfa 2022 12 Sept 2022. 16. Chiesi data on file. UK Clinical Expert Interviews April 2022. 2022. 17. NHS England. The Innovative Medicines Fund Principles. 2022 June 2022. 18. NICE. NICE real world evidence framework. 2022 23 June 2022. 19. NICE. NICE health technology evaluations; the manual. 2022. 20. NICE. HST19: Elosulfase alfa for treating mucopolysaccharidosis type 4A (review of HST2): committee slides. 2021 6 October. 21. Lipiński P, Różdżyńska-Świątkowska A, Iwanicka-Pronicka K, Perkowska B, Pokora P, Tylki-Szymańska A. Long-term outcome of patients with alpha-mannosidosis – A single center study. Molecular Genetics and Metabolism Reports. 2022;30:100826. 22. Leiro B, Phillips D, Duiker M, Harmatz P, Charles S. Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome): defining and measuring functional impacts in pediatric patients. Orphanet Journal of Rare Diseases. 2021;16(1). 23. Dhanani S, Quenneville J, Perron M, Abdolell M, Feldman BM. Minimal difference in pain associated with change in quality of life in children with rheumatic disease. Arthritis Rheum. 2002;47(5):501-5. 24. Borgwardt L, Guffon N, Amraoui Y, Dali CI, De Meirleir L, Gil-Campos M, et al. Efficacy and safety of Velmanase alfa in the treatment of patients with alpha-mannosidosis: results from the core and extension phase analysis of a phase III multicentre, double-blind, randomised, placebo-controlled trial. J Inherit Metab Dis. 2018;41(6):1215-23. 25. Chiesi data on file. SPARKLE interim baseline EQ-5D data. 2022. 26. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. Journal of Health Economics. 2017;55:139-52. 27. NICE. CHTE methods review, Health-related quality of life: Task and finish group report. 2020 July 2020. 28. Beck M, Olsen KJ, Wraith JE, Zeman J, Michalski JC, Saftig P, et al. Natural history of alpha mannosidosis a longitudinal study. Orphanet J Rare Dis. 2013;8:88. 29. Chiesi data on file. Etoile Alpha: individual patient data synopses. 2021.

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Chiesi wish to highlight that all previous company and stakeholder comments submitted during the original consultation of the ECD2 from 07 July-14 August 2022 are still relevant and should be taken into account in committee decision-making.
2	Since the original consultation of the ECD2 from 07 July-14 August 2022, results of the French Etoile Alpha study and baseline demographics of the latest datalock of the SPARKLE registry have been published as poster presentations at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium in September 2022. The posters have been provided in a reference pack and the AIC checklist has been updated. Details of the new publications are below: • **Guffon, N et al., SSEIM September 2022: PO20-2659. Long-term Efficacy of Velmanase Alfa in Patients with Alpha-mannosidosis (AM): Retrospective Analysis of a French Registry for up to 9.5 Years.** o Largest observational study of AM treated with velmanase alfa (VA) (N=16). Mean age, 26 years (range: 10–52 years; 68.8% ≤ 18 years); 56.3% male; mean VA treatment duration, 54 months (range: 13–114 months) • **Hennerman JB et al., SSEIM September 2022: PO12-2512. Baseline Characteristics from the International Retrospective and Prospective SPARKLE Registry of Patients with Alpha-Mannosidosis.** o As of datalock on 21 October 2021, 49 participants had been enrolled at 23 sites in 16 European countries. Baseline data showed mean age at enrollment was 20.7 years (range: 3–51 years; 57.1% ≥ 18 years) and 36 participants (73.5%) were male. At datalock, 24 patients (49%) had received VA treatment.
3	Chiesi wish to highlight that factual inaccuracies were presented by NICE in the committee slides on 8 June 2022; each of these inaccuracies were raised verbally by the Chiesi company representative at the committee meeting, but have not been corrected in the public committee slides that were uploaded to the NICE project webpage on 27 September 2022. The factual inaccuracies in the committee slides are detailed below: • **Slide 7:** data from the multidomain responder analysis was used in the economic model (the rate of discontinuation) so should have been marked in red • **Slide 16:** Etoile Alpha had a mean treatment duration of 54 months, in children this was 64.8 months and 7 of 16 patients were treated long-term for over 6 years and up to 9.5 years, which is relevant to the disease progression assumption. The lack of respiratory infections and improvements in 6MWT and FVC %predicted also has relevance to the additional on-treatment utility benefit. The SPARKLE registry although immature is relevant for the feasibility of data collection in a managed access agreement. Individual case reports from all patients in the Etoile Alpha study (n=16) detailing all symptomatic and functional changes pre- and post-treatment were also reported in the submission but have not been included. • **Slide 23:** should say “some people <6 years” at diagnosis instead of “>6 years at diagnosis” • **Slide 26:** the rationale for ECM3 base case is EQ-5D data from rhLAMAN-10 (0.05 in all; 0.08 in children and 0.03 in adults) – this is also the rationale for ECM4 CS base case in addition to the UK KOL opinion and assumption. The rationale for the post-TE base case is surrogate utility estimates from FVC and 6MWT from both rhLAMAN-10 and Etoile Alpha. As such, relevant rhLAMAN-10 outcomes in the bottom table should also include the surrogate outcomes FVC (n=28) and 6MWT (n=33). • **Slide 27:** lung function is an important health benefit not captured in the model that was not

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	included in the list (as well as minor surgeries) – as the inadequate capturing of lung function is key to the rationale for using FVC as a surrogate utility estimate, it should be included in this list. • **Slide 27:** The Etoile Alpha QoL figure does not provide the number of patients reporting these data, so could be misinterpreted as the whole population: baseline data from the CHAQ, and for the most part the EQ5D5L was not fully available, and only 7 of 16 reported CHAQ and only 5 of 16 reported EQ-5D at month 30. As such, no cluster or global trend can be observed for QoL, but some positive outliers are noted. • **Slide 28:** FVC and 6MWT in rhLAMAN-10 in <18 years = **0.258 utility benefit in <18 years;** face validity also supported by the similar disease manifestation of MPSIVa and AM. Reduced pain is also supported by reduced analgesic use in case series and rhLAMAN-10 CHAQ-DI scores: -17% reduction (minimally important difference is -8.2%). Substantial reduction in minor infections and improved cognition is evidenced in all case series, as well as Etoile Alpha.
4	Since the previous consultation from 07 July-14 August 2022, additional evidence has been published in 3 new case reports describing the real-world effectiveness of VA and/or the natural disease progression of untreated patients. As highlighted in our previous consultation response, it is important in an ultra-rare disease such as AM affecting only ~25 people in the UK, that all evidence is considered appropriately by the committee, including case reports. The 3 new published case reports provide additional information on the progression of symptoms of AM that are not captured adequately in the health states of current model health, including hearing loss, lung function, minor infections, pain and cognitive issues. The case reports also describe the impact of the disease on the social and educational aspects of patients, as well as the diagnostic delay from the time of first symptoms to a confirmed genetic diagnosis. • **Crescitelli, V. and Gasperini, S., 2022. Alfa-mannosidosi: una malattia da riconoscere, scoprire e curare**. (Italian): Available at https://www.malattierare.eu/pages/rivista/Alfa-mannosidosi-una-malattia-da-riconoscere-scoprire-e-curare-idA166 - translation provided in reference pack. Case report of a 7 year old girl with frequent infections, chronic lung disease, bilateral hearing loss and intellectual disability. After 18 months treatment with VA, the case report describes substantial improvement in hyperactivity, motor performance (6MWT), comprehension, verbal expression and hearing loss, net reduction in respiratory infection with the need for antibiotics reduced to 3 times a year from 20 times a year before treatment, no apnoea or night desaturation and no more electrical abnormalities on EEG. The girl attends third grade school with support and has physiotherapy and speech therapy 2 times a week. The treatment has had a marked improvement in the quality of life of the family. • **Kharbanda M, Cook P and Nurse, J. 2022 Alpha-mannosidosis diagnosed in a 47-year-old male: the importance of re-visiting undiagnosed patients**. Poster presented at SSIEM 2022 - provided in reference pack. Case report of an untreated male in UK, diagnosed late in life at 47 years. Initially presented with hearing impairment at 9 months and was subsequently found to have craniosynostosis, dysmorphic features and developmental delay. His sister had a similar phenotype raising the suspicion of a recessive disorder. He was followed-up throughout childhood in a specialist unit, but early genetic tests were normal and further investigations were unavailable at the time. He attended a school for deaf children and went on to college and vocational training. By 2012 he was living in supported accommodation with 24 hour supervision. He was reviewed again aged 37 having developed osteoarthritis in both hips requiring bilateral hip replacement surgery. He subsequently developed ataxia with cognitive decline, with cerebellar atrophy on neuroimaging. • **Hennermann JB. Die α-Mannosidose: eine seltene, aber unterdiagnostizierte Erkrankung?. Monatsschrift Kinderheilkunde. 2022 Sep 20:1-7**. (German) – translation provided in reference pack. Case report of an untreated female patient diagnosed at 20 years. At 2 years, slight motor weakness; at 4 years bilateral hearing loss and speech developmental delay. Due to the developmental delay, the girl attended a special education

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	class for 2 school years, then a school for children with hearing loss, and then a school for children with mental disabilities. An intelligence test at the age of 12 revealed a moderate intellectual disability. At the age of 11, the patient underwent a squint operation and at the age of 12 the surgical treatment of a lumbosacral spondylolisthesis. In adolescence, additional symptoms of facial dysmorphia, dysarthria (difficulty speaking), gait ataxia, genu valgum position (knocked knees) and slight hepatosplenomegaly were noted.
5	Since the previous consultation from 07 July-14 August 2022, additional evidence has been submitted by Chiesi to the FDA in October 2022 as part of its BLA filing in response to a request for further information on paediatric efficacy, which has been provided in the reference pack (**Chiesi data on file, Clinical Information Amendment – Response to FDA Day 74 – Pediatric Efficacy, October 2022**). The FDA response contains the following new information summarised below: • A review of the heterogeneity of the clinical manifestations of untreated patients, including summaries of case series and natural history studies. Despite no clear relationship between the degree of alpha-mannosidase activity loss and the clinical phenotype or a defined genotype-phenotype relationship, it is generally recognisable that older patients are more severely affected, as would be expected from the progressive nature of the disease. Most children appear normal at birth, but clinical manifestations begin at a very early age followed by progression of clinical symptoms. In younger patients (≤10 years), hearing impairment and/or speech delay are the main symptoms. The more severe the clinical manifestations of the disease, the earlier is their onset and progression. Of note, no reported adult patient has managed to live independently, due to the presence of cognitive and motor impairment progression and/or psychiatric manifestations. • A summary of the 2-year natural history study in 43 patients (rhLAMAN-01, originally published as **Beck M, et al. Orphanet J Rare Dis. 2013;8:88**). All subjects over the age of 3 years had significant hearing loss at baseline and the musculoskeletal area showed typical abnormal findings including macrocephaly, contractures, scoliosis, hip dysplasia and deformities of feet. In the younger age group (<18 years), 62% of the subjects had abnormal findings for this body area, but in older subjects (>18 years of age), the rate was higher (92%). Both groups showed a significant range of walking ability, making it difficult to clearly separate the age groups. Over the 2-year study period, there was slight progression of a few clinical findings: a minor change of hearing loss, increases in psychiatric troubles in both groups, and respiratory dysfunction under 18 years. For the younger age group, there was a mean 10% decrease in lung function as measured by FVC% predicted, whereas for the older age group, mean FVC% predicted remained stable. The rate of adult subjects with abnormal musculoskeletal findings increased from 92% to 94% after 2 years. In a predictive model of 6MWT outcomes, younger subjects showed functional capacity between 50% and 60% of the values for normal subjects of the same age and for older subjects, the functional capacity was further reduced to 40% – 45%. • Population PK modelling – [redacted] • Further information on the effect of VA on FVC %predicted. As lung function changes are particularly relevant to the paediatric population and the surrogacy link for FVC to on-treatment utility benefit is used in company base case of the economic model in the <18 subgroup, FVC% predicted is discussed in more detail: ○ In rhLAMAN-05, for FVC% predicted, the adjusted mean absolute change (% of predicted) from Baseline to Week 52 was 8.21 (95% CI: 1.79, 14.63) in the VA group (n=12) and 2.30 (95% CI: - 6.19, 10.79) in the placebo group (n=9). The adjusted mean difference favoured VA: +5.91 (95% CI: -4.78; 16.60), p=0.278. For the paediatric subgroup, the absolute change from Baseline to Week 52 was 14.2 (% of predicted) and 8.0 (% of predicted) in the VA and placebo groups, respectively, yielding a between group difference of +6.2% in favour of VA. For the adult

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	subgroup, the absolute change from baseline to week 52 was +2.2 (% of predicted) and -2.8 (% of predicted) in the VA and placebo groups, respectively, yielding a between group difference of +5.0% in favour of VA. Although both age subgroups showed similar directionally positive results favouring VA from Baseline to Week 52, paediatric findings for FVC% predicted were stronger. o Additional perspective for the FVC % predicted change for VA vs placebo of 5.91% (95% CI: -4.78; 16.60), p=0.278 can be derived from clinical data with avalglucosidase alfa, a new enzyme replacement therapy (ERT) for Pompe Disease. The FVC improvement seen in the pivotal study for the new ERT versus the older ERT showed a treatment difference from baseline to week 49 of 2.4% (95% CI -0.1 to +5.0), which met the non-inferiority lower boundary of -1.1%. Notably, the comparator ERT had previously performed a placebo-controlled trial (AGLU02704 or LOTS) showing a change from baseline in FVC% predicted of +1.7% while the placebo arm fell by -2.0%, yielding a between arm treatment difference between arms of 3.7% (95% CI 1.7%, 5.6%). Thus, while the VA finding of a 5.91% placebo-subtracted difference in FVC% for the overall population predicted lacks statistical significance, it is a robust and clinically significant mean numerical improvement in lung function. o Any uncertainty left by the lack of statistical significance in rhLAMAN-05 can be addressed by the wider experience of patients in rhLAMAN-10, where FVC changes were assessed versus baseline, and where improvements, beyond the generally recognised 2-3% variability are not generally anticipated. In the rhLAMAN-10 overall integrated analysis, the mean FVC% predicted was 84.9% (18.57%) at Baseline, 93.2% (20.76%) at Month 12, and 93.1% (21.74%) at Last Observation. Gains in FVC versus Baseline were statistically significant at Month 12 and the Last Observation with mean absolute changes of +6.6% (95% CI 1.60%, 11.51%), p = 0.011, and +8.1% (95% CI 2.43%, 13.68%), p = 0.007. In AM generally, and without treatment, spontaneous significant rises in FVC% predicted over time are not anticipated. Small increases, simply due to variability in the test, may be seen. Indeed, in rhLAMAN-05, the 9 patients on placebo had a mean (SD) FVC% predicted at Baseline, Month 6 and Month 12 of 90.4% (10.39%), 91.0% (14.12%), and 92.4% (18.15%), and an increase in FVC% predicted of approximately 2% over a year of follow-up. These findings help frame the mean rise in FVC% predicted in n=33 patients treated with VA in rhLAMAN-10: mean gains in FVC% predicted of 6.6% (95% CI 1.60%, 11.51%) were observed from Baseline to Month 12, while mean gains of 8.1% (95% CI 2.43%, 13.68%) were observed from Baseline to Last Observation. o Across all treated subjects, FVC% predicted improved within the first year of treatment and continued to improve with longer term treatment. This degree of improvement in FVC% predicted versus baseline reflects the efficacy of VA and is very unlikely to have occurred by chance alone. The positive and robust change in FVC% predicted vs baseline observed in rhLAMAN-10 integrated analysis who were all treated with VA further corroborate and support the validity of the mean change in FVC% predicted for VA over placebo in rhLAMAN-05 of 5.91%, as well as the improvements seen in the Etoile Alpha real-world study. o The FVC improvements observed in the paediatric subset of rhLAMAN-10 integrated analysis were particularly robust: a mean absolute 11.6% improvement in FVC% predicted (p value = 0.007) was seen from baseline to last observation in this population. Since FVC% predicted measurements are automatically adjusted by age norms, this does not represent lungs that are growing, rather it represents a large improvement in lung function during treatment with VA, a key factor when considering paediatric approval. • A new Multi-component Analysis: 3MSCT, 6MWT, FVC% Predicted, CHAQ-DI and CHAQ-VAS Pain was requested by the FDA to identify to potential multi-component endpoints using O'Brien's test statistic. Results include both an O'Brien's ordinary least squares (OLS) statistic as well as a generalised least squares (GLS) statistic, with an emphasis on the latter

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because it accounts for the correlation among the endpoints that form the multi-component endpoint, resulting in greater power. This approach is particularly useful in heterogenous diseases where a single efficacy endpoint may not be feasible to access in all subjects, and a combination of endpoints is therefore more useful. The endpoints constituting various multi-component combinations in rhLAMAN-05 were the primary outcome 3MSCT, the prioritised secondary outcomes 6MWT and FVC% predicted, and the additional secondary outcomes CHAQ-DI and CHAQ-VAS. For the analysis of the endpoints of choice, all possible combinations of ≥2 endpoints were considered and both O'Brien's OLS and GLS statistics were computed. Only results limited to combinations with significance levels < 0.10 for ≥ 1 of the 2 tests were considered.

- The combinations of [redacted] and [redacted] had the smallest significance level for O'Brien's GLS statistic ([redacted] reflecting the most statistically significant difference between VA and placebo groups.
- When computing O'Brien OLS and GLS statistics for the paediatric (6 to <18 years) and adult (≥18 years) age groups separately, the combinations with the smallest significance level for O'Brien's GLS statistic in paediatrics were [redacted] and [redacted].
- For the adult age group, the combinations of [redacted] and [redacted] had the smallest significance level for O'Brien's GLS statistic ([redacted]). These combinations reflected the most statistically significant difference between VA and placebo groups in their respective age groups.
- Overall, in this computed analysis, the most statistically significant difference between VA and placebo groups was observed for a combination of [redacted] of the selected endpoints across all age groups and within paediatric and adult age groups.
- This highlights that a selection of 1 single endpoint to determine efficacy for all subjects equally in a clinical trial for a heterogeneous disease like AM may not be appropriate. Furthermore, the high degree of overlap within adult and paediatric subgroups for the combinations of endpoints providing the most significance is highly supportive of the applicability of extrapolation to the <6 years age group.

- New real-world data of use of VA in 3 patients <6 years of age, including use of VA as a bridging treatment while awaiting haematopoietic stem cell therapy (HSCT):
  - A [redacted]: after 2 months of VA treatment (ie, 8 x once-weekly treatments), there was an overall improvement in some clinical features and significant reduction from baseline in urine oligosaccharides ([redacted] mean reduction) and serum oligosaccharides ([redacted] mean reduction); reduction in oligosaccharides was observed as early as 2 weeks after treatment initiation. There was also a constant increase of serum alpha mannosidase activity that was observed as soon as 1 week after first infusion (i.e., four times normal values).
  - A [redacted]diagnosed with AM. As the patient was being considered for HSCT, she was started on VA treatment at 2 years and 4 months of age at 1mg/kg body weight. The patient received VA treatment for a total of 49 weekly infusions prior to HSCT and a total of 10 weekly infusions post-HSCT. The patient received a collective total of 59 weekly infusions of VA. After the first 4 weekly infusions of VA, urine oligosaccharides were reduced significantly from [redacted] and the patient showed notable clinical improvement in walking ability and stability compared to pretreatment (pre- and post-treatment videos are provided)
  - A [redacted] (i.e. in utero, during the third trimester of the mother's pregnancy) due to a symptomatic older sibling diagnosed with AM. Upon birth, alpha mannosidase in leukocytes was reportedly significantly reduced and MAN2B1 variants similar to her older sibling were identified. The infant had reportedly mild features of AM including mild hepatomegaly and mild adenoid hypertrophy. No dysmorphic features, motor or

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		neurodevelopmental delays were reported. The treating physician proposed initiation of VA infusions to delay or prevent development of irreversible AM features. The patient was started on VA treatment at 6 weeks of age at 1mg/kg body weight. The patient has received VA treatment for a total of 39 weekly infusions with premedication with antipyretic and antihistamine and continues on treatment.

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- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

NICE National Institute for Health and Care Excellence

Velmanase alfa for treating alpha-mannosidosis

Consultation on the evaluation consultation document – deadline for comments 5pm on 04 August 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**The MPS Society**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**NA**]
Name of commentator person completing form:	[**Sophie Thomas**]

Comment number	**Comments** Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Velmanase alfa for treating alpha-mannosidosis

Consultation on the evaluation consultation document – deadline for comments 5pm on 04 August 2022. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Despite the committees uncertainties regarding the longer term outcomes and benefits; we were pleased that they had also recognised that Velmanase alfa was a promising and innovative treatment.
2	We are concerned that the ECD is almost a carbon copy of the unpublished 2019 FED, with only a few references to the additional data, and cost analysis submitted by the company. Disappointingly, additional stakeholder engagement, technical engagement discussions and submitted evidence does not appear to have been reflected in an inclusive and meaningful way.
3	The company have committed to the ongoing collection of data and evidence through the Etoile alpha study and their Sparkle registry. Additional published real-world evidence was also submitted and this does not appear to have been considered or reflected in the committee's decision, despite the positive clinical improvements and long term stabilisation as demonstrated in submitted published reports such those by Borgwardt et al 2018 whose paper showed improvements over a sustained period of more than five years, and Harmatz et al 2018 who used an alternative responder anaylsis model to demonstrate clinically meaningful treatment effects of velmanase alfa.
4	It is concerning that a recent ERT has been given a positive recommendation despite the limited evidence and lack of data for one treatment group. In this case the committee accepted that assumptions about efficacy were needed due to the rarity of the condition despite the limited data available. However for velmanase alfa the committee felt that there was bias in the assumptions, that there was an over reliance on KOL interpretation and that despite the EQ-5D being aligned and comparable for adults, there was uncertainty for children. This in our view reflects inconsistent decision making, with velmanase alfa being discriminated against for being a first in disease therapy technology. In addition to this, EQ-5D has a number of limitations due to its inability to capture many aspects of ultra-rare diseases such as alpha mannosidosis, as well as cognitive impairment and is not appropriate for use in children. Has the committee therefore interpreted the utility benefits taking into consideration the limitations and NICE's decision to no longer use EQ-5D for this population?
5	The committee queried whether benefits seen in the clinical trial reflected what might be seen in clinical practice but then state that the company submission relied too much on clinical opinion rather than clinical trial evidence.
6	We are concerned that the committee concluded that the evidence submitted did not include people with progressed disease requiring the use of a wheelchair and this raised uncertainty over whether treatment would be considered for this patient cohort. Having reviewed the data, there were patients requiring the use of a wheelchair at baseline. This was reflected in the ERG report and further demonstrated in the Etoile alpha case reports submitted by the company.
7	It was unclear from the ECD which uncertainties remained and what had been resolved.
8	It is unclear whether the patient and clinical testimonies for our UK treated patient were considered in their entirety as there is no reference to these in the draft guidance. The only reference to individual patient case studies is in the ERG's concerns related to selection bias. The clinical opinion that our UK patient's outcomes are better than the trial data, is not reflected. Nor is the view that the trial data does not reflect the positive impact on their cognitive function, ADL or the impact on carers.
9	The committee agreed to consider the long term follow up data for velmanase alfa in its decision making. However, I could not see this reflected within the ECD or the outcome of

Velmanase alfa for treating alpha-mannosidosis

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	the consideration. Without out this it is difficult to fully understand the committee's basis for their decision, and whether velmanase alfa will ever meet NICE's requirements for reimbursement.
10	We felt that the committee's rational for not proceeding with a MAA were contradictory. In one statement it was specified that due to the substantial challenges in collecting robust evidence for small patient numbers a MAA would not help resolve the issues and uncertainties. However later on it was reflected that despite the small patient numbers an MAA could be considered if deemed value for money.
11	The committee commented that the amount of evidence available to be fairly small, and that it would have been better if the trials had run for longer, to allow for additional data to be collected. The committee later commented that no additional data would be of value. Another example of inconsistent decision making.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Evaluation consultation consultation comments

User	Email Address	Consultation Name	Document Name
REDACTED	REDACTED	Evaluation consultation	Velmanase alfa for treating alpha-mannosidosis
REDACTED	REDACTED	Evaluation consultation	Velmanase alfa for treating alpha-mannosidosis
REDACTED	REDACTED	Evaluation consultation	Velmanase alfa for treating alpha-mannosidosis

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Chapter Name	Section Header	Section Number
consideration-of-the-evidence	Place in the treatment pathway	4.1
the-condition		2.2

the-technology	3 The technology	3.2
the-technology	3 The technology	3.1
consideration-of-the-evidence	Effect of alpha-mannosidosis on people with the condition, and their families and carers	4.1
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recommendations	1 Recommendations	1.2
the-condition	2 The condition	2.4
the-technology	3 The technology	3.2
consideration-of-the-evidence	Place in the treatment pathway	4.2

Selected Text	Comment
	I would like to add results of 1 adult patient treated with Velmanase alfa. Diagnosed with alpha mannosidosis at 7 years. Condition at 18 years (before treatment): - Bad quality of life - patient cannot attend many activities (low endurance, damaged joints, worsening respiratory function); - 6 minute walk test - 150 m; - Stair climb test - climbed 1 floor in 2min 10s with support; test discontinued due to tiredness; - Spirometry - FEV1 - 87%; FVC - 76%. After 1 year of treatment: - 6 minute walk test - 120 m - Stair climb test - climbed 1,5 floors, with support. - Spirometry - FEV1 - 89%; FVC - 77%. 3 years of treatment: - 6 minute walk test - 110 m - Stair climb test - climbed 2 floors, with support. Oligosaccharides have decreased to normal concentration Patient and parents observe reduced joint pain, increased endurance, improved cognitive function
	If there was only a small sample number of under 6 year olds used, can you be sure that the evidence is a correct representation of the drug effectiveness?
The clinical presentation is associated with a very wide range of impairments with varying degrees of severity. Signs and symptoms of alpha-mannosidosis can occur at a very young age. The most severe forms occur during infancy (before 5 years) and are associated with rapid progression, leading to early death. More moderate forms are characterised by slower disease progression with people surviving into adulthood. These more moderate forms are associated with a very wide range of impairments, complications and comorbidities that increase with time. The impairments include:facial and skeletal deformities (especially scoliosis and deformed hips and feet)speech and language deficienciesmental health difficultiesbone deterioration, and joints and muscle weakness (leading to pain)reduced lung function because of an enlarged liver and spleen, and spinal abnormalitiesimmunodeficiency with recurring infections (mainly respiratory and ear).	My son (20 years old) also has all the symptoms described in the literature. The symptoms appeared in different ways at different ages. At a younger age, it was mainly respiratory and ear inflammations, and at an older age, stomach problems were typical.He also has stomach bleeding. He had unkwnon seizers too.

The most common adverse reactions listed in the summary of product characteristics for velmanase alfa include weight gain, immune-related responses, diarrhoea, headache, arthralgia (joint pain), increased appetite and pain in the extremities. For full details of adverse reactions and contraindications, see the summary of product characteristics.	For my son, during 1 year and 10 months, we did not notice any significant side effects. However, the enzyme replacement therapy is carried out with strict adherence to the protocol.
	Peter (Pall Peter, patient with alpha mannosidoses) has been receiving the enzyme treatment once a week for 1 year and 10 months. Since then, his condition has improved a lot, e.g. his seizures have stopped, his stomach problems have also been solved, his general physical condition has also improved. He has become much calmer and sleeps better. The size of the liver also became normal. In general, it can be said that the treatment was definitely very useful and his life became better.
The patient experts explained that alpha-mannosidosis affects all aspects of life for people with the condition, and their families and carers. They also emphasised the all-consuming nature of the condition. The clinical and patient experts also explained that the clinical manifestations of alpha-mannosidosis can be associated with a very wide range and level of impairments. The patient experts highlighted the effects of physical symptoms, and psychological and behavioural complications, and the need for a high level of care, including repeated hospital appointments, surgical procedures and medical interventions. Social and professional life can also be compromised for people with alpha-mannosidosis, and their families and carers. A patient testimony received during consultation emphasised the extent of the burden of the condition. This included difficulty in finding a job and the demoralising effect of being perceived as less capable. One patient expert explained that alpha-mannosidosis has negatively affected their education and social interactions at school. They explained that cognitive impairments associated with the condition may also affect a person's ability to learn to drive, which affects their independence. The committee recognised that alpha-mannosidosis is an exceptionally rare condition, and the patient experts highlighted that this could mean diagnosis is delayed because it is not immediately recognised. It also recognised that many people with alpha-mannosidosis are children and young people, and that this influences the effects of the condition. The committee concluded that alpha-mannosidosis is a rare, serious and debilitating condition that severely affects the lives of people with the condition, and their families and carers.	This disease affects all areas of life. My son was diagnosed at almost 18 years old (17 years and 10 months).This disease significantly complicates his and his family's daily life. Due to his poor mental ability, constant hospitalizations and behavioral skills, he needs constant help.
Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?	Long term gains should be considered before short term cost savings.

There are also uncertainties in the economic modelling. In particular, there is very little observed evidence to inform the model, and most of the data used in the model is based on expert opinion rather than clinical trial evidence. Also, the assumed benefits of velmanase alfa treatment in the model are very uncertain.	The cost of treatment is high but an example of economic modelling should be observed, after the government ban on smoking in public places, offset the reduction in tax revenue by a cost saving to the NHS. An extended clinical trial would have shown that my daughter's intellectual and physical decline was halted after the first month of this infusion. She remains healthy at 40.
Treatments aim to manage symptoms and improve quality of life. They include walking aids, physiotherapy, infection management, ventilation support, general treatment of comorbidities, supportive measures at home and major surgical interventions (for example, ventriculoperitoneal shunts, cervical spine decompression, joint replacement). An allogeneic haematopoietic stem cell transplant from a matched sibling or matched umbilical cord donor is an option for some people when clinically indicated, but is associated with significant risks.	My daughter's physical decline was halted after the first month of this infusion. Thus saving the trauma and the financial cost to the NHS of all of the above.
The most common adverse reactions	Contraindications are mild compared to the the illness.
detection in children under 6 when there is clinical suspicion, but diagnosis needs confirmation by genetic and biochemical testing.diagnosis in children who are asymptomatic and have siblings with alpha-mannosidosis, which can only be done by laboratory investigation.	Early detection of any MPS illness would ultimately be beneficial to all concerned, socially and financially. Costs to special needs departments\integration within the education system (as an example) would benefit.
	I would like to report results of 1 pediatric patient treated with Velmanase alfa. Diagnosed with alpha mannosidosis at 3 years. Treatment with Velmanase alfa started at 4 years. 6 minute walk test: 5 years: 410m 6 years: 469m 7 years: 505m 8 years: 519m 100 stair climb time: 5 years: 75s 6 years: 59s 7 years: 57s 8 years: 60s Oligosaccharides (GlcNac-(Man)2): 6 years: 4,1 mcmol/L 7 years: 2,7 mcmol/L 8 years: 3,6 mcmol/L Parents observe positive effect of treatment on patient's abilities and socialisation. oligosaccharides have decreased to normal concentration.

Question Text	Yes/No Answer	Answer Text

Represents An Organisation	Organisation	Has Tobacco Links
No		No
No		No
No		No

No		No
No		No
No		No
No		No

No		No
No		No
No		No
No		No
No		No

Tobacco Link Details