NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Velmanase alfa for treating alpha-mannosidosis [ID800]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Velmanase alfa for treating alpha-mannosidosis [ID800]

Contents:

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

Pre-meeting briefing

Velmanase alfa for treating alpha-mannosidosis [ID800]

This slide set is the pre-meeting briefing for this evaluation. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first evaluation committee meeting and should be read with the full supporting documents for this evaluation

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key abbreviations			
3-MSCT	3-minute stair climb test	IgG	Immunoglobulin G
6-MWT	6-minute walk test	IRRs	Infusion-related reactions
AE	Adverse event	LY	Life year
AM	Alpha-mannosidosis	LSD	Lysosomal storage disorder
BSC	Best supportive care	MCID	Minimal clinically important differences
CHAQ	Childhood health assessment questionnaire	MPS Society	Society for Mucopolysaccharide Diseases
CHMP	Committee for Medicinal Products for Human Use	QALY	Quality-adjusted life years
EQ-5D	EuroQol five-dimension questionnaire	SI	Severe immobility
EQ-5D-Y	EuroQol 5-Dimensions-Youth	SAE	Serious adverse event
ERT	Enzyme replacement therapy	VA	Velmanase alfa
FEV1	Forced expiratory volume in 1 second	WC	Wheelchair dependent
FVC	Forced vital capacity	WU	Walking unassisted
HSCT	Haematopoietic stem cell transplant	WWA	Walking with assistance
HUI-3	Health Utility Index-3	WC	Wheelchair dependent
ICER	Incremental cost-effectiveness ratio		

Disease background

Alpha-mannosidosis (AM)

- Autosomal recessive inherited lysosomal storage disorder caused by deficiency of alpha-mannosidase
- Both chromosome copies carry mutations in the alpha-mannosidase gene MAN2B1
- Leads to systemic accumulation of oligosaccharides in various tissues, especially the central nervous system, liver and bone marrow
- Ultra-rare condition; incidence of 1:500,000 to 1:1 million live births
  - Currently 25* cases of AM in the MPS registry in England
  - Likely incidence of [redacted] per year
- Severe forms manifest during infancy (< 5 years), associated with rapid and lethal progress leading to early death and poor survival rates
- More moderate disease is characterised by slow progression leading to survival into adulthood associated with a very wide range of impairments, infections and comorbidities that increase with time

* Extracted from MPS Society patient expert statement received on 31 March 2018

Disease background
Alpha-mannosidosis (AM)

- AM is highly heterogeneous and can cause a very wide range of symptoms and complications*
  - Facial and skeletal deformities (especially scoliosis and deformation of the hips and feet)
  - Developmental deficiency affecting speech and language abilities
  - Mental health difficulties
  - Deterioration of bones and joints and muscle weakness
  - Reduced lung function due to enlarged liver and spleen and spinal abnormalities
  - Immunodeficiency and recurring infections (mainly respiratory and ear). Infections are a key cause of mortality
  - Pain caused by impairments

* Extracted from the company submission, scope and experts' statement

Current treatment options

- No licenced pharmacologic disease-modifying treatment options
- Treatment options aimed at managing symptoms, delaying progression and improving quality of life
  - e.g., walking aids, physiotherapy, infection management, ventilation support, general treatment of comorbidities, supportive measures at home (hoists etc.), major surgical interventions (ventriculoperitoneal shunts, cervical spine decompression, joint replacement)
- Allogeneic hematopoietic stem cell transplantation
  - Treatment option for some patients, although associated with significant risks
  - Typically reserved for patients with extensive disease presenting in early infancy (≤5 years), with no additional comorbidities/recurrent infections, and where a matched sibling or matched umbilical cord donor is available
  - However, no universally accepted criteria regarding patients for whom allogeneic HSCT is not suitable and/or not possible
  - MPS Society: of the 20 adult AM patients in England, 3 had received HSCT in childhood (<6 years)

Source: section 8.2.4 (page 64) from company submission

Velmanase alfa (Lamzede)

Chiesi

Marketing authorisation	Indicated for the treatment of patients with non-neurological manifestations of mild to moderate alpha-mannosidosis (AM)
Mechanism of action	Enzyme replacement therapy identical to the natural alpha-mannosidase, produced using recombinant DNA technology, that helps with the degradation of mannose-rich oligosaccharides
Administration & dose	• Intravenous infusion • Recommended dose: 1 mg/kg of body weight once every week, for lifetime
List price and PAS discount	• List price: £886.61 per 10 mg vial • Simple discount PAS approved

Decision problem (1/2)

	NICE final scope	Company submission	ERG comments
Population	People with AM aged ≥ 6 years	As per scope Although MA is not restricted by age, no evidence available for patients <5 years; clinical and economic case is presented for people aged ≥ 6 years	• Uncertainty on generalisability of the trial results to children <5 years, who were excluded from the trials • Clinical evidence relates to patients with 'moderate or mild AM' (rather than severe form that usually affects <5 years or adults that have progressed)
Intervention	Velmanase alfa	As per scope	
Comparator	Established clinical management without velmanase alfa (including, where clinically indicated, allogeneic HSCT)	Allogeneic HSCT not considered as a relevant comparator as not indicated in ≥6 years	• HSCT could be a valid comparator for a minority of patients ≥6 years as well as patients aged <5 years • Submission does not include any data for patients for whom HSCT is suitable

AM: alpha-mannosidosis; HSCT: haematopoietic stem cell transplant

Decision problem (2/2)

	Final Scope	Company submission	ERG comments
Outcomes	• mobility and motor function • hearing and language • cognition • lung function • rates of infection • mortality • adverse effects of treatment (including immune response) • health-related quality of life (for patients and carers)	As per scope, with the addition of serum oligosaccharides and serum IgG (see next slide for details)	• Infections only reported as adverse events. Should have been captured in efficacy outcomes as source of mortality and morbidity • Serum oligosaccharides are a surrogate of low clinical relevance; not measured in clinical practice in the UK • Language not measured • Psychiatric problems (e.g. acute psychosis) are important symptoms but not expected to be affected by treatment (velmanase alfa does not cross the blood-brain barrier)

IgG: Immunoglobulin G

Serum oligosaccharides (SO) as a surrogate outcome

- Company's rationale for using SO as a surrogate outcome:
  - Due to nature of the condition, patients with AM accumulate mannose-rich oligosaccharides throughout the body, including the serum
  - Therefore, a reduction in SO is an important biomarker that demonstrates the effect that VA has at the cellular level and is a surrogate marker of potential clinical complications
  - 'Change in SO' is a primary endpoint in the rhLAMAN clinical trial programme and a component of the post-hoc, multi-domain responder analysis
  - Low oligosaccharide levels measured in the urine is known to correspond to a longer walking distance (6-MWT) and more steps climbed (3-MSCT), suggesting that the level of oligosaccharides may be clinically relevant. SO preferred to urine oligosaccharides because found to be more reliable in the clinical trial setting
- ERG had concerns around the clinical relevance of SO as a surrogate outcome :
  - poor link between oligosaccharide levels and clinical outcomes
  - no formal assessment of whether SO was a surrogate for clinical outcomes using standard criteria
    - correlations between last observation values for SO and other outcomes were all negligible in rhLAMAN-10, and not reported for rhLAMAN-05
  - SO not currently measured in UK practice

Source: section 9.4 (page 86) of company submission

Clinical expert (1/2)

- Alpha-mannosidosis (AM) is a slow progressive disease, with limited natural history
- Currently managed with best supportive care and, in some cases (generally in patients <5 years) with allogeneic hematopoietic stem cell transplant
- Velmanase alfa (VA) aims to reduce progression rate and development of visceral complication of alpha-mannosidosis
- Clinically meaningful endpoints difficult to demonstrate in limited trial duration (although trials demonstrated reversal of some disease manifestations)
- Study showed greater trend for improvement in paediatric and adolescent patients than in adults
- VA expected to improve quality of life due to improvement in ambulatory state and infection rate, and improve safety compared to HSCT

Clinical expert (2/2)

- Patients expected to receive up to 3 infusions in the highly specialist lysosomal storage disorder centre and the subsequent infusions at home. Centres are already in place, no need for additional staff training
- Early treatment initiation would be expected to reduce comorbidities and therefore the need for supportive care
- Adverse events mostly related to the infusion of VA with the need for intravenous access (VA may require insertion of a central line especially in paediatric population)

Impact of alpha-mannosidosis

Patient experts

- AM has a wide spectrum of severity and its effects are extremely varied between patients
- Symptoms include sleeplessness, behavioural difficulties, significant problems with bone growth and formation often resulting in osteoarthritis, severe joint stiffness and swelling that restricts movement and causes acute pain, spinal difficulties such as scoliosis and kyphosis, hearing difficulties
- Patients can need a high level of care (repeated hospital appointments, surgeries and medical interventions) and the burden for carers and wider family can be significant. Professional life can be compromised for both patient carers
- VA is the only treatment in adults with AM. HSCT is usually offered only to children among people with AM
- Although 25 patients have the condition in England, only 17 may want to have treatment if they meet eligibility criteria
- Access to treatment might be limited for some people depending on their geographic location

Impact of alpha-mannosidosis

Patient experts

- Major impact on patient and carer's quality of life:

"The impact of this illness from a patient and a family's view is social physical and spiritual… because the sufferer is isolated from their peers at school and therefore in later life, because he has to rely on others and because of the demoralising nature of the illness…because families of the same age tend to socialise and their children will play and interact. But with this illness, the child's peer group interaction is not fully achieved and the families' socialisation becomes difficult."

Impact on patients and carers

UK MPS Society survey

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]

Source: confidential appendix A from clarification response (Tier 2)

Impact on patients and carers

UK MPS Society survey

Source: confidential appendix A from clarification response (Tier 2)

Impact on patients and carers

UK MPS Society survey

- [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Source: confidential appendix A from clarification response (Tier 2)

Benefit of velmanase alfa

Patient's perspective

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

Patient: *"I no longer use calipers, nor sticks nor (at one point) a wheelchair, nor do I qualify for a blue parking badge now. I am now more independent and able to walk further"; "Since being on the trial I can now do more, I have more energy and don't get as breathless"*

Carer: *"Improved quality of life for both. Our daughter is more independent and able to socialise more which has lessened the burden on us to provide that support and to deal with the pain of watching her deteriorate"; "Improved mental health for both our daughter and for us as parents as we now see a future"*

Clinical effectiveness evidence

Company submission section C

Clinical effectiveness evidence

Source

Source	Description	Note
Clinical trials	• rhLAMAN-02 (Phase 1) • rhLAMAN-03 (Phase 2a) • rhLAMAN-04 (Phase 2b) • rhLAMAN-05 (Phase 3) • rhLAMAN-10 (non controlled study)	• Patients could enrol in subsequent trials or compassionate use (CU) programme • rhLAMAN-10 is an integration of data collected from all trials and single efficacy assessment point for patients who enrolled in CU programme
Multi-domain responder analysis	• Post-hoc analysis for rhLAMAN-05 and rhLAMAN-10	• Aim is to combine multiple endpoints into single domains representing clinical important effects • Conducted in response to a request by the EMA for a responder analysis

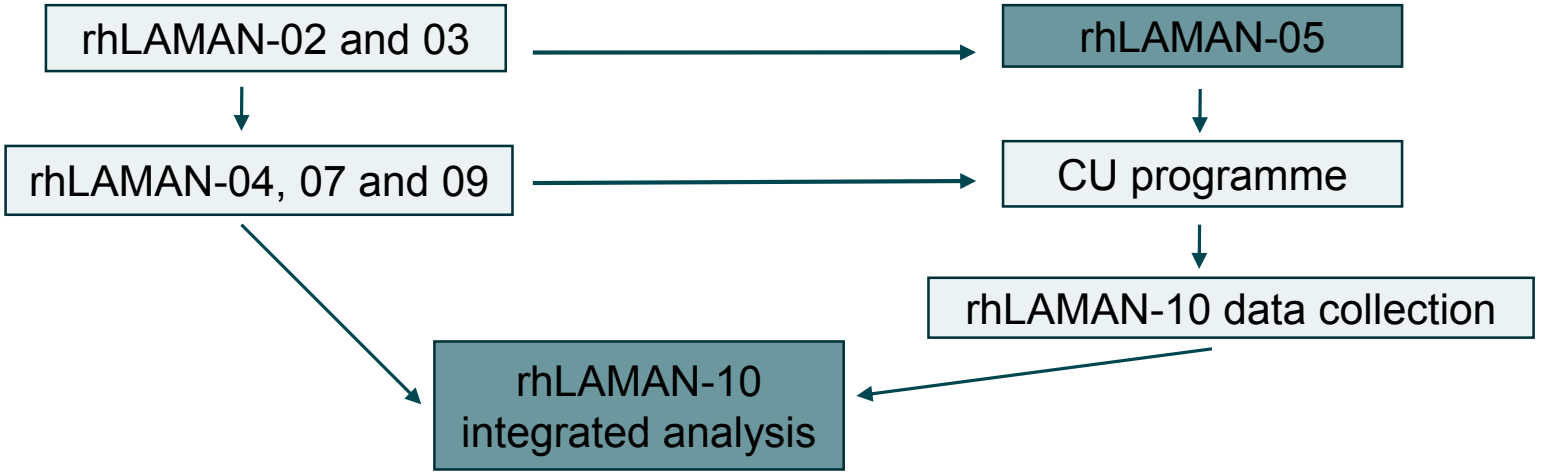
Pivotal evidence relevant to the decision problem

Clinical trial evidence

	rhLAMAN-02	rhLAMAN-03	rhLAMAN-04	rhLAMAN-05	rhLAMAN-10
Design	Phase I	Phase IIa	Phase IIb	Phase III randomised controlled	Phase III open label non-controlled
Interv.	VA 5 doses	VA 2 doses	VA 1 mg/kg	VA 1 mg/kg	VA 1 mg/kg
Comp.	baseline	baseline	baseline	placebo	baseline
N	10	10	9	25	33
Duration	1-5 weeks	6 months (+ 6 mo. extension)	6 months	12 months	Up to 48 months follow up *(n=31 patients followed up at 12 months, n=9 at 48 months)*
Inclusion	AM patients aged 5-20			AM patients aged 5-35	AM patients from rhLAMAN trials and CU programme
Outcomes	Safety	Safety and efficacy	Efficacy	**1º** Serum oligosaccharides; 3-MSCT; **2º** 6-MWT; FVC; PFTs; BOT-2; Leiter-R; CSF oligosaccharides; CSF neurodegeneration markers; PTA; CHAQ; EQ-5D	

3-MSCT- 3 minute stair climb test; 6-MWT – 6 minute walk test; AM - alpha-mannosidosis; BOT-2 - Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ - childhood health assessment questionnaire; CSF - cerebrospinal fluid; CU – compassionate use; FVC - forced vital capacity; PFT - pulmonary function test; PTA - pure tone audiometry; VA – velmanase allfa

Patient disposition and baseline characteristics



Characteristic	rhLAMAN-10			Phase I/II trial (N=9)	rhLAMAN-05 (N=24)*
	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)		
Mean age at baseline, years	17.1	11.6	24.6	12.4	18.9
Gender: female, n (%)	13 (39.4)	6 (31.6)	7 (50.0)	2 (22.2)	11 (45.8)

*excluding the patients transitioning from rhLAMAN-03

CU: compassionate use

Source: Reproduced from Figures 9 and 10 (page 120) of company submission

Clinical results: Serum oligosaccharides

rhLAMAN-05

Analysis at 12 months	VA (n=15)	Placebo (n=10)
Actual value (SD)	1.6 (0.8)	5.1 (1.4)
Adjusted mean relative change (95% CI)	−77.60 (−81.58, −72.76)	−24.14 (−40.31, −3.59)
Adjusted mean difference % (95% CI)	−70.47 (−78.35, −59.72), p<0.001	

- **Serum oligosaccharides**: statistically significant improvement vs placebo at 12 months

rhLAMAN-10

Analysis at last observation	Overall (N=33)
Actual value (SD)	2.31 (2.19)
Absolute mean change (95% CI)	−4.59 (−5.74, −3.45), p<0.001
Relative mean change % (95% CI)	–62.8 (–74.7, –50.8), p<0.001

- **Serum oligosaccharides**: statistically significant improvement vs baseline at last observation

Clinical results: Mobility/functional capacity

rhLAMAN-05

Analysis at 12 months	VA (n=15)	Placebo (n=10)
3-MSCT (steps/min)		
Actual value (SD)	53.5 (15.7)	53.1 (15.6)
Adjusted mean relative change (95% CI)	−1.07 (−9.05, 7.61)	−3.97 (−13.38, 6.47)
Adjusted mean difference % (95% CI)	3.01 (−9.86, 17.72), p=0.648	
6-MWT (metres)		
Actual value (SD)	464.0 (82.51)	461.1 (138.7)
Adjusted mean relative change (95% CI)	0.64 (−4.74, 6.32)	−1.20 (−7.63, 5.68)
Adjusted mean difference % (95% CI)	1.86 (−6.63, 11.12), p=0.664	

- **3-MSCT and 6-MWT**: no statistically significant difference vs placebo at 12 months

Clinical results: Mobility/functional capacity

rhLAMAN-10

Analysis at last observation	Overall (N=33)
3-MSCT (steps/min)	
Actual value (SD)	59.98 (16.29)
Absolute mean change (95% CI)	6.38 (2.65, 10.12), p=0.001
Relative mean change % (95% CI)	13.77 (4.61, 22.92), p=0.004
6-MWT (metres)	
Actual value (SD)	489.0 (85.7)
Absolute mean change (95% CI)	22.4 (0.0, 44.8), p=0.050
Relative mean change % (95% CI)	7.1 (–0.7, 14.9), p=0.071

- **3-MSCT:** statistically significant difference vs baseline at last observation
- **6-MWT**: no statistically significant difference vs baseline at last observation

Clinical results: Lung function

rhLAMAN-05

Analysis at 12 months	VA (n=15)	Placebo (n=10)
Lung function: FVC% predicted normal value		
Actual value (SD)	91.36 (21.80, n=14)	92.44 (18.15, n=9)
Adjusted mean relative change (95% CI)	10.11 (1.31, 19.67)	1.58 (−9.48, 13.99)
Adjusted mean difference % (95% CI)	8.40 (−6.06, 25.08), p=0.269	

- **FVC**: no statistically significant difference vs placebo at 12 months

rhLAMAN-10

Analysis at last observation	Overall (N=29)
Lung function: FVC% predicted normal value	
Actual value (SD)	93.1 (21.7)
Absolute mean change (95% CI)	8.1 (2.4, 13.7), p=0.007
Relative mean change % (95% CI)	10.5 (2.6, 18.5), p=0.011

- **FVC:** statistically significant difference vs baseline at last observation

Infections and immunodeficiency

Post-hoc analyses and additional data

- Infection rates measured as an AE (rather than efficacy outcome):
  - rhLAMAN-05 trial: 86.7% (n=13/15) of patients receiving VA, 70% (n=7/10) of patients receiving placebo
  - rhLAMAN-10 trial: 72.7% (n=24/33) of patients receiving VA
- Because infection rates appeared high in VA arm and the ERG was unable to establish if infection rates were correctly monitored, the company provided additional data and post-hoc analyses:

Serum IgG in rhLAMAN-05	Adjusted mean difference vs placebo: 3.47 g/L; p<0.0001
Changes from baseline in serum IgG (n=9/25)	•VA (n=5): 3 achieved normal levels; 2 improved •Placebo (n=4): 0 improved/achieved normal levels
Antibiotic use in low serum IgG	VA patients had fewer antibiotic uses than the placebo patients after the first month
Caregivers reports	Reduction in infections for patients in rhLAMAN-10

- Results interpreted by the company as there were likely to be improvements in infection rates

IgG: immunoglobulin G

Clinical results: quality of life

rhLAMAN-05

Analysis at 12 months	VA (n=15)	Placebo (n=10)
CHAQ disability		
Actual value (SD)	1.36 (0.76)	1.76 (0.50)
Absolute change from baseline (SD)	-0.01 (0.32)	0.18 (0.36)
CHAQ pain (VAS)		
Actual value (SD)	0.97 (1.02)	0.50 (0.62)
Absolute change from baseline (SD)	0.19 (0.69, n=14)	0.15 (0.71, n=9)
EQ-5D-5L index score		
Actual value (SD)	0.64 (0.18, n=14)	0.62 (0.15)
Absolute change from baseline (SD)	0.04 (0.09, n=14)	0.03 (0.16, n=8)
EQ-5D-5L VAS		
Actual value (SD)	68.20 (17.34)	67.70 (16.62)
Absolute change from baseline (SD)	2.00 (17.95, n=14)	3.70 (15.71)

- No comparative or adjusted analyses of CHAQ, EQ-5D were provided
- Company interpreted data as demonstrating a trend towards improvement
- ERG considers the data inconclusive

Clinical results: quality of life

rhLAMAN-10

Analysis at last observation	Overall (N=33 when not specified)
CHAQ disability	
Actual value (SD)	1.23 (0.66)
Absolute mean from baseline (95% CI)	–0.13 (–0.29, 0.02), p=0.095
CHAQ pain (VAS)	
Actual value (SD)	0.431 (0.616)
Absolute change from baseline (95% CI)	–0.17 (–0.41, 0.06), p=0.139, N=32
EQ-5D-5L index score	
Actual value (SD)	0.67 (0.17)
Absolute change from baseline (95% CI)	0.05 (0.01, 0.11), p=0.080, N=24
EQ-5D-5L VAS	
Actual value (SD)	71.6 (15.0)
Absolute change from baseline (95% CI)	3.3 (-4.5, 11.1), p=0.391, N=24

- CHAQ, EQ-5D-5L: no statistically significant difference
- EQ-5D-5L index: relative change from baseline p=0.036 (CS table 36 p.137) although this analysis only included 24/33 patients with the reason for this unclear

Multi-domain responder analysis
Method

- Key clinical endpoints grouped into 3 domains to reflect the pathophysiology and the burden of the disease:
  - Pharmacodynamic: serum oligosaccharide response
  - Functional: 3-MSCT, 6-MWT and FVC* (% of predicted)
  - Quality of life: CHAQ disability index and CHAQ pain (VAS)
- Patients were considered as responders to treatment if they achieved the response criteria in ≥2 out of 3 domains **
- To achieve response in 1 domain, patients had to show response in at least 1 efficacy parameter (within that domain) by achieving the adopted **minimal clinically important differences (MCID)** for that outcome

Because there are no pre-existing MCIDs defined for AM, the company defined **de novo MCID** with literature review of similar conditions and clinical expert review
(details of MCIDs in section 9.4.14 of CS)

*As muscular weakness is a key symptom of the disease, FVC is included within the functional domain as representative of muscular effort ** Requiring a response in two domains provides treatment-effect sensitivity, whereas a single response domain does not.

Multi-domain responder analysis

Results

Responder	rhLAMAN-10 (N=33)			rhLAMAN-05 (N=25)	
	All (N=33)	<18 (n=19)	≥18 (n=14)	VA (n=15)	Placebo (n=10)
Responder (≥2 domains), %	88%	100%	71%	87%	30%
3 domains, %	45%	53%	36%	13%	0
2 domains, %	42%	47%	36%	73%	30%
1 domain, %	9%	0	21%	13%	30%
No domains, %	3%	0	7%	0	40%

- rhLAMAN-05: 30% of patients in the placebo arm of were classed as responders; 87% of patients in the velmanase alfa arm were classified as responders
- rhLAMAN-10: more patients in the <18 years of age group were classified as responders than in the ≥18 years of age group

Adverse events

- Data from rhLAMAN-05 and 10; all patients in rhLAMAN-10 had been exposed to velmanase alfa for at least 12 months
- 88-100% of patients experienced adverse events (AE)
  - Approx. 50% experienced a treatment-related AE and 33% experienced a serious AE (including knee deformity, joint swelling, Sjogren's syndrome*, sepsis and acute renal failure)
  - Most AEs reported as mild or moderate
  - Most frequent AEs was infection and infestation experienced by 86.7% (n=13/15) of patients receiving velmanase alfa arm in rhLAMAN-05 trial (placebo arm: n=7/10; 70%); and 72.7% (n=24/33) of patients receiving velmanase alfa arm in rhLAMAN-10 trial
- No patient discontinued treatment due to AEs
- No deaths were reported
- The ERG notes that the safety over a lifetime of treatment is unknown and there is a possible correlation between treatment exposure and higher rates of AEs

*Sjogren's syndrome is a long-term autoimmune disease that mainly affects the glands that produce saliva and tears, it can also affect the joints

Clinical results by age group

rhLAMAN-05 post-hoc analyses

Change from baseline to Month 12	Mean (SD)			
	<18 years*		≥18 years*	
	VA (n=7)	Pbo (n=5)	VA (n=8)	Pbo (n=5)
Serum oligosaccharides (µmol/L)				
Relative change, %	−70.6 (14.6)	−7.2 (19.3)	−80.3 (4.4)	−33.4 (22.2)
Difference	-63.4		-46.9	
3-MSCT (steps/min)				
Relative change, %	5.8 (18.0)	−4.4 (10.8)	−4.1 (13.7)	−2.8 (16.4)
Difference	10.2		-1.3	
6-MWT (metres)				
Relative change, %	2.0 (7.8)	1.2 (9.4)	0.4 (11.7)	–2.8 (12.8)
Difference	0.8		3.2	
FVC (% of predicted)				
n	6	4	6	5
Relative change, %	20.5 (11.2)	9.5 (5.6)	2.3 (7.5)	–4.1 (18.7)
Difference	11.0		6.4	

3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; Pbo, placebo; FVC, forced vital capacity; SD, standard deviations; VA, velmanase alfa

*Note: analysed according to age class (<18 vs ≥18 years) as part of a post-hoc analyses; this classification is the age of patients at the time of starting treatment. This was to investigate whether the efficacy of VA was impacted by the age of the patient at time of initiation. No interaction test was performed (to test whether the two age group results were statistically significantly different) but ANCOVA model included baseline value and subject age.

Clinical results by age group

rhLAMAN-10 post-hoc analyses

Change from baseline to last observation*	Mean (SD)		
	6–11**	12–17**	≥18**
n	9	10	14
Serum oligosaccharides (µmol/L)			
Absolute	-4.60 (3.78)	-5.86 (3.79)	-3.68 (2.20)
Relative, %	-60.9 (44.8)	-71.6 (27.5)	-57.6 (30.5)
3-MSCT (steps/min)			
Absolute	10.56 (12.59)	10.73 (8.49)	0.60 (7.97)
Relative, %	28.46 (37.05)	18.29 (14.57)	1.08 (17.65)
6-MWT (metres)			
Absolute	23.33 (71.33)	53.25 (64.38)	-0.29 (50.50)
Relative, %	12.67 (37.10)	11.25 (13.74)	0.67 (11.55)
6-MWT (% of predicted)			
Absolute	-2.54 (11.01)	5.83 (8.87)	0.21 (7.51)
Relative, %	1.73 (29.49)	8.64 (13.16)	1.09 (11.86)
FVC (% of predicted)			
n	7	10	12
Absolute	8.64 (19.59)	13.70 (12.98)	3.00 (12.35)
Relative, %	15.51 (28.52)	17.05 (17.77)	2.14 (16.67)

3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; VA, velmanase alfa; FVC, forced vital capacity; SD, standard deviation.

*Last observation is a composite value comprising a range of follow-up times (12–48 months of active treatment); ** patients were analysed according to the following age classes: 6–11, 12–17 and ≥18 years old as part of a post-hoc analyses; analysis according to age group (<18 years vs ≥18 years) was pre-planned

ERG critique of clinical evidence (1/3)

Issue	Critique
Quality of trials	• Well conducted studies, reasonable quality
Generalisability	• Trial population is likely to be younger than clinical practice in England (inclusion of 5-35 years patients); easier to detect effect in younger patients as disease progress more rapidly • Exclusion patients with IgE >800 IU/mL reduces the generalisability of safety findings in those patients
rhLAMAN-10 has high risk of bias and results difficult to interpret	• No comparator arm (baseline) lead to bias e.g. placebo effect • Key limitations include lack of consistency across functional outcomes (6-MWT and 3-MSCT), lack of clarity on attrition, possible confounding of results due to disease heterogeneity; subjective measures impacted by open-label design • Variation of follow-up duration with different patient number at time; last observation analysis generally included all patients • No imputation was used (for missing data) which could be a problem if only patients who tolerated and responded to treatment continued to be followed up

3-MSCT- 3 minute stair climb test; 6-MWT – 6 minute walk test; AM – alpha-mannosidosis; HSCT: haematopoietic stem cell transplant; IgE – immunoglobulin E

ERG critique on clinical evidence (2/3)

Issue	Critique
Difficult to interpret efficacy outcomes in rhLAMAN-05	• May be under- or over-estimated because there are more compromised patients in VA arm than placebo that could affect 3-MSCT, 6-MWT, FVC, BOT-2 or CHAQ disability but unclear how (those patients may provide more scope for improvement, or alternatively may have irreversible deterioration due to the disease) • Unclear if efficacy is statistically different between age groups: Company did not perform interaction test for rhLAMAN-05; only serum oligosaccharides (non-significant interaction) and 3-MSCT (a significant interaction) were tested in rhLAMAN-10
Unclear if rhLAMAN-05 meet its definition of efficacy	• No definition given for a “trend for improvement” • Observed differences between treatment groups in clinical outcomes did not meet the minimal clinically important differences defined by the company post-hoc
6-MWT not normalised for age	6-MWT correlates with age but company did not conduct age-normalised assessment for rhLAMAN-5

3-MSCT- 3 minute stair climb test; 6-MWT – 6 minute walk test; AM – alpha-mannosidosis; BOT-2 - Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ - childhood health assessment questionnaire; IgE – immunoglobulin E

ERG critique on clinical evidence (3/3)

Issue	Critique
Infections: question the relevance of results of additional data and post-hoc analyses	• Number of patients and events was extremely low and no statistical analysis was provided • Inclusion of only patients with low IgG: unclear what happened to the remaining patients • Company stated that patients with low IgG was the only group where a correlation between an increase in serum IgG and improvement in rate and/or severity of infections was demonstrated – may indicate that infections were not improved for other patients • Carers' statements suggest that not all impactful infections were captured (infections are common and impact on social life, rates of 4 events for 10 patients over 12 months in the placebo arm) and bring into question the relevance of the results reported • IgG analysis and carer report do not match infection rate reported in trials

ERG critique on multi-domain responder analysis

- ERG raised a number of concerns with the multi-domain responder analysis:
  - Dichotomising continuous data based on arbitrary cut-off values
  - Assumption that the domains are of equal importance
  - Use of a potentially clinically irrelevant surrogate outcome (serum oligosaccharides)
  - Omission of infection rates from the domains
  - Post-hoc nature of the analysis and minimal clinically important differences cause high risk of bias

Key issues for consideration

Clinical evidence

- Is HSCT a relevant comparator?
- Is velmanase alfa clinical evidence generalisable to clinical practice in England?
- Is the technology clinically effective?
  - What is the committee's view on the significance of the findings from rhLAMAN-05 and rhLAMAN-10?
  - What is the committee's view on the multi-domain responder analysis? How does it inform decision-making?
- How does the committee view the safety profile of velmanase alfa?

Cost effectiveness evidence

Company submission section D

Company model structure

- Markov model compares velmanase alfa + BSC vs. BSC; 5 health states: walking unassisted, walking with assistance, wheelchair dependent, severe immobility and dead
- 3 cohorts from post-hoc analysis rhLAMAN trials: paediatric (6-11 years), adolescent (12-17 years), adult (≥ 18 years)
- Lifetime duration (100 years); 1.5% discount (outcomes and costs); annual cycle length; NHS/PSS perspective

BSC: best supportive care; SI: severe infection; WC: wheelchair dependent; WWA: walking with assistance; WU: walking unassisted.
Source: adapted from figure 27 (page 192) from company submission

Starting state distribution

- The company assumed that all patients were at the lowest age within each age band (6-11; 12-17; >18 years)
  - Reflects KOLs' comments: *"the earlier the intervention with an enzyme replacement therapy, the more potential for a treatment benefit to be realised…future patients with AM are likely to be diagnosed as an incident population in childhood"*
- Distribution of patients' functional status across primary health states was taken from rhLAMAN-10
- Paediatric and adolescent patients on model entry were assumed to incur the costs associated with adult patients once they became 17 years of age

Cohort	Lowest age within age band (years)	WU	WWA	WC	SI
Paediatric	6	78%	22%	0%	0%
Adolescent	12	73%	27%	0%	0%
Adult	18	62%	38%	0%	0%

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

- ERG note there is no reason to believe that patients would be diagnosed at 12 rather than at 11 or 13 (if not diagnosed in early childhood)
- In scenario analyses, ERG used the average age per band, and explored cost effectiveness for each health state individually

Source: Table 28 (page 97) of ERG report

Source of clinical data used in the model

Source	What data did it inform in the model?
rhLAMAN-05 (multi-domain responder analysis)	Treatment discontinuation due to lack of efficacy
rhLAMAN-10	Starting health state of population
UK expert elicitation panel (EEP)	• Time to disease progression (VA, BSC) • Probability of major surgery conditional on health state (BSC) • Probability of severe infection conditional on health state (BSC) • Probability of mortality associated with severe infection (BSC)
Clinical trial Key Opinion Leader (KOL) interviews	• Improvement in health state (VA) • Treatment discontinuation (due to transition of health states, annual risk of withdrawal) (VA, BSC) • Mortality and complications associated with surgery and severe infection (VA, BSC) • Requirement for ventilation (VA, BSC)

UK Expert elicitation panel

- Method followed the Sheffield Elicitation Framework (SHELF); 5 clinical experts (all experience of treating AM with BSC, only 1 had experience of treating AM with an enzyme replacement therapy) participated, representing 4 LSD centres in the UK.
- Objective: to provide information on the number of years it was expected that a patient would reside in each of the primary health states before progressing to the next more severe health state when treated with BSC (transition probabilities).
  - 1: disease progression under BSC alone (formally elicited)
  - 2: disease progression under velmanase alfa + BSC (formally elicited)
  - 3: disease improvement under velmanase alfa + BSC (formally elicited)
  - 4: data on severe infections and major surgery by ambulatory status (captured via the experts completing a pre-meeting questionnaire, before the pooled responses were presented and discussed qualitatively during the elicitation panel)

UK KOL interviews

- Method: 10 KOLs were contacted of which 5 participated in at least one stage of the interview process (3 stages)

Stage	Objective	Key questions
Stage 1	To support the early scoping/design stages of developing the model	• Clinical features and complications of AM • Natural disease progression • Drivers of mortality and morbidity in AM • Definition of BSC
Stage 2	To generate and validate key assumptions and model parameters	• Clinical features and complications of AM • Structural model assumptions • Surgical procedures and associated outcomes • Severe infections and associated outcomes • Natural disease progression • Resource utilisation • Patient and carer disutility
Stage 3	To validate assumptions and parameters used in the final model	• Pathway of care • Impact of AM on patients and carers • Validation of key model assumptions (e.g. surgery rates)

Benefits of velmanase alfa in the model

- The company assumed that, in comparison to BSC:
  - VA delays disease progression in multi-domain responders
  - VA improves disease e.g. reduced dependency on aids/assistance and wheelchair use for walking, compared with BSC-treated patients
  - VA reduces patients' requirements for ventilation ('responders' and 'non-responders') e.g. delay to ventilation, more simple ventilation requirements once on ventilation
  - VA-treated patients have a better capacity to respond to/manage severe infections
  - VA-treated patients have a better capacity to respond to/manage major surgery e.g. lower risk to anesthesia due to improved upper airways and lung function, better ability to regain mobility
  - VA improves quality of life throughout treatment

Time to disease progression (VA, BSC)

			Walking Unassisted (WU)	Walking With Assistance (WWA)	Wheelchair Dependent (WC)	Severe Immobility (SI)
BSC	**Years** in primary HS before progressing (95% CrI)		[redacted]	[redacted]	[redacted]	[redacted]
Velmanase alfa	**Additional years** in primary HS (vs BSC) (95% CrI)	Paediatric	[redacted]	[redacted]	[redacted]	[redacted]
		Adolescent	[redacted]	[redacted]	[redacted]	[redacted]
		Adults	[redacted]	[redacted]	[redacted]	[redacted]

- ERG noted a relative reduction in deterioration of disease progression observed for VA treatment compared with BSC (from rhLAMAN-05) but not taken into account in the model
- Possible double-counting

BSC: best supportive care; CrI: credible interval, HS: health state; VA: velmanase alfa
Source: Table 29 (page 97) of ERG report

Disease improvement (VA)

	Health state	Probability of improvement	95% Credible Interval
Years 1 and 2 with VA	WWA → WU	20%	0% to 70%
	WC → WWA		
Year 3 and beyond with VA	WWA → WU	2.5%	0% to 5%
	WC → WWA		

WC – Wheelchair dependent; WU – Walking unassisted; WWA – Walking With Assistance

- It was assumed that no patients improved with best supportive care
- ERG noted that no relative gain in improvement was observed for VA treatment compared with BSC (from rhLAMAN-05) but was not taken into account in the model
- ERG explored a scenario analysis in which there are no improvements after the initial year (which is the duration of rhLAMAN-05)

Source: Table 31 (page 98) of ERG report

Severe infections and major surgery (BSC)

	Annual probability of patients **treated with BSC**		
	Death following a severe infection	Severe infections	Major surgery
Walking Unassisted	[redacted]	[redacted]	[redacted]
Walking With Assistance	[redacted]	[redacted]	[redacted]
Wheelchair Dependent	[redacted]	[redacted]	[redacted]
Severe Immobility	[redacted]	[redacted]	[redacted]

Annual risks of surgery were reduced by 50% for patients receiving VA (assumption)

- ERG explored a scenario analysis in which VA does not reduce the probability of severe infections and major surgery (vs. BSC)

Source: Tables 33, 35, 36 (page 100-102) of ERG report

Stopping rules

Company proposed that in clinical practice, treatment may be discontinued according to 'stopping rules'; may change following consultation with UK experts

Definition	• Treatment would be stopped for those with life-limiting conditions, those who cannot tolerate the treatment, those who cannot comply with monitoring (either for practical reasons or due to worsening of disease) and those gaining no benefit • 'Gaining no benefit' defined as failing to meet 2 of 3 criteria as defined in multi-domain responder analysis at 12 months • Applied at 12 months
Implication for effectiveness	• Results at 12 months would not be affected • Results after 12 months (for patients who continued treatment) may have met the stopping criteria

- The company stated that the stopping rules are likely to result in **more favourable outcomes in the long term** than those observed in the trials, because patients who get lower efficacy are excluded from treatment

Source: section 4.2.4.2 (page 40) of ERG report

Stopping rules applied to the model

- Patients can discontinue VA treatment via 3 routes:
  - 'Non-response': based on the post hoc, multi-domain response in the first year of treatment (13.3%; rhLAMAN-05)
  - Annual risk of withdrawal (10%; KOL interview)
  - Health state (KOL interview):
    - patients entering the 'Severe Immobility' state would continue to receive VA for one year to reflect "*that once a person moves into the severe immobility state, there will be a period where their health status in confirmed by their specialist consultant, and the decision is made in collaboration with the patient and their carer to withdraw active treatment.*"
    - patients entering the 'Short end Stage' state would have treatment withdrawn

Resource use

	Items	Value	Source
Drug	Annual acquisition cost	• [redacted] per 10 mg vial (including PAS) • Recommended dose is 1 mg/kg	Company
Administration	Administration cost in hospital, per infusion (once weekly)	£213	NHS National prices and national tariff 2015-16
	Number of infusions at LSD centre before transfer to home infusion or local hospital setting	3 once weekly	UK KOL Interviews
	Proportion of patients receiving home infusion	98% (no additional cost)	
	Proportion of patients receiving local hospital infusion	2%	
AE	Infusion-related reactions only AE included in model	0	Company assumption
Ventilation	Proportion of patients requiring ventilation assistance in VA arm	50% reduction compared to BSC	UK KOL Interviews; company assumption
	Ventilation annual cost	£80,279 – £301,888	Noyes 2006
Carer	Hours of care required per day by health state	1.3 (WU), 3.9 (WWA), 13.8 (WC and SI)	Hendriksz 2014 (MPS IVa)
	Proportion of care provided by health professional	10% (WU), 20% (WWA), 50% (WC), 80% (SI)	Company assumption

- ERG note that the company did not use the outcome of the MPS Society survey on carer's time spent by day [redacted] which is explored in ERG's scenario analysis
- ERG explored scenario analysis for cost of severe infections, proportion of patients requiring ventilation for VA, and carer's time

Health state utilities

Sources and methods

Source	Methods

UK MPS Society survey	• [redacted]
	  • [redacted]
	  • [redacted]
	• [redacted]
	  • [redacted]
	  • [redacted]
	• [redacted]

rhLAMAN -10 trial	• Utilities derived using CHAQ and EQ-5D-5L for only 2 health states: 'walking unassisted' and 'walking with assistance' • No data for patients 'wheelchair-dependent' or 'severely immobile' because those patients were excluded from trial

- *Scenario 2: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC, i.e. patients who had received HSCT or VA were excluded from the pooled analyses. A resulting missing data point for the 'walking with assistance' health state was imputed using the EQ-5D-5L utility for this health state as reported previously in an unpublished UK KOL audit
- [redacted]

Health state utilities

Values

			Mean utility values (SD)			
		n	WU	WWA	WC	SI
UK MPS Society survey	Company base case (‘Scenario 2’)	5	0.906 (0.000)	[redacted]	0.100 (N/A)	-0.011 (0.053)
rhLAMAN-10 trials	Baseline	24	0.652 (0.149)	0.577 (0.200)	N/A	N/A
	Last observation	31	0.702 (0.171)	0.635 (0.085)	N/A	N/A

BSC – best supportive care; N/A – Not Available; SES – Short End State; SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

Further utility data used in the model

Parameters	Assumptions & sources
Utility gain associated with VA treatment to account for aspects not completely captured in the model*	**0.1** (assumed, based on EQ-5D improvements seen in rhLAMAN-10 trial [0.05 for WU and 0.058 for WWA] and the possibility that some benefits of VA '*will only be apparent after a number of years of treatment*') Validated by UK KOL
Disutility associated with severe infection	• BSC: **0.18 for 6 months** (assumed; same as patients with sepsis; Drabinski 2001) • VA: **50% reduction** vs. BSC (UK KOL interview)
Disutility associated with major surgery	• BSC: **0.25 for 6 months** (assumed; MPS IV, NICE HST2) • VA: **50% reduction vs. BSC** (UK KOL interview)
Disutility associated with minor surgery and AE	**No disutility** was assumed for either minor surgery or infusion-related reactions
Caregiver disutility	**0.01** (WU), **0.02** (WWA), **0.05** (WC), **0.14** (SI, SES); from UK KOL interview, Gani et al. 2008

AE – adverse events; BSC – best supportive care; MPS- mucopolysaccharidosis; N/A – Not Available; SES – Short End State; SI – Severe Immobility; VA – velmanase alfa; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

- ERG explored scenario analysis on: utility gain for VA patients (0.05), exclusion of caregiver disutility

*Including reducing rates of minor infections; reducing rates of psychiatric problems, reduced ventilator dependency; providing intra-ambulatory health state improvements', for example, moving from multiple aids/assistance for walking to only requiring one minimal aid for walking (e.g. footwear for stability); and the provision of a structured homecare visit programme with regular (weekly) nurse visits

Cost effectiveness result

List price (probabilistic analysis)

	Total costs (£)	Total QALYs (disc.)	Total QALYs (undisc.)	Inc. costs (£)	Inc. QALYs	Cost per QALY gained (£/QALY)
Paediatrics						
VA	[redacted]	9.90	12.17	[redacted]	2.50	[redacted]
BSC	[redacted]	7.40	9.08	-	-	-
Adolescents						
VA	[redacted]	9.65	11.84	[redacted]	2.64	[redacted]
BSC	[redacted]	7.02	8.60	-	-	-
Adults						
VA	[redacted]	8.82	10.78	[redacted]	2.61	[redacted]
BSC	[redacted]	6.21	7.54	-	-	-

BSC – best supportive care; inc – incremental; QALY - quality-adjusted life years; VA – velmanase alfa

Note: As the decision model is linear, the probabilistic ICER is almost identical to the deterministic ICER. Only the probabilistic analyses are presented.

Source: Table 14-16 (page 15) of PAS submission (Tier 2 response to clarification)

Cost effectiveness result

PAS price (probabilistic analysis)

	Total costs (£)	Total QALYs (disc.)	Total QALYs (undisc.)	Inc. costs (£)	Inc. QALYs	Cost per QALY gained (£/QALY)
Paediatrics						
VA	[redacted]	9.92	12.17	[redacted]	2.51	[redacted]
BSC	[redacted]	7.41	9.08	-	-	-
Adolescents						
VA	[redacted]	9.69	11.84	[redacted]	2.65	[redacted]
BSC	[redacted]	7.04	8.60	-	-	-
Adults						
VA	[redacted]	8.76	10.78	[redacted]	2.61	[redacted]
BSC	[redacted]	6.15	7.54	-	-	-

BSC – best supportive care; inc – incremental; QALY - quality-adjusted life years; VA – velmanase alfa

Note: As the decision model is linear, the probabilistic ICER is almost identical to the deterministic ICER. Only the probabilistic analyses are presented.

Source: Table 14-16 (page 15) of PAS submission (Tier 2 response to clarification)

Deterministic sensitivity analysis

List price

Deterministic sensitivity analysis

PAS price

Parameter	Value			Δ ICERs (max-min)		
	Base case	Min	Max	Peadiatric	Adolescent	Adults
Acquisition cost VA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate applied on outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Discontinuation of treatment due annual probability of withdrawal	10%	8%	13%	[redacted]	[redacted]	[redacted]
Probability of disease improvement with VA at Year 1 - WWA →WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate applied on costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Probability of disease improvement with VA at Year 2 - WWA →WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Time to disease progression with VA Paediatric - WU to WWA	1.54	-0.31	3.64	[redacted]	[redacted]	[redacted]
Utility - VA on-treatment increment (post discontinuation)	0.1	0.00	0.05	[redacted]	[redacted]	[redacted]
Probability of disease improvement with VA from Year 3 onwards - WWA →WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Time to disease progression with BSC (WU to WWA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to disease progression with VA - Adolescent (WU →WWA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to disease progression with VA - Adult (WU →WWA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICERs are most sensitive to acquisition cost, discount rate applied on outcomes, probability of disease improvement at years 1 and 2 with VA and time to disease progression with BSC

Scenario analyses

List price

- Company also investigated some alternative scenarios to address uncertainties around the efficacy of velmanase alfa

Scenario		ICER			Δ ICER
		Paediatric	Adolescent	Adult	All
Company base case		[redacted]	[redacted]	[redacted]	-
Time to progression (EEP values)	Upper estimate of EEP study	[redacted]	[redacted]	[redacted]	↓
	Reduced by 50% with VA compared with BSC	[redacted]	[redacted]	[redacted]	↓
	No progression	[redacted]	[redacted]	[redacted]	↓↓
Probability of improvement (WWA→WU) (2.5%)	5% from year 3 onwards	[redacted]	[redacted]	[redacted]	↓
	No improvement from year 3 onwards	[redacted]	[redacted]	[redacted]	↑
Utility wheelchair dependent (0.100)	Equal to severe immobility of -0.010	[redacted]	[redacted]	[redacted]	↑

↓↓ *shows larger decrease than* ↓

Scenario analyses

PAS price

- Company also investigated some alternative scenarios to address uncertainties around the efficacy of velmanase alfa

Scenario		ICER			Δ ICER
		Paediatric	Adolescent	Adult	All
Company base case		[redacted]	[redacted]	[redacted]	-
Time to progression (EEP values)	Upper estimate of EEP study	[redacted]	[redacted]	[redacted]	↓
	Reduced by 50% with VA compared with BSC	[redacted]	[redacted]	[redacted]	↓
	No progression	[redacted]	[redacted]	[redacted]	↓↓
Probability of improvement (WWA→WU) (2.5%)	5% from year 3 onwards	[redacted]	[redacted]	[redacted]	↓
	No improvement from year 3 onwards	[redacted]	[redacted]	[redacted]	↑
Utility wheelchair dependent (0.100)	Equal to severe immobility of -0.010	[redacted]	[redacted]	[redacted]	↑

↓↓ *shows larger decrease than* ↓

ERG critique (1/3)

Limitations	ERG justification	Corrected in ERG's base case
General questioning on appropriateness of the model	• Most parameters estimates are generated by expert elicitation and interviews rather than observed data • Values from the interviews and arbitrary distributions used by the company do not benefit from using a formal elicitation process • ERG is therefore concerned that parameter estimates may not reflect genuine beliefs	**No possible change** – ERG's base ICERs are constrained by the same limitations
Utility values for WU and WWA in the company base case were reported from MPS Society survey rather than rhLAMAN-10	[redacted] (n=[redacted] in MPS Society survey; n=[redacted] in rhLAMAN-10 trial)	**Yes** - rhLAMAN-10 baseline value used • Baseline more appropriate than last observation value as [redacted]
Discount rate of 1.5% per annum	VA does not meet NICE method criteria as the intervention does not restore a patient to full or near full health	**Yes** – an annual discount rate of 3.5% was applied

ERG critique (2/3)

Limitations	ERG justification	Corrected in ERG's base case
Using a utility gain associated with VA of 0.10	• Values the company based their choice on (EQ-5D in rhLAMAN-10) may be confounded by different patient numbers, with different disease severities because trial is non-comparative (no patient received BSC) • Possible double-counting when patient improves or maintains health state • Additional time to progression (from elicitation) is not sufficiently high to support evidence	**Yes** – a utility gain of 0 was applied
Assumption related to costs post discontinuation of VA	Assumption that VA reduce patients' requirements for ventilation even after stopping VA should be amended	**Yes** - patients who discontinued VA have BSC ventilation costs
Implementation error	ERG amended errors relating to transition probabilities	**Yes**
Model does not allow any improvement in health state for BSC arm	Likely to change the ICER; although the direction is not known it could be large. A more accurate ICER would be obtained by using the absolute values of improvement for both VA and for BSC rather than setting BSC to zero and VA to the difference between the treatments	**No***
Increase in life expectancy elicited from clinicians	Increase in life expectancy (i.e. additional time in each health state a person would be in were they provided with VA) predicted by the model likely to be higher than that predicted by the clinicians	**No***

*Errors could not be fixed by ERG due to time constraint

ERG critique (3/3)

Limitations	ERG justification	Corrected in ERG's base case
Using fixed average body weights rather than distribution to calculate the number of vials	May not provide an accurate answer or reflect the true uncertainty. Unclear if this is favourable or unfavourable to VA	**No***
Discontinue treatment assumed to be at midpoint of the first year rather than at 12 month	Implementation issue which will be marginally unfavourable to VA as the full 12 months' benefit relating to surgery, or severe infection would not be captured, and any assumed utility increase due to VA treatment would not be fully realised	**No***

*Errors could not be fixed by ERG due to time constraint

ERG's base case

List price

Parameter	Values		ICER*		
	Company base case	ERG's base case	Paediatric	Adolescent	Adult
Utility from rhLAMAN-10 (WU; WWA)	0.906; [redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
Discount rate	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed utility gain associated with VA	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending assumption ventilation costs when patients discontinue VA	50% reduction vs. BSC	Same as BSC	[redacted]	[redacted]	[redacted]
Amending error transition probabilities	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

VA – velmanase alfa; WU – Walking Unassisted; WWA – Walking With Assistance

*subject to the caveats that some limitations relating to the model could not be fixed within the time frames of the appraisal (see previous slides for detailed errors not addressed in ERG base case)

Source: Table 54 (page 143) of ERG report

ERG's base case

PAS price

Parameter	Values		ICER*		
	Company base case	ERG's base case	Paediatric	Adolescent	Adult
Utility from rhLAMAN-10 (WU; WWA)	0.906; [redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
Discount rate	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed utility gain associated with VA	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending assumption ventilation costs when patients discontinue VA	50% reduction vs. BSC	Same as BSC	[redacted]	[redacted]	[redacted]
Amending error transition probabilities	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

VA – velmanase alfa; WU – Walking Unassisted; WWA – Walking With Assistance

*subject to the caveats that some limitations relating to the model could not be fixed within the time frames of the appraisal (see previous slides for detailed errors not addressed in ERG base case)

Source: Table 54 (page 143) of ERG report

ERG's scenario analysis (1/2)

List price

			ICER		
			Paediatric	Adolescent	Adult
ERG base case			[redacted]	[redacted]	[redacted]
Assessing cost effectiveness for each health state	100% in WU		[redacted]	[redacted]	[redacted]
	100% in WWA		[redacted]	[redacted]	[redacted]
	100% in WC		[redacted]	[redacted]	[redacted]
	ERG base case	**Scenario**	[redacted]	[redacted]	[redacted]
Starting age	Bottom of band	Average per band	[redacted]	[redacted]	[redacted]
Disease improvement	*20% after 1 yr, 2.5% after 3 yrs*	0 after 1 yr	[redacted]	[redacted]	[redacted]
Effect of VA on surgery	50% reduced vs. BSC	0	[redacted]	[redacted]	[redacted]
Effect on serious infection	50% reduced vs. BSC	0	[redacted]	[redacted]	[redacted]
Costs of severe infection	£11,255 - £14,286	£2742	[redacted]	[redacted]	[redacted]
Ventilation costs benefit of VA	50% reduced vs. BSC	0	[redacted]	[redacted]	[redacted]

ERG's scenario analysis (2/2)

List price

			ICER given individual change		
			Paediatric	Adolescent	Adult
ERG base case			[redacted]	[redacted]	[redacted]
	ERG base case	**Scenario**	[redacted]	[redacted]	[redacted]
Caregiver time required in each health state (hours)	*WU:1.3h, WWA: 3.9h; WC and SI: 13.8h*	MPS Society [redacted]	[redacted]	[redacted]	[redacted]
Utility gain for VA patients	*0*	0.05	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility			[redacted]	[redacted]	[redacted]
Including personal expenditure by the family			[redacted]	[redacted]	[redacted]
Including caregiver productivity losses			[redacted]	[redacted]	[redacted]

CONFIDENTIAL

ERG's scenario analysis (1/2)

PAS price

			ICER		
			Paediatric	Adolescent	Adult
ERG base case			[redacted]	[redacted]	[redacted]
Assessing cost effectiveness for each health state	100% in WU		[redacted]	[redacted]	[redacted]
	100% in WWA		[redacted]	[redacted]	[redacted]
	100% in WC		[redacted]	[redacted]	[redacted]
	ERG base case	**Scenario**	[redacted]	[redacted]	[redacted]
Starting age	Bottom of band	Average per band	[redacted]	[redacted]	[redacted]
Disease improvement	*20% after 1 yr, 2.5% after 3 yrs*	0 after 1 yr	[redacted]	[redacted]	[redacted]
Effect of VA on surgery	50% reduced vs. BSC	0	[redacted]	[redacted]	[redacted]
Effect on serious infection	50% reduced vs. BSC	0	[redacted]	[redacted]	[redacted]
Costs of severe infection	£11,255 - £14,286	£2742	[redacted]	[redacted]	[redacted]
Ventilation costs benefit of VA	50% reduced vs. BSC	0	[redacted]	[redacted]	[redacted]

ERG's scenario analysis (2/2)

PAS price

			ICER given individual change		
			Paediatric	Adolescent	Adult
ERG base case			[redacted]	[redacted]	[redacted]
	ERG base case	**Scenario**	[redacted]	[redacted]	[redacted]
Caregiver time required in each health state (hours)	*WU:1.3h, WWA: 3.9h; WC and SI: 13.8h*	MPS Society [redacted]	[redacted]	[redacted]	[redacted]
Utility gain for VA patients	*0*	0.05	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility			[redacted]	[redacted]	[redacted]
Including personal expenditure by the family			[redacted]	[redacted]	[redacted]
Including caregiver productivity losses			[redacted]	[redacted]	[redacted]

Overview of ERG comments

- ERG's base case ICERs are approximately double compared to the company's base case ICERs
- ERG's base case ICERs are mostly sensitive to
  - Assumed utility gain associated with VA
  - Assumption that VA reduces patients' requirements for ventilation even after stopping VA
  - Utility for WU and WWA health state
- ICERs are more favourable to VA in the paediatric group (compared with adolescent and adult groups) due to the smaller doses of interventions required as the treatment has weight-based dosing
- Most parameters estimates are generated by expert elicitation and interviews rather than observed data; and some values used do not benefit from using a formal elicitation process. ERG is therefore concerned that parameter estimates may not reflect genuine beliefs

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime incr QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr)
Greater than or equal to 30	3

QALY gain discounted and undiscounted

	Outcome	QALY gain	
		Undiscounted	Discounted
Company base case	Paediatric	3.09	2.51
	Adolescent	3.24	2.65
	Adults	3.24	2.61
ERG base case	Paediatric	1.89	1.08
	Adolescent	2.00	1.14
	Adults	2.00	1.17
ERG's scenario analysis with the highest QALY gains (0.05 utility gain associated with VA)	Paediatric	2.24	1.36
	Adolescent	2.35	1.43
	Adults	2.35	1.45

Budget impact *PAS price*

- Budget impact is based on [redacted] in England and Wales
  - [redacted] paediatric patients, assumed [redacted] uptake every year
  - [redacted] adolescent patients, assumed [redacted] uptake every year
  - [redacted] adults, assumed [redacted] uptake every year
- Budget impact estimates accounts for market share estimates (uptake), incident patients, discontinuation and mortality
  - [redacted] patients will be treated with VA in Year 1

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Annual cost						
Paediatric	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adolescent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* From the company submission, numbers identified by UK MPS Society Patient Registry

NHS England comments

- Main cost to the NHS will be for the acquisition of velmanase alfa
- Some additional costs for monitoring treatment
  - Further monitoring may be needed if a managed access scheme is required
- VA is expected to be used within the existing expert centres for lysosomal storage disorders, although a small number of adult patients are currently managed in local or regional hospitals
- Need for staff training

Equality

- No equality issues was raised.

Innovation

The company considers velmanase alfa is an innovative treatment because:

- velmanase alfa is the first pharmacological disease-modifying therapy for patients with alpha-mannosidosis
- velmanase alfa represents a ‘step-change’ in the management of alpha-mannosidosis on the basis of its potential to change the natural course of the disease by offering improvements to patients’ ambulation and/or delaying disease progression in patients

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key issues for consideration

Cost-effectiveness evidence

- What is the committee's view of the structure and assumptions in the economic model?
  - Use of data based on expert elicitation belief rather than observed data
  - Benefits of velmanase alfa
  - Is the model fit for decision-making?
- What is the most appropriate source of utility for each health state?
  - from the MPS Society survey (company) or the from the rhLAMAN-10 integrated trial (ERG)?
  - Is a utility gain associated with velmanase alfa (0.1) realistic?
- Should a 1.5% or 3.5% discount rate should be used?
- What factors affecting the guidance need to be taken into account?
- What are the most plausible ICERs?
- What QALY weighting should be used in decision-making?

Authors

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  Technical Lead
- **Ian Watson**
  Technical Adviser
- with input from the Lead Team:
  - Linn Phipps – lay lead
  - Sarah Davis – cost lead
  - Ayesha Ali – clinical lead

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Velmanase alfa for treating alpha-mannosidosis

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of velmanase alfa within its licensed indication for treating alpha-mannosidosis for national commissioning by NHS England.

Background

Alpha-mannosidosis is a rare genetic disease caused by the deficiency of an enzyme called alpha-mannosidase. It is inherited as an autosomal recessive disorder, which means that both chromosome copies carry mutations in the alpha-mannosidase gene MAN2B1, and both parents may be unaffected carriers. Alpha-mannosidase breaks down oligosaccharides and in the absence of this, oligosaccharides accumulate inside cells, resulting in damage of tissues and organs and leading to cell death. This is characterised by skeletal changes, deterioration of bones and joints, muscle weakness, hearing loss, recurring infections and developmental impairment.

Alpha-mannosidosis can present at infancy, childhood or early adolescence. The onset and severity of symptoms varies widely across a broad spectrum. The most severe forms of alpha-mannosidosis manifest during infancy and are typically characterised by enlargement of the liver, severe infections and poor survival rates. More moderate disease is associated with slow progression but the characteristics of alpha-mannosidosis are evident and have a substantial impact on physical and mental wellbeing. These characteristics may be absent in people with mild disease.[1]

The exact prevalence of alpha-mannosidosis is not known, but has been estimated to be approximately 1 in 500,000.[2] The MPS Society has identified 30 people with alpha-mannosidosis in the UK, although it is expected that there may be more patients whose disease has not been diagnosed.[3]

There are currently no pharmacological treatments for alpha-mannosidosis. Treatment options are aimed at managing symptoms, delaying progression and improving quality of life. Allogeneic haematopoietic stem cell transplant (HSCT) from a family member or unrelated donor is a treatment option for some patients when clinically indicated, although there are significant risks associated with allogeneic HSCT.

The technology

Velmanase alfa (Lamzede, Chiesi) is a long-term enzyme replacement therapy for people with alpha-mannosidosis. It is administered by intravenous infusion.

Velmanase alfa does not currently have a marketing authorisation in the UK for alpha-mannosidosis. It has been studied in clinical trials, compared with placebo, in people with a confirmed diagnosis of alpha-mannosidosis as defined by alpha-mannosidase activity less than 10% of normal activity.

Intervention(s)	Velmanase alfa
Population(s)	People with alpha-mannosidosis aged 6 years or older
Comparators	Established clinical management without velmanase alfa (including, where clinically indicated, allogeneic haematopoietic stem cell transplant)
Outcomes	The outcome measures to be considered include: • mobility and motor function • hearing and language • cognition • lung function • rates of infection • mortality • adverse effects of treatment (including immune response) • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)

Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements • Where evidence allows consideration may be given to clinical characteristics (such as, age of onset and severity of disease)
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf

References

1. Beck, M. et al. (2013). Natural history of alpha mannosidosis a longitudinal study. Orphanet Journal of Rare Disease 8:88.

2. Malm, D. (2008). Alpha-mannosidosis. Orphanet Journal of Rare Disease 3:21.

3. The MPS society. What is Mannosidosis?
http://www.mpssociety.org.uk/diseases/related-diseases/mannosidosis/
Accessed October 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Velmanase alfa for treating alpha-mannosidosis [ID800]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Chiesi Ltd (velmanase alfa) Patient/carer groups • Climb (Children Living with Inherited Metabolic Diseases) • Contact a Family • Findacure • Genetic Alliance UK • Genetic Disorders UK • Jnetics • MPS Society • Muslim Council of Britain • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of British Neurologists • Association of Genetic Nurses and Counsellors • British Inherited Metabolic Disease Group • British Paediatric Neurology Association • British Society for Gene and Cell therapy • British Society for Genetic Medicine • British Society for Human Genetics • British Society of Paediatric Gastroenterology, Hepatology and Nutrition • Institute of Neurology • Metabolic Pharmacists Group • National Metabolic Biochemistry Network • Primary Care Neurology Society • Royal College of Nursing • Royal College of Paediatrics and Child Health • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society	General • All Wales Therapeutics and Toxicology Centre • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Heath Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • NHS National Services Scotland • Scottish Medicines Consortium • Welsh Government • Welsh Health Specialised Services Committee Comparator companies • None Relevant research groups • Cochrane Cystic Fibrosis and Genetic Disorders Group • MRC Clinical Trials Unit • National Institute for Health Research • Society for the Study of Inborn Errors of Metabolism Associated Public Health Groups • Public Health England • Public Health Wales

Consultees	Commentators (no right to submit or appeal)
• Royal Society of Medicine • UK Clinical Pharmacy • UK Genetic Testing Network <u>Others</u> • Addenbrooke's Lysosomal Disorders Unit • Birmingham Children's Hospital NHS Foundation Trust Lysosomal Storage Disorders Unit • Department of Endocrinology, University Hospital Birmingham Foundation Trust • Department of Health • Great Ormond Street Hospital Metabolic Unit • National Hospital for Neurology and Neurosurgery Charles Dent Metabolic Unit • NHS England • Royal Free Lysosomal Storage Disorders Unit • Salford Royal NHS Foundation Trust Mark Holland Metabolic Unit • Willink Unit, Genetic Medicine, Central Manchester Foundation Trust	

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical experts and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland;; related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical or patient experts.

[1] Non company consultees are invited to submit statements relevant to the group they are representing.

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

January 2018

CHLAM20171840| Date of preparation: January 2018

Contents

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows companies what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the company to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme'. After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with 'see appendix X'. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication

('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document 'Related procedures for evidence submission'.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Abbreviations

3-MSCT	3-minute stair climb test
6-MWT	6-minute walk test
ADA	Anti-drug antibody
AE	Adverse event
AM	Alpha-mannosidosis
AME	Attention and memory
ANCOVA	Analysis of covariance
BOT-2	Bruininks-Oseretsky test of motor proficiency, second edition
BMI	Body-mass index
BSC	Best supportive care
CEV	Clinical evaluation visit
CHAQ	Childhood health assessment questionnaire
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebral spinal fluid
CSR	Clinical study report
dBHL	Decibel hearing loss
DMD	Duchenne muscular dystrophy
EMA	European Medicines Agency
ENT	Ears, nose and throat
EQ-5D	EuroQol five-dimension questionnaire
ERT	Enzyme replacement therapy
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GFAp	Glial fibrillary acidic protein
GVDH	Graft versus host disease
HLA	Human leukocyte antigen
HSCT	Haematopoietic stem cell transplantation
HST	Highly specialised technology
HSUV	Health state utility value
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G
IRR	Infusion-related reaction
ITT	Intention to treat
IV	Intravenous

KOL	Key opinion leader
LS	Least squares
LSD	Lysosomal storage disorder
MCID	Minimal clinically important difference
MDT	Multidisciplinary team
MPS	Mucopolysaccharidosis
MRI	Magnetic resonance imagining
MRS	Magnetic resonance spectroscopy
NFLp	Neurofilament protein
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
NNH	Number needed to harm
PASLU	Patient Access Schemes Liaison Unit
PEF	Peak expiratory flow
PFT	Pulmonary function test
PK	Pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PTA	Pure tone audiometry
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
SR	Systematic review
SRT	Substrate replacement therapy
TEA	Total equivalence age
UK-EEP	UK Expert Elicitation Panel
UK MPS Society	UK Society for Mucopolysaccharide Diseases
VA	Velmanase alfa
VAS	Visual analogue scale
VR	Visualisation and reasoning

Executive Summary

Nature of alpha-mannosidosis (AM)

Ultra-rare disease (Section 6.2):

- There are only [redacted] patients with AM registered in the MPS Registry in England and Wales
- The incidence of AM is reported to be low, with [redacted] new case of AM expected each year in England and Wales

Inadequate standard of care (Section 8.3):

- For AM patients, there are no pharmacological, disease-modifying interventions available
- Best supportive care (BSC) does not alter the underlying pathological driver (accumulation of serum oligosaccharides) of AM

Heterogeneous disease (Section 6.1):

- AM is a heterogeneous condition and the clinical features, and associated morbidity, experienced by an individual may be strikingly different to another patient

Progressive and life-limiting (Section 6.1.3 and 7):

- AM is multi-morbid, progressive and life-limiting. Patients experience a reduced quality of life (QoL), are highly dependent on third-party assistance and will never achieve social independence
- Aberrations to the musculoskeletal, central nervous, respiratory and immunological systems lead to cumulative effects on patients' health and risk of early death

Access to velmanase alfa

Disease improvement (Section 7.2 and 9.6)

- Velmanase alfa reduces the symptom burden experienced by patients, including a beneficial impact on their mobility, which reduces the amount of walking assistance required and improves patients' ambulation

Delayed disease progression (Section 7.2, 9.6 and 12.2)

- Clinical data and expert opinion support the ability of velmanase alfa to alter the natural course of AM, delaying disease progression and extending patients' life expectancy

Reduction in clinical sequelae (Section 7.2)

- Reduced rates of minor and severe infections have been observed following treatment with velmanase alfa – this is anticipated to improve disutility and mortality associated with severe infections

Better quality of life (Section 7.2 and 9.6)

- The impact of velmanase alfa improves the QoL of both patients and their carers/family members

Value for money (Section 12 and 13)

- Introduction of velmanase alfa will have a low budget impact
- A low budget impact should be carefully considered alongside the cost-effectiveness results with the aim of ensuring that a very small number of patients with a significant unmet need get access to an effective, life improving and life-extending treatment

The technology

Velmanase alfa (LAMZEDE®) is a recombinant form of human alpha-mannosidase, which is an enzyme that catalyses the sequential degradation of hybrid and complex high-mannose oligosaccharides in the lysosome. Through enzyme replacement therapy (ERT), velmanase alfa treats alpha-mannosidosis (AM) by supplementing or replacing natural alpha-mannosidase in patients with AM (who have minimal to no alpha-mannosidase activity), reducing the amount of accumulated mannose-rich oligosaccharides that cause the multi-morbid, life-limiting, chronic disease.

The licensed indication for velmanase alfa is as an ERT for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis. A positive Committee for Medicinal Products for Human Use (CHMP) opinion was granted in January 2018, with full marketing authorisation granted in March 2018.

The recommended dose of velmanase alfa is 1 mg/kg of body weight, once every week, administered by intravenous (IV) infusion at a controlled speed. As velmanase alfa is dosed by weight, dose adjustments will be required as/if the patient's weight changes. Velmanase alfa will be used continuously throughout a patient's lifetime, subject to the 'start' and 'stop' criteria defined in Section 10.1.16.

The average cost of velmanase alfa per patient is presented for paediatric, adolescent and adult patients with AM in Table 1.

Table 1: Average cost of velmanase alfa for paediatrics, adolescents and adults

Age group	Age (years)	Average weight (kg)†	Vials per week‡	Cost per week	Cost per year
Paediatrics (6–11 years)	6	22.39	3	£2,660	£138,637
Adolescents (12–17 years)	12	44.09	5	£4,433	£231,062
Adult (≥18 years)	18	64.06	7	£6,206	£323,486

†Average weight taken from UK WHO growth curves using a 61% male-to-female ratio based on the rhLAMAN-10 integrated analysis data (n=33) (1). ‡The recommended dose regimen of velmanase alfa is 1 mg/kg of body weight administered once every week by IV. Once the vial(s) is reconstituted, only the volume corresponding to the recommended dose should be administered. Due to the very low patient numbers, vial sharing is not assumed as practical.

Nature of the condition

AM is an ultra-rare (approximately 1 in 500,000 (2) to 1 in 1,000,000 (3) world-wide), genetically-inherited, lysosomal storage disorder (LSD). The known prevalence of AM in England and Wales is [redacted] and the expected incidence of AM is [redacted] AM is caused by an impairment in α-mannosidase activity due to mutations in the MAN2B1 gene (5). Reduced activity of α-mannosidase results in an intracellular (lysosomal) accumulation of mannose-rich oligosaccharides (a complex of 2–10 simple sugars), which causes impaired cell function and organ toxicity (5). As α-mannosidase is present in all cells (6), oligosaccharides can potentially accumulate throughout the body and affect multiple systems, resulting in the range of complex clinical features observed in patients with AM (5).

AM encompasses a continuum of clinical findings from a perinatal-lethal form to one that is not diagnosed until adulthood; patients with AM may appear normal at birth, but their condition progresses with age (2). AM presents as a highly heterogeneous condition in which the clinical features observed for an individual (and the associated morbidity, mortality-risk and impact on quality of life [QoL]) may be strikingly different to the experiences of another patient (7). AM is a multi-morbid, progressive, life-limiting condition that impacts on many systems at any one time – e.g. aberrations to the musculoskeletal, central nervous, respiratory and immunological systems (7).

Patients with 'classical' AM may have distinct physical features, such as abnormal facial features (large forehead, broad nose with flattened bridge, widely spaced teeth and a large tongue), skeletal deformities (in hips, femur, chest, spine [i.e. scoliosis]), joint stiffness, and knocked knees (touching knees) (7, 8). There may also be evidence of central nervous system (CNS) pathology including demyelination (9) and hydrocephalus (8, 10). Together, these abnormalities contribute to a loss of function including reduced mobility/functional capacity, impaired motor function, impaired cognitive function, reduced lung function, immunodeficiency and recurrent infections, and hearing loss (5); of these symptoms, hearing impairment, cognitive impairment and functional impairment are common findings in patients with AM (11). Patients also have increased pain, with older patients appearing to experience a greater level of pain than younger patients due to progressive bone and joint disease (12). Psychiatric problems have also been reported and can lead to a severe loss of function, which may be permanent in some patients. Through natural disease progression and subsequent deterioration in functional capacity (through neuromuscular and skeletal deterioration), patients typically require an increasing amount of assistance from walking aids/assisted means. Ultimately, most patients become wheelchair-dependent or severely immobile (2, 13).

Patients with AM experience a reduced QoL due to the effect the disease has on many areas of their life. [redacted] causing considerable burden to both patients and parents/caregivers. [redacted] and the progressive loss of mobility can result in depressive feelings, which may be related to an increased insight into their worsening condition (15). Patients are generally unable to complete activities of daily living (e.g. eating, dressing and washing) independently, which further impacts on the QoL of patients (16). Patients can also become isolated, as they are unable to socialise or play due to immobility and/or cognitive impairment (17, 18). Patients are highly dependent on third-party assistance, which is often the responsibility of the parents to manage their daily lives, mobility and behaviour (12, 18). The impact of AM on the caregiver's and/or family's QoL is also likely to be significant and heterogeneous between patients, depending on the socioeconomic status, structure of the caregiver/family unit (e.g. sole caregiver; multiple caregivers; presence or absence siblings), and the severity and impact of the patient's specific symptoms.

Current treatments and interventions for AM are largely symptomatic in nature and focus on treating manifestations and optimising QoL (7). There are no licensed pharmacologic, disease-modifying treatments for AM currently available for the population in which velmanase alfa is expected to be licensed. Bone marrow transplant, or allogeneic haematopoietic stem cell transplant (HSCT), is a treatment option for some patients

when clinically indicated, although it is associated with significant treatment-related morbidity and mortality (2, 5, 18), the degree of which depends on factors such as a patient's clinical status, age and the availability of a well-matched donor. In the UK, allogeneic HSCT is typically only reserved for AM patients with extensive disease presenting in early infancy (≤5 years), and who do not have additional comorbidities/recurrent infections, and where a matched sibling or matched umbilical cord donor is available (17, 18). Additionally, the risk of allogeneic HSCT-associated morbidity and mortality increases with age (17, 18). Therefore, patients over the age of 6 are less likely to have any treatment options. In line with the expected license indication, velmanase alfa is positioned in patients with AM alongside BSC for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible.

Impact of the new technology

Velmanase alfa is considered to be a 'step change' in the management of AM on the basis of its potential to change the natural course of the disease (17) in a patient group for whom there are currently no licensed pharmacologic, disease modifying treatment options. Clinical data and expert opinion support the ability of velmanase alfa to change the natural course of the disease by:

- Improving patients' entire ambulatory status
    - For example, allowing a patient to transition from relying on aids/assistance for ambulation, to being able to walk unassisted
- Decreasing patients' reliance on walking aids/assistance
    - For example, allowing a patient to transition from using multiple walking aids/assistive means (wheelchair for long distances, use of stair rails, use of crutches continuously, etc.) for ambulation, to requiring fewer aids/assistive means with an increase in walking speed and improved balance
- Delaying or stabilising disease progression in patients
    - Allowing patients to remain in less severe, better ambulatory health states for longer and ultimately providing extension to patients' life expectancy

This impact on the natural course of the disease is expected to improve the ability of patients to carry out activities of daily living (such as washing and dressing themselves), increase their independence, improve their QoL, reduce the burden on their caregivers and potentially lead to an extension to patients' life expectancy.

Velmanase alfa clinical development programme

The efficacy and safety of velmanase alfa is demonstrated in three Phase I/II trials (rhLAMAN-02 (19), rhLAMAN-03 (20) and rhLAMAN-04 (21)) and two Phase III trials (rhLAMAN-05 (22) and rhLAMAN-10 (1)), with a total patient population of 33. The results from rhLAMAN-05 and rhLAMAN-10 are the most relevant to the decision problem:

- rhLAMAN-05 provides data on the relative 12-month efficacy and safety of velmanase alfa (N=15) compared with placebo (N=10)

- rhLAMAN-10 provides data on the efficacy and safety of velmanase alfa (N=33) for up to 48 months

In view of the multiple organ systems adversely affected in AM, and in response to a request by the European Medicines Agency (EMA), a post-hoc, multi-domain responder analysis combining multiple endpoints into single domains representing clinically important effects was conducted for rhLAMAN-05 and rhLAMAN-10. In addition, clinical interviews with trial investigators were conducted to obtain feedback on the clinical relevance of the results from rhLAMAN-05, rhLAMAN-10 and the post-hoc, multi-domain responder analysis (14). Expert clinical feedback on the impact that velmanase alfa had on patients was also obtained, including the patients' most meaningful improvements and the impact these had on the patients' lives and the lives of their families/carers. These data formed part of the EMA regulatory submission for velmanase alfa.

Efficacy and safety of velmanase alfa compared with placebo

Treatment with velmanase alfa for 12 months (rhLAMAN-05) significantly (statistically) improved (reduced) serum oligosaccharide levels and resulted in numerical differences for measures of mobility/functional capacity (3-minute stair-climb test [3-MSCT] and 6-minute walk test [6-MWT]) and lung function (forced vital capacity [FVC] % of predicted) compared with placebo. Levels of serum immunoglobulin G (IgG) were significantly (statistically) improved (greater) in the velmanase alfa group compared with the placebo group at Month 12. These data suggest that velmanase alfa may help to improve immune function in patients with AM. Overall, treatment with velmanase alfa was generally well tolerated. Infusion-related reactions (IRR) occurred in only one patient (receiving velmanase alfa); although this patient experienced 11 IRR events (all mild or moderate in intensity), they were still able to continue treatment.

Long-term efficacy and safety of velmanase alfa

Long-term treatment (up to 48 months) with velmanase alfa in rhLAMAN-10 resulted in significant (statistically) and sustained improvements in serum oligosaccharide and IgG levels, mobility/functional capacity (3-MSCT and 6-MWT), lung function, QoL, motor function, cognitive function, and hearing from baseline to last observation. Of note, of the ten patients who required a device or third-party assistance for ambulation at baseline, seven (70%) became independent of assistance at last observation. Two paediatric patients and one adult who required a wheelchair for long-distance mobility at baseline discontinued using the wheelchair at last observation. Overall, velmanase alfa was well tolerated – no special safety concerns were raised, including immunogenicity, and the long-term safety profile of velmanase alfa was found to be acceptable. Overall, 19 IRR events were recorded in three patients, of which 14 occurred in a single patient. All IRRs were mild or moderate in intensity and were resolved.

Post-hoc, multi-domain responder analysis

Key endpoints (serum oligosaccharides, 3-MSCT, 6-MWT, FVC [% of predicted], childhood health assessment questionnaire (CHAQ) disability index and CHAQ pain [visual analogue scale; VAS]) were grouped into three domains that reflect the pathophysiology and the burden of AM (23). Patients were considered as responders if they achieved the response criteria in ≥2 out of 3 domains (23).

In rhLAMAN-05, 87% of patients in the velmanase alfa group achieved a response to treatment at 12 months, compared with 30% in the placebo group; therefore, the use of a two-domain responder criterion provides enough sensitivity to observe a treatment effect compared with placebo (23).

Following long-term treatment with velmanase alfa in rhLAMAN-10, 88% (100% of paediatric patients and 71% of adult patients) achieved a response at last observation (between 12–48 months of treatment) (23). The higher proportion of three-domain responders at last observation in rhLAMAN-10 (46%) compared with rhLAMAN-05 (13%) may also be indicative of benefit received from long-term treatment (up to 48 months) with velmanase alfa (23).

Overall magnitude of health benefits to patients and carers

Velmanase alfa was shown to positively impact patients' QoL throughout the clinical development programme, as measured by improvements in the CHAQ disability index (a measure of overall disability) and CHAQ pain (VAS) (a measure of pain experienced) from baseline to last observation (12–48 months of treatment with velmanase alfa).

UK key opinion leaders (KOLs) stated that velmanase alfa has the potential to reduce the symptom burden (particularly with respects to mobility, pain, lung function and rates of infections) experienced by patients, which in turn should improve their QoL (17) (Section 7.2.3). [redacted] Furthermore, the impact of small improvements should not be underestimated. For patients, even improvements in completing simple tasks that increase their independence can be life changing (such as the ability to now tie their shoe laces and get dressed independently) (14, 17). Disease improvement in patients also benefit the carers and the wider family, allowing them more time to focus on other important aspects of their lives that may be neglected through their commitment to care (14, 17).

Heterogeneity of health benefits within the population

While both adult and paediatric patients receiving velmanase alfa had improvements across the majority of endpoints:

- the difference between velmanase alfa and placebo was greater in the paediatric group (6–11 years) and adolescent group (12–17 years) than in adults (≥18 years) after 12 months of treatment with velmanase alfa (rhLAMAN-05)
- greater changes from baseline to last observation (12–48 months of treatment) were observed in paediatric patients compared with adults (rhLAMAN-10)

These results suggest that velmanase alfa is of particular value in patients who start treatment at <18 years of age; therefore, it may be important to start treatment with velmanase alfa as early as clinically possible, following diagnosis of AM within the expected licensed population.

Disease improvement with velmanase alfa was observed in adult patients and was most evident in the assessment of serum IgG levels and CHAQ pain (VAS), which both improved from baseline to last observation in rhLAMAN-10. Furthermore, 71% of adults achieved a response (in the multi-domain responder analysis) to velmanase alfa treatment at last observation in rhLAMAN-10. These data provide support for disease improvement with velmanase alfa in adults, as disease stabilisation is not formally captured in the multi-domain responder analysis.

Robustness of the current evidence and the contribution the guidance might make to strengthen it

Currently, there is a scarcity of robust evidence and guidance for the treatment of AM. A recommendation from this submission will represent the first national guidance on the treatment of AM in England and Wales. In addition to the clinical data reported for velmanase alfa, which represents the first attempt at assessing a pharmacological intervention in the treatment of AM, this submission has also been developed through extensive interaction with UK and European KOLs in the field of AM and LSDs.

Treatment continuation rules

In order to provide guidance on the appropriate management of patients treated with velmanase alfa, Chiesi has developed a start-stop criteria (Section 10.1.16). It should be noted that Chiesi are currently in discussion with UK KOLs on the suitability of these criteria to UK clinical practice; therefore, the details provided on the treatment continuation rules may be updated during the submission process in light of this UK KOL consultation. Chiesi have proposed the following:

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

Patients will not be eligible to receive treatment with velmanase alfa if any of the following apply:

- the patient does not have a confirmed diagnosis of AM; or
- the patient has experienced a severe allergic reaction to velmanase alfa or to any of the excipients (disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol and glycine); or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient is unwilling or unable to comply with the associated monitoring criteria, i.e. that all patients are required to attend their appointed clinics two times per year for assessment

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

- Patient eligibility criteria must be met, as defined above

- A full set of baseline biochemical, functional and QoL assessments have been obtained

Patients will stop treatment with velmanase alfa if any of the following apply:

- the patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 18-month period); or
- the patient fails to meet two of the three criteria as defined in the multi-domain responder analysis at their Year 1 assessment (see Section 9.4.1.4 and 9.6.1.3)
- the patient is unable to tolerate infusions due to treatment related severe adverse events (AEs) that cannot be resolved; or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g. due to repeated recurrent chest infections or progressive and sustained lack of mobility; or
- the patient misses more than four infusions of velmanase alfa in any 12-month period, excluding clinical reasons for missing dosages.

Patients whose treatment with velmanase alfa is discontinued due to stop criteria will continue to be monitored for disease progression and supported with other clinical measures.

Value for money

Incremental cost effectiveness using cost per QALY adjusted life year

To fulfil the requirements of the updated NICE HST process, Chiesi has developed a de novo economic model and cost-utility analysis to estimate the impact of treatment with velmanase alfa in terms of costs and effects (quality-adjusted life years [QALYs]) on patients with AM. However, it should be noted that the analysis is based on little published information regarding the long-term progression of AM under standard clinical practice and the capacity for ERT to benefit patients with AM in the long term. The lack of longer-term data is due to the extremely ultra-rare nature of the condition. Only [redacted] have ever been identified as having AM in the UK according to the UK Society for Mucopolysaccharide Diseases (UK MPS Society) Registry (4). Therefore, any economic model developed in this disease area is going to be speculative and heavily reliant on expert KOL opinion to design and parameterise. As a result, Chiesi has interacted extensively with UK KOLs in the field of AM through formal data synthesis techniques (expert elicitation) and structured teleconference interviews in order to design, validate and parameterise the model as robustly as possible.

Model development is extremely challenging when no patient can be perceived as 'typical' in reality. Therefore, the model is unlikely to truly capture the expected costs and QALYs for a cohort/average patient. While Chiesi believes the model is verified, robust and informative, it should be used with caution to make definitive comments regarding the cost-effectiveness of velmanase alfa, particularly with respect to meeting, or not

meeting, strict willingness to pay thresholds. Additionally, it should also be noted that there are potentially wider benefits of velmanase alfa that were not possible to capture in the model. Finally, the ultra-rare nature of this condition and its low budget impact should be carefully considered alongside the cost-effectiveness results, with the aim of ensuring a very small number of patients with a significant unmet need get access to an effective, life-improving and life-extending treatment.

The analysis compares best supportive care (BSC) without velmanase alfa (the “best supportive care” strategy) against velmanase alfa plus BSC (the “velmanase alfa” strategy). The base case analysis is conducted from an NHS/Personal Social Services (PSS) perspective and estimates costs and QALYs over a lifetime time horizon (Section 12.1.7).

The model is a cohort Markov design, with four primary health states representing different levels of ambulatory status (walking unassisted, walking with assistance, wheelchair dependent, and severe immobility); the model has a 1-year time cycle. The model can present three different cohorts based on age at treatment initiation with velmanase alfa: a paediatric cohort (6–11 years), an adolescent cohort (12–17 years) and an adult cohort (≥18 years). These cohorts correspond to a post-hoc analysis of the rhLAMAN clinical programme by three age groups (Section 9.6.1.2). The starting state distribution for the model is based on the ambulatory status of the rhLAMAN-10 baseline population, which is used as a proxy for the prevalent population in England and Wales.

The chronic and progressive nature of AM is modelled via the gradual progression (deterioration) of ambulatory status and functional capacity. Patients move through the health states in sequence unless they die due to background mortality, a severe infection, or major surgery; they may also move directly to the severe immobility health state due to a surgical complication. The primary benefit of velmanase alfa is to delay the rate of disease progression, but the modelled benefit of velmanase alfa also includes the ability for disease improvement (the ability for a patient’s ambulatory status to improve, and revert to a less severe health state), a reduction in the rates, recovery disutility and mortality from severe infections, and a reduction in the recovery disutility, complications and mortality from major surgery. Velmanase alfa is also modelled to have a benefit by reducing the necessity and complexity of ventilation required by patients in the more severe health states.

In the base case analysis (presented in Section 12.5), the incremental cost-effectiveness ratio (ICER) for velmanase alfa vs BSC was [redacted] in the paediatric cohort, [redacted] in the adolescent cohort and [redacted] in the adult cohort. The budget impact analysis, which uses the prevalent AM patient population in England and Wales according to the UK MPS Society patient registry, estimates that the treated cohort will comprise [redacted] paediatric patients, [redacted] adolescent patients, and [redacted] adult patients. Using these proportions, the weighted cohort ICER is [redacted].

After discounting costs at 1.5%, BSC was associated with a lifetime total cost of £894,169, £899,375, and £914,049 in the paediatric, adolescent, and adult cohorts, respectively. Velmanase alfa was associated with a lifetime incremental cost of [redacted], and [redacted] in the paediatric, adolescent and adult cohorts, respectively.

After discounting QALYs at 1.5%, BSC was associated with lifetime total QALYs of 5.65, 5.26, and 4.41 in the paediatric, adolescent, and adult cohorts, respectively. Velmanase alfa was associated with a lifetime incremental QALYs (vs BSC) of 2.25, 2.38, and 2.39 in the paediatric, adolescent and adult cohorts, respectively.

The disaggregated results (Table 85) show that treatment with velmanase alfa will lead to PSS cost savings.

The one-way sensitivity analysis shows that the parameters in the model affecting the ICER are the discount rate used for QALYs and the cost of velmanase alfa. The ICER was also sensitive to the rate of backwards transitions (disease improvement to patients' ambulatory health state) on velmanase alfa. Assuming that 70% of patients treated with velmanase alfa experience a reverse transition from 'walking with assistance' to 'walking unassisted' in Year 1, the ICER vs BSC was [redacted] in the paediatric cohort, [redacted] in the adolescent cohort, and [redacted] in the adult cohort.

The probabilistic sensitivity analysis (PSA) demonstrated combined parameter uncertainty in the model, with mean probabilistic results that were very similar to the deterministic analysis, and broad 95% CIs around the ICERs (paediatric ICER [95% CI]: [redacted], adolescent ICER [95% CI]: [redacted], adult ICER [95% CI]: [redacted]).

The results of the multi-way scenario analysis demonstrated that there are more optimistic analyses to explore. For example, assuming the upper limit of the treatment effect of velmanase alfa from the UK Expert Elicitation Panel (UK-EEP) lowers the ICER to [redacted], [redacted], and [redacted] for paediatrics, adolescents, and adults, respectively. Assuming that velmanase alfa slows disease progression by 50% lowers the ICERs further to [redacted], and [redacted], for paediatrics, adolescents, and adults, respectively. An optimistic scenario where velmanase alfa halts disease progression lowers the ICERs further to [redacted], and [redacted], for paediatrics, adolescents, and adults, respectively. It is noted that such levels of optimism with respect to delayed disease progression (i.e. 50% reduction to halting disease progression) have been considered as part of other enzyme replacement therapy (ERT) NICE HST appraisals.

Patient access schemes and other commercial agreements

Chiesi has submitted a confidential simple discount patient access scheme to the Department of Health and Patient Access Schemes Liaison Unit (PASLU) alongside this appraisal, to support patient access to velmanase alfa. Chiesi welcomes further discussions with relevant stakeholders should other commercial agreements (e.g. managed access agreements) be considered an appropriate measure to support patients gaining access to an innovative treatment.

The nature and extent of the resources needed to enable the new technology to be used (including budget impact in the NHS and PSS, including patient access schemes)

The UK MPS Society Patient Registry has identified [redacted] with AM over the age of 6 years in England and Wales. Specifically, there are [redacted] paediatric patients (aged 6–11), [redacted] adolescent patients (aged 12–17) and [redacted] adults (aged ≥18) (4). The

budget impact model estimates that after accounting for market share estimates, incident patients, discontinuation and mortality, [redacted] patients will be treated with velmanase alfa in Year 1, rising to [redacted] in Year 5. These patient numbers account for a budget impact associated with velmanase alfa treatment and administration of £1.3m in Year 1, rising to £1.9m in Year 5, and a total cumulative budget impact over 5 years of £7.8m.

Impact of the technology beyond direct health benefits

As chronic, multi-morbid and progressive disease, there are benefits to effective treatment that fall beyond simple costs or improved health. It is evident from the UK KOL interviews and the case study derived from the UK MPS Society survey that AM has a substantial, albeit unquantifiable, impact on the financial and social wellbeing of patients and carers. This impact includes a limited social life and lost employment opportunities for both patients and carers, and out-of-pocket expenses borne by the family. By improving patients' ambulation and/or delaying disease progression, treatment with velmanase alfa may relieve some of the burden of care and help deliver improvements in the overall wellbeing of patients and their families.

It is also anticipated that velmanase alfa may provide significant cost savings to the government outside of the NHS. These savings include benefits to budgets concerning education, the local government and welfare, due to the reduction in care and support a patient receiving velmanase alfa may require as a result of greater independence. A reduction in care requirements may also allow carers and families of patients with AM to maintain a higher level of employment.

As the first pharmacological disease-modifying therapy for patients with AM, the clinical and economic evidence generation programme has provided innovation to the field of ultra-rare conditions in the UK. It is anticipated that the use of velmanase alfa will lead to greater understanding of the epidemiology, pathology, and management of rare LSDs. The rhLAMAN clinical development programme is a global collaboration between clinicians, industry and patients, and the UK has been a key participant within the programme and associated evidence generation activities, including KOL interviews, formal expert elicitation exercises, and the development of an economic model.

While velmanase alfa is a novel disease-modifying therapy for patients with AM, the impact on the delivery of specialised services should be minimal. Designated LSD specialist centres are responsible for the assessment of patients and the initiation and monitoring of treatments. As such, these centres will have experience of administering ERTs via infusion for other LSDs. Therefore, no additional infrastructure is required to ensure the safe and effective use of velmanase alfa in those centres and if any training is required for the administration of velmanase alfa, it is likely that this will be minimal. As is the case for other ERTs, velmanase alfa will be offered to patients via homecare following initiation of treatment in the LSD specialist centre. Homecare administration will be performed by a trained nurse, as is standard practice for the administration of other ERTs in the UK. [redacted].

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 2: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with alpha-mannosidosis aged 6 years or older	As per scope. Since the final scope was issued there has been a change to the expected licence indication to VA so this no longer excludes <6 years.	N/A.
Intervention	Velmanase alfa	As per scope	N/A
Comparator(s)	Established clinical management without velmanase alfa (including, where clinically indicated, allogeneic HSCT)	Allogeneic HSCT is not considered as a relevant comparator in this submission	Allogeneic HSCT is not clinically indicated in the same patient population as covered in the licence indication and positioning of velmanase alfa; therefore, allogeneic HSCT is not considered a suitable comparator (see Section 8.3 for further discussion).
Outcomes	The outcome measures to be considered include: • mobility and motor function • hearing and language • cognition • lung function • rates of infection • mortality • adverse effects of treatment (including immune response) • health-related quality of life (for patients and carers)	As per scope, with the inclusion of serum oligosaccharides and serum IgG	Serum oligosaccharides are an important biomarker that demonstrate the effect that velmanase alfa has at the cellular level and is a surrogate marker of potential clinical complications. It is also a primary endpoint in the rhLAMAN clinical trial programme and a component of the post-hoc. multi-domain responder analysis. Frequent infections are a hallmark of AM and patients may suffer from hypogammaglobulinemia; measuring change in serum IgG is a way to

			capture this clinical aspect of AM. In addition, improvements in serum IgG are considered clinically important according to expert clinical guidance; improvements in serum IgG may result in fewer infections, which is an important clinical issue for these patients.
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	As per scope	N/A
Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)	As per scope	N/A
Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	As per scope	N/A

Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.	As per scope with societal costs also included as a sensitivity analysis	The economic model incorporates estimates of the impact of AM on patient/caregiver expenditure and productivity; however, as no AM-specific costs were identified, these have not been included in the base case analysis, and only included in sensitivity analysis.
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements • Where evidence allows consideration may be given to clinical characteristics (such as, age of onset and severity of disease)	As per scope	N/A

Abbreviations: AM, alpha-mannosidosis; HSCT, haematopoietic stem cell transplant; NHS, National Health Service.

2 Description of technology under assessment

2.1 *Give the brand name, approved name and when appropriate, therapeutic class.*

Brand name: LAMZEDE® ▼

Approved name: Velmanase alfa

Therapeutic class: Mannosidases; recombinant proteins for ERT

2.2 *What is the principal mechanism of action of the technology?*

Velmanase alfa, the active substance, is a recombinant form of human lysosomal alpha-mannosidase and is produced in Chinese hamster ovary cells using recombinant DNA technology. The amino acid sequence of the monomeric protein is identical to the naturally occurring human enzyme, alpha-mannosidase (α-mannosidase).

Lysosomal alpha-mannosidase is necessary for the catabolism of asparagine-linked carbohydrates (oligosaccharides) released during glycoprotein turnover (24). Glycoproteins include such biologically-important molecules as cell-surface receptors, cell-adhesion molecules, immunoglobulins and other serum proteins, and tumour antigens. The enzyme catalyses the hydrolysis of terminal, non-reducing alpha-D-mannose residues in alpha-D-mannosides, and can cleave all known types of alpha-mannosidic linkages (25). Defects in the gene (MAN2B1) cause lysosomal alpha-mannosidosis (AM), a lysosomal storage disorder caused by the accumulation of unbranched oligosaccharide chains (26). The accumulation of these oligosaccharides cause the multi-morbid chronic disease, characterised by cognitive impairment and skeletal deformities resulting in immobility.

Velmanase alfa supplements and/or replaces natural lysosomal alpha-mannosidase, which is missing or defective in patients with AM. Following administration into the blood stream, velmanase alfa enters the cell and is targeted to lysosomes through both mannose-6-phosphate receptor-dependent (24) and independent mechanisms (27). Treatment with velmanase alfa works by reducing the amount of accumulated oligosaccharides in tissues, which are the main pathological driver of the multi-morbid, life-limiting chronic disease.

2.3 *Please complete the table below.*

Table 3: Dosing Information of technology being evaluated

Pharmaceutical formulation	White to off-white powder (10 mg vial)
Method of administration	The 10-mg vial of velmanase alfa is reconstituted to provide a final concentration of 10 mg/5 ml (2 mg/ml) per vial. Velmanase alfa is administered by intravenous infusion (IV) at a controlled speed. The infusion duration should be calculated individually considering a maximum infusion rate of 25 ml/hr (50 mg/hr) over a minimum of 50 mins to control the protein load.
Doses	The recommended dose regimen of velmanase alfa is 1 mg/kg of body weight.
Dosing frequency	Once every week
Average length of a course of treatment	Lifetime, subject to the 'start-stop' criteria defined in Section 10.1.16. Treatment may be 'stopped' due to reasons of non-compliance, non-response and/or deterioration of functional capacity (e.g. a patient becomes severely immobile).
Anticipated average interval between courses of treatments	Treatment is continuous; the recommended dose regimen of velmanase alfa is 1 mg/kg of body weight, once every week.
Anticipated number of repeat courses of treatments	Treatment is considered continuous and lifelong subject to the 'start' and 'stop' criteria defined in Section 10.1.16.
Dose adjustments	Velmanase alfa is dosed by weight; therefore, dose adjustments will be required as/if the patient's changes, including children as they grow.

3 Regulatory information

3.1 *Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).*

The licensed indication for velmanase alfa is as an ERT for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

A positive Committee for Medicinal Products for Human Use (CHMP) opinion was granted in January 2018, with full marketing authorisation granted in March 2018.

3.2 *If the technology has not been launched, please supply the anticipated date of availability in the UK.*

Velmanase alfa is expected to be commercially available in Q4 2018/Q1 2019, in line with the expected publication of NICE HST guidance and subsequent reimbursement by National Health Service (NHS) England.

3.3 *Does the technology have regulatory approval outside the UK? If so, please provide details.*

Regulatory approval will be provided by the European Medicines Agency (EMA). Velmanase alfa is currently not subject to any other regulatory approval outside the UK.

3.4 *If the technology has been launched in the UK provide information on the use in England.*

While the product has not formally been launched in the UK, two patients in England were enrolled in the rhLAMAN clinical trial programme and both received velmanase alfa in the compassionate use programme. One patient, who received placebo in the Phase III study rhLAMAN-05, switched to velmanase alfa upon entering the compassionate use programme and continues to receive treatment. This patient has been receiving velmanase alfa since 2014, i.e. has received over 3 years of treatment at time of this submission.

The second patient commenced treatment with velmanase alfa in January 2011 before suspending treatment in September 2016; suspension was unrelated to any adverse event (AE) or clinician-led decision-making. Instead, the suspension was due to the patient's preference due to repeated hospital visits.

4 Ongoing studies

4.1 *Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.*

The rhLAMAN-07 and rhLAMAN-09 are two open-label studies that are currently ongoing; however, no results are likely to be available in the next 12 months. These studies form part of the velmanase alfa clinical development programme and were designed to provide aftercare treatment with velmanase alfa for participants of the Phase I/II trials and the Phase III trial, rhLAMAN-05 (see Section 9.4 for further details). Chiesi are working with the UK Society for Mucopolysaccharide Diseases (UK MPS Society) to conduct a patient/carer survey to gain qualitative and quantitative data on the quality of life (QoL) of patients/carers with AM in the UK (Section 7.2.4). This survey is currently ongoing and additional evidence likely to be available in the next 12 months.

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

Velmanase alfa is not currently subject to any other health technology assessment in the UK. Chiesi plan to submit to the Scottish Medicines Consortium (SMC) in [redacted]

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 *Please let us know if you think that this evaluation:*

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

No equality issues are anticipated for the appraisal of velmanase alfa.

5.2 *How will the submission address these issues and any equality issues raised in the scope?*

N/A, as above.

Section B – Nature of the condition

- Alpha-mannosidosis (AM) is an ultra-rare, genetically-inherited, lysosomal storage disorder (LSD) caused by an impairment in α-mannosidase activity (5)
    - AM has been estimated to affect between 1 in 500,000 (2) and 1 in 1,000,000 (3) world-wide
    - The known prevalence of AM in England and Wales is [redacted] and the incidence of AM in England and Wales is expected to be [redacted] patient a year
- The loss of α-mannosidase activity results in the systemic accumulation of oligosaccharides. This results in a multi-morbid chronic disease, characterised by cognitive impairment and skeletal deformities resulting in immobility
- As a very heterogeneous disease, AM encompasses a continuum of clinical findings from a perinatal-lethal form (severe) to one that is not diagnosed until adulthood
    - The clinical features observed for an individual (and the associated morbidity, mortality-risk and impact on quality of life [QoL]) may be strikingly different to the experiences of another patient (7) and contribute to both patient and parent/caregiver burden
    - Furthermore, there may be multiple factors contributing to the key clinical features of AM. For example, reduced mobility may be driven by musculoskeletal issues or cognitive impairment, while both central nervous system involvement and/or hearing issues may be contributing to cognitive impairment
- As a progressive and lifelong disease, the condition of patients worsens with age (2):
    - some symptoms or features of the disease may stabilise over time, while others continue to worsen; the rate at which symptoms progress also varies between patients (2, 10)
    - Most patients become wheelchair dependent/severely immobile and patients will never achieve social independence (2)
    - While many patients survive into adulthood, the disease is life-limiting, with infections (in particular respiratory infections) cited as a major driver of mortality in patients with AM (17, 18)
- Patients with AM experience a reduced QoL due to the effect the disease has on many areas of their lives
    - In addition to the symptom burden, such as recurrent infections, pain and psychological issues, which are detrimental to the overall well-being of patients, [redacted]
    - The progressive impairment of mobility/functional capacity, resulting in wheelchair dependence or severe immobility, substantially impacts the

patient's independence and their ability to carry out activities of daily living (18)

    - Adult and paediatric patients are consequently highly reliant on third-party assistance (12); cognitive impairment and reduced self-care are key reasons behind this dependency, in addition to reduced mobility (16)

- Despite the disease burden experienced by patients, the actual impact the disease has on the QoL of patients is difficult to ascertain:
    - Patients typically experience cognitive impairment (5, 10), which can make it difficult to obtain information (28) and also gain consent for the purpose of research
    - Generally, patients do not realise the full implications of their disease and may often appear content (18); however, they may understand that they are different, particularly if a healthy sibling is present
- As with other chronic conditions, the impact of AM on carers/family is greatly underestimated (17). Carers (typically parents) of patients with AM experience a reduced QoL, which worsens over time (17, 18). The disease prevents many carers from working and greatly impacts their social life; ultimately, their life may be focused solely on the welfare of the patient (17). The disease is also likely to represent a financial burden to carers; however, the extent of this burden is unknown
- Current treatments for AM are largely symptomatic in nature and focus on treating manifestations and optimising QoL (7)
    - There are no licensed pharmacologic, disease-modifying treatments for AM currently available for patients
    - Allogeneic haematopoietic stem cell transplant (HSCT) is a treatment option for some patients when clinically indicated, although it is associated with significant treatment-related morbidity and mortality (2, 5, 18)
    - In the UK, allogeneic HSCT is typically only reserved for AM patients (17, 18):
        - with extensive disease presenting in early infancy (≤5 years),
        - without additional comorbidities/recurrent infections and,
        - where a matched sibling or matched umbilical cord donor is available
    - Additionally, the risk of allogeneic HSCT-associated morbidity and mortality increases with age (17, 18). Therefore, patients over the age of 6 are less likely to have any treatment options
- In line with the expected license indication, velmanase alfa is an enzyme replacement therapy (ERT) that is positioned in patients with AM alongside BSC for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible.
- Whilst velmanase alfa is not a cure for this disorder, it moves the treatment of AM from symptomatic management to therapeutic intervention. UK key opinion

leaders (KOLs) considered velmanase alfa to be a ‘step change’ in the management of AM on the basis of its potential to change the natural course of the disease by offering improvements to patients’ ambulation and/or delaying disease progression in patients (17)

- UK KOLs stated that velmanase alfa may reduce the symptom burden (particularly with respects to mobility, pain, lung function and rates of infections) experienced by patients, which in turn should improve their QoL (17)

[redacted]

- Furthermore, the impact of small improvements should not be underestimated. For patients, even improvements in completing simple tasks that increase their independence can be life changing (such as the ability to now tie their shoe laces and get dressed independently) (14, 17)

[redacted]

- Velmanase alfa will also allow healthcare professionals to offer a treatment, which will encourage pro-active management of patients and help to improve long-term outcomes (17)

6 Disease morbidity

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

6.1.1 *Aetiology and pathophysiology*

AM is an ultra-rare, genetically-inherited, lysosomal storage disorder (LSD) caused by an impairment in α-mannosidase activity (5). The reduction in α-mannosidase activity observed in AM is caused by mutations in the MAN2B1 gene (5). As an ultra-rare disease, the prevalence of AM is difficult to define and the disease is likely to be under diagnosed (13); however, AM has been estimated to affect between 1 in 500,000 (2) and 1 in 1,000,000 globally (3). The known prevalence of AM in England and Wales is [redacted] patients [redacted] and the expected incidence of AM is [redacted] case a year (4).

In healthy individuals, α-mannosidase is present in lysosomes (the main intracellular site of biomolecular degradation) of all cells where it is involved in the degradation of N-linked carbohydrates (oligosaccharides) (5, 6) that are released from glycoproteins during their degradation (24). Glycoproteins include such biologically-important molecules as cell-surface receptors, cell-adhesion molecules, immunoglobulins and other serum proteins, and tumour antigens. The loss of α-mannosidase activity consequently causes a block in the degradation of these important glycoproteins and results in an accumulation of oligosaccharides in lysosomes (29). These oligosaccharides can also be detected in the tissue, serum and urine of patients (5, 30). The accumulation of oligosaccharides impairs cellular function (5), however, the precise mechanism is unknown (10). As α-mannosidase participates in the degradation of glycoproteins involved in important pathways, the accumulation of oligosaccharides may disrupt these pathways. Circulating oligosaccharides are known to interfere with molecules of the immune system resulting in the immunodeficiency observed in some patients with AM (31).

6.1.2 *Clinical course of AM*

AM has been historically classified into two (5) or three subtypes (2) in order to differentiate between early lethal and milder forms of the disease. While the intent of this sub-typing was to provide patients with prognostic information, the definitions of these phenotypes as distinct have several scientific and practical flaws:

- No pathophysiological basis has been found to support the existence of distinct phenotypes rather than a continuous spectrum of disease. No clear genotype-phenotype or biochemical-clinical correlations have been identified
- Phenotypes are impractical for use in clinical studies in such a rare disease
- The phenotypes mentioned above do not provide a clear and full description of the disease. For example, a patient with mild clinical manifestations and without skeletal abnormalities presenting in his first years of life may be identified through genetic testing but could not be classified using the three-type system. The same

would be true for a patient with skeletal abnormalities not diagnosed until the teenage years

It is now recognised that AM encompasses a continuum of clinical findings from a perinatal-lethal form to one that is not diagnosed until adulthood (5, 17).

6.1.3 *Patient burden*

Patients with AM may appear normal at birth; however, their condition progresses with age (2). AM causes a broad range of symptoms that manifest differently from person to person, including both cognitive and physical symptoms (7) that contribute to significant patient and parent/caregiver burden. Furthermore, there may be multiple factors contributing to the key clinical features of AM. For example, reduced mobility may be driven by musculoskeletal issues or cognitive impairment, while both central nervous system (CNS) involvement and/or hearing issues may be contributing to cognitive impairment. Over time, some of the symptoms or features of the disease may stabilise, while others continue to worsen; the rate at which symptoms progress also varies between patients (2, 10). Eventually, most patients become wheelchair dependent/severely immobile and patients will never achieve social independence (2).

6.1.3.1 Clinical presentation

Abnormal physical features

The main physical features of AM are summarised below and almost all contribute to a loss of function:

- Facial features: Patients with AM may present with both normal or abnormal facial features; the latter may include a large forehead, broad nose with flattened bridge, widely spaced teeth and a large tongue (2, 8)
- Brain: Analysis with magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) may show evidence of CNS pathology including demyelination (9) and hydrocephalus (8, 10); hydrocephalus can be a repeating issue requiring ventriculoperitoneal shunting (17)
- Skeletal deformities: Patients with AM often present with skeletal abnormalities, including deformities in the hips and the head of the femur (8). The chest may also be abnormal in shape, with reduced flexibility between the ribs and sternum (8). Patients may also have poorly formed vertebrae that do not stably interact with each other; the vertebrae in the lower back are occasionally smaller than the others and are set back in line, causing a kyphosis or Gibbus deformity (a rounded or hunched deformity of the spine) (8). Scoliosis (a side to side deformity of the spine) may also be present (8); spinal abnormalities may also adversely affect lung function by reducing the available space for respiration. Joint stiffness is also common and contributes to restricted movement (8)
- Hands: Carpal tunnel syndrome may be present, which may result in muscle wasting at the base of the thumb (8)
- Legs and feet: Hips and knees may be flexed when standing and some individuals may have knocked knees (touching knees) (8). Tight Achilles tendon may also cause patients to walk on their toes; their toes may be curved under (8)

Reduced functional capacity and impaired motor function

Patients with AM have reduced functional capacity (5), i.e. the ability to perform day-to-day tasks or activities and some patients eventually become wheelchair dependent (2) or severely immobile. Functional capacity can be measured using tests designed to assess walking (6-minute walk test [6-MWT]) and stair climbing (3-minute stair climb test [3-MSCT]), which show that the functional capacity of patients with AM is reduced by up to 60% compared with age-matched healthy peers (12). However, both the 3-MSCT and 6-MWT are effort-dependent, which may be problematic in paediatric or neurologically- or cognitively-impaired patients whose performance is often influenced by their developmental stage, understanding of the instructions, and willingness to cooperate.

Reduced functional capacity may manifest because of abnormal physical features such as bone deformities, which affect gait and may contribute to a restriction in movement. Functional capacity can also be affected by patients' impaired motor function (10), with children with AM learning to walk later than normal and generally being described as clumsy (10). Muscle weakness, joint abnormalities and ataxia (a lack of muscle coordination which may be caused by muscle weakness and/or CNS pathology) or gait abnormality all contribute to the observed motor function disturbances (2, 10) and typically worsen over time (10).

Arthritis is also prevalent in many patients and increases with age (10), which can cause joint damage (5) that may further limit the physical abilities of patients with AM and result in the need for weight-bearing joint replacement; joint disease may also contribute to greater pain observed in older patients (12). Patients with AM may also present with varying levels of bone disease, from osteopenia (a precursor to osteoporosis) to osteonecrosis (death of bone tissue) (7). Functional capacity may also be reduced due to impaired lung function (12) (see below).

Reduced lung function

Reduced lung function (12) is associated with the chest/spinal abnormalities and the enlarged liver and spleen that are seen in patients with AM also reduce lung space (8). These defects may contribute to a reduction in lung function as assessed by spirometry methods (forced vital capacity [FVC]) (12). In addition, patients with AM also suffer from repeated respiratory infections due to their immunodeficiency, which are also thought to contribute to impaired lung function (32).

Impaired cognitive function

All patients will present with some degree of cognitive impairment and IQ typically ranges from 30 to 81 across all affected patients (5). The cause of cognitive impairment is not clear; however, CNS pathology and demyelination have been observed in AM which may be linked to an accumulation of oligosaccharides in the brain (9). Cognitive impairment can be recognised as early as the first decade of life and may slowly progress over time (2, 5). Speech and language disabilities are a prominent feature in patients with AM with some patients unable to speak entirely, while others will show some ability, albeit less advanced than their aged-matched healthy peers (5).

Impaired mental health function

Approximately 25–44% of patients experience psychiatric problems, such as confusion, delusions, anxiety and depression (11, 15). Psychiatric problems appear to be periodic and may be followed by weeks of prolonged sleepiness; however, they can lead to a severe loss of function, which may be permanent in some patients (15). Such problems may be linked to impaired cognitive function or may represent an independent psychiatric co-morbidity (15).

Immunodeficiency and infections

Patients with AM suffer from recurrent infections, suggestive of immunodeficiency (33). While it is unclear how elevated oligosaccharide levels cause the majority of defects in AM, a mechanism has been proposed where circulating oligosaccharides directly interfere with molecules of the immune system (31). Consequently, patients with AM are prone to a range of bacterial and viral infections (31). In particular, patients have an increased risk of respiratory infections and infections of the middle ear (5, 8). Infections are more common in the first decade of life and diminish towards to the second and third decades (5); however, infections are a key driver of mortality and adult patients are still more prone to infections than the general population (17, 18).

Hearing and sight impairment

Difficulties in hearing are prevalent in patients with AM (10), with 97% reported as having hearing impairment (11). Hearing impairment is typically a combination of both conductive hearing loss (due to recurrent infections) and sensorineural hearing loss (due to damage to the middle ear) (5). Hearing impairment appears early in childhood and the degree of hearing loss is largely consistent between age groups (12). Furthermore, hearing loss can subsequently impact the patient's social interactions as their ability to communicate is adversely affected (17). Patients may also present with sight abnormalities (7).

Increased pain

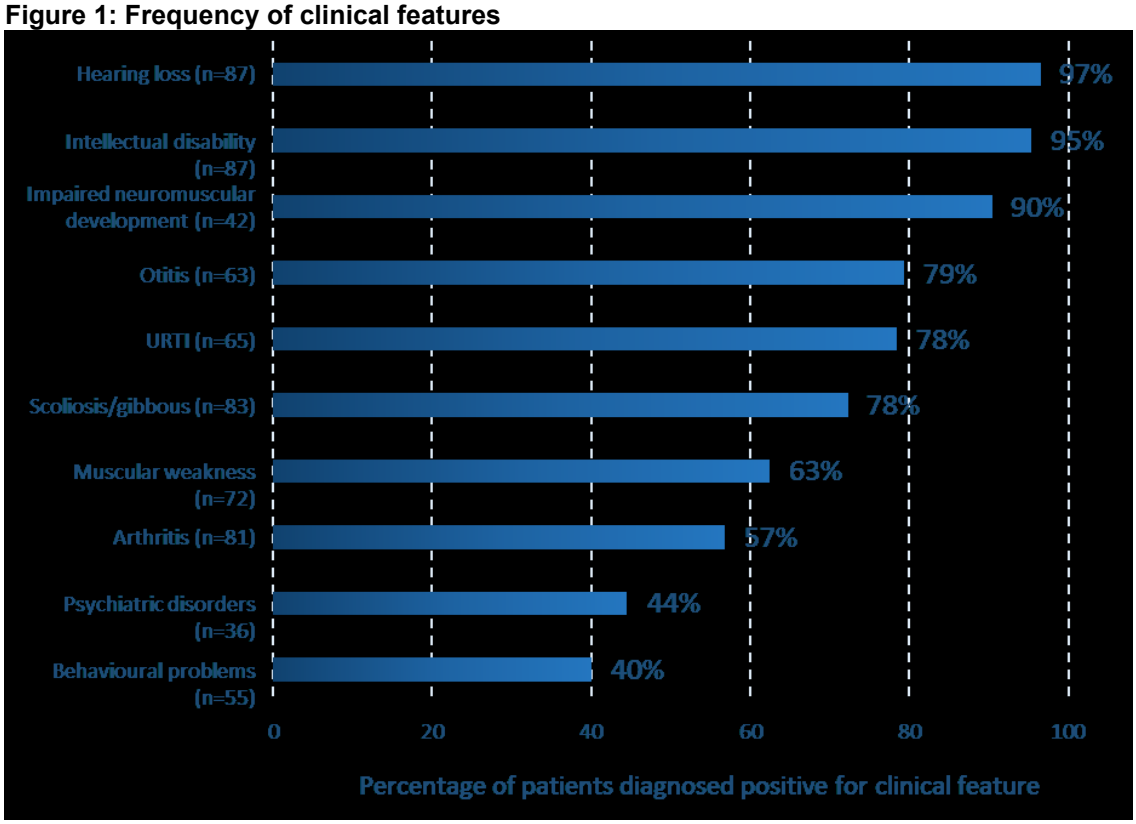
Patients are reported to experience pain, with older patients appearing to experience a greater level of pain due to progressive bone and joint disease (12). [redacted]

6.1.3.2 Frequency of symptoms/features

Coordinated by the University of Tromsø in Norway, the AM mutation database documents 191 patients with AM across 41 countries, compiled from the published literature; this database includes the frequency of clinical features (where assessed) in 92 of these patients (11).

Figure 1 demonstrates that while some features are consistent findings, others are less frequent, highlighting the heterogeneous nature of the disease. Hearing loss, cognitive impairment and impaired neuromuscular development were the most consistent findings in this cohort of patients, while infections (such as otitis [middle ear infection] and upper respiratory tract infections) and scoliosis were also frequently observed. Over half the population developed arthritis, while psychiatric and behavioural disorders were less frequently reported.

Figure 1: Frequency of clinical features



Adapted from: AM Mutation Database as of June 2016 (11); the data from this database has not been updated since June 2016 according to the website.
Note: n=number of patients with available data on clinical feature.
Abbreviations: URTI, upper respiratory tract infection.

6.1.3.3 Mortality

Publications describing the life expectancy of patients with AM are limited; however, survival into adulthood is described (5, 34). Mortality data specific to the UK is provided in Section 6.3.

The most frequent causes of death reported by healthcare professionals are infections and complicated/severe infection(s) (e.g. sepsis), pneumonia and scoliosis, heart attack and surgery complications (34). UK key opinion leaders (KOLs) concurred that infections (in particular respiratory infections) were a major driver of mortality in patients with AM (data sourced via UK KOL interviews, see Section 12.2.5) (17).

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

As an ultra-rare disease, the prevalence of AM is difficult to define and the disease is likely to be under diagnosed (13); however, AM has been estimated to affect between 1 in 500,000 (2) and 1 in 1,000,000 (3) globally.

In the UK, the UK MPS Society coordinates a registry, which is an ongoing database that monitors over 1,200 children and adults with mucopolysaccharidosis (MPS) or related diseases, including AM (35). At the time of this submission, there were [redacted] patients with

AM in England and Wales registered on the UK MPS Society registry, of which [redacted] are aged ≥6 years old and [redacted] patient is aged <6 years old. Of these [redacted] are aged 6–11 years old, [redacted] patients are aged 12–17 years old, and [redacted] patients are aged ≥18 years old (4). It should be noted that there may be more patients with AM in England and Wales who are not included in the registry; to be included in the registry, patients must be registered with the UK MPS Society and consent to inclusion. Furthermore, there may be a number of undiagnosed patients across England and Wales. Not all identified prevalent patients with AM may be eligible for treatment with velmanase alfa; eligibility and start/stop criteria are described in Section 10.1.16.

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

There is limited information regarding the long-term outlook for people with AM in the UK. In England and Wales, the UK MPS Society registry has recorded [redacted] since 1982 (the date of the foundation of the society); [redacted]

7 Impact of the disease on quality of life

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

7.1.1 *Patient quality of life*

The impairment experienced by patients with AM in functional capacity (mobility and lung function), cognitive ability, and hearing can have a substantial burden on the patient and would be expected to impair their QoL relative to population norms. The progressive impairment of mobility/functional capacity, resulting in wheelchair dependence or severe immobility, substantially impacts the independence of the patient (18). For example, reduced mobility can make it difficult for patients to complete activities of daily living or leave their house, leading to feelings of isolation (18). Cognitive and hearing impairment also impact the independence and confidence of patients (18) and affect many aspects of social functioning; patients with AM will require extra education/special schooling and are unlikely to ever obtain full-time employment. Coping with the periodic psychiatric problems experienced by some patients with AM (25–44% of patients (11, 15)) can also be difficult and the first episode is typically frightening for both the patient and their parents/caregivers (15). Although future episodes may be dealt with more easily (15), there are few services available that can provide mental health support to patients with AM. This issue is exacerbated when patients transition to adult services, where such support is further limited when compared with paediatrics (18). Despite the symptom burden experienced by patients, the actual impact the disease has on the QoL of patients is difficult to ascertain. Generally, patients do not realise the full implications of their disease and may often appear content (18); however, they may understand that they are different, particularly if a healthy sibling is present. Furthermore, assessing the QoL of patients with AM is challenging as they typically experience cognitive impairment (5, 10), which can make it difficult to obtain information (28) and also gain consent for the purpose of research.

Patients with cognitive impairment are more likely to respond unfaithfully to questions, such as providing an answer that they think the questioner wants to hear, choosing the last option as the correct answer, and responding in the negative to all questions, compared with subjects with normal cognition (28). The use of proxies (parents or caregivers) can help overcome this limitation; however, the extent to which proxy responses converge with the patient's assessment of their own QoL is uncertain (28). Furthermore, if the parents of older patients are elderly or deceased, or the patient is in full time residential care, obtaining proxy responses may be difficult. Evaluating QoL is likely to be further compounded by the challenges of assessing QoL in children; symptoms of AM, in particular hearing loss, begin to emerge during childhood (2, 5). Children naturally have less-developed cognitive skills and less life experience compared with adults, which can confound the interpretation of events and comprehension of abstract concepts (36). Children also have a different view of what is important compared with adults (36). QoL questionnaires have therefore been specifically designed for children which can help to provide more relevant information. In

adult patients, whose mental age is lower than their age-matched peers such children-specific questionnaires may be more appropriate than questionnaires designed for adults.

As AM is an ultra-rare disease, the true QoL burden experienced by patients is poorly defined and there is currently a lack of high quality evidence regarding the long-term impact of AM on patients' QoL. This is likely due to the rarity of the disease, which limits the size of study cohorts. Furthermore, the main driver of decrements in QoL will differ in heterogeneous populations, making it challenging to describe QoL. Overall, the few studies which have assessed QoL in patients with AM demonstrate that patients have a reduced capacity to carry out activities of daily living such as eating independently, dressing/undressing, washing, walking and climbing stairs (16). It has also been reported that patients experience increased pain, with older patients appearing to experience a greater level of pain, which may be due to progressive bone and joint disease (12). [redacted] The progressive loss of mobility can result in depressive feelings, which may be related to an increased insight into their worsening condition (15). Together with an increased risk of infections, hearing impairment and reduced lung function, it is therefore likely that patients with AM experience a substantial QoL burden due to their symptoms. However, given the issues discussed around measuring QoL in patients with difficulties communicating and cognitive impairment, there is a need to further quantify the true impact that the disease has on their QoL.

7.1.2 *Caregiver burden*

Due to the multiple systems affected, patients with rare diseases often require complex care and support from a range of healthcare services (37). For patients with AM, most become wheelchair dependent or severely immobile and patients never achieve social independence (2). Adult and child patients are consequently highly reliant on third-party assistance (12), with cognitive impairment, reduced self-care and reduced locomotive abilities thought to be the key reasons behind this dependency (16). The burden of caregiving is usually the responsibility of the parent (18). However, the wider family and unaffected siblings of patients with AM often provide a supportive caregiver role (18), which may impact their life decisions and ability to work; caregiver siblings may decline offers which require moving away from the family home, such as university (18). This suggests that the effects of AM on QoL can extend beyond the parent to all members of the family, such as to limit the educational potential and reduce the QoL of siblings.

The burden of caring for patients with AM is largely attributed to the appropriate management of the patient's daily life (38). While social care is available, this service appears to be more readily accessible for children rather than adults (18). This lack of social care for adult patients may substantially impact the caregiver, as adults with AM will never achieve social independence (2) and caring for them will be an ongoing commitment. Whilst published data on caregivers in AM is not available, many parents of children with a rare disease are often absent from work, while some decide to retire due to the large amount of weekly management required (37); it could reasonably be expected that this would also apply to parents of children with AM.

Loss of work will inevitably have financial implications, which are exacerbated by the costs and time associated with traveling to medical appointments and the acquisition of

daily living aids, which in some cases must often be funded by the caregiver (37). The burden of care is likely to increase as the parents age and accumulate health problems of their own, and parents often worry how they will continue to provide care for their child as their own health declines with age (18). The lack of professional caregiver support may therefore result in older parents experiencing substantial pressure when caring for a person with AM (18).

7.1.3 *Key opinion leader testimonials*

Interviews were conducted with four UK KOLs (Interview three, Section 12.2.5) to gain further understanding on the impact that AM has on QoL of patients and carers (17). The following is a summary of common themes and key points provided by the KOLs on this topic.

7.1.3.1 Patients

Overall quality of life

The symptoms of the disease typically affect many aspects of the patient's life. This includes basic tasks that are important for everyday living:

"It is the simple things that impact patients' lives. For example, a patient who has lost fine motor control and arm mobility can struggle to tie shoe laces, dress or eat independently. These symptoms prevent a child from socialising and taking part in education."

However, due to the heterogeneity of AM, the impact of the disease on the patient is usually specific to the individual. In terms of symptoms, there are no specific symptoms which affect QoL the most, as this is typically individual to the patient and dependent on which stage of the disease the patient is in. However, reduced mobility, recurrent infections, pain and learning difficulties were cited as particularly burdensome. The symptoms experienced by patients are also thought to cause secondary effects. For example, fatigue is an issue for some patients because their stiff/painful joints prevent them from sleeping. Furthermore, chronic hearing infections and subsequent hearing loss can impact the patient's social interactions as their ability to communicate is affected.

Overall, QoL is thought to decline with the natural progression of the disease. The largest reduction in QoL is thought to be related to a deterioration in ambulatory status. In particular, transition to wheelchair dependency is believed to be associated with the largest reduction in QoL. This is because patients become self-aware of the severity of their situation. However, it was noted that this substantial reduction in QoL at transition to wheelchair dependency may not be replicated in all patients, as each patient's symptom profile and subsequent impact on QoL is likely to be heterogeneous. In addition, a rapid decline in QoL can occur following a clinical event that has a profound impact on the patient (e.g. a fall, or ligament damage).

Ambulation and ability to complete everyday tasks

Mobility was identified as a key factor in the overall health and QoL of patients with AM. Patients who remain mobile for longer may experience fewer infections. Mobile patients will also remain socially integrated, have a better perception of wellbeing and retain a

certain level of independence. Consequently, a loss of mobility can have a substantial impact on health and QoL. One KOL highlighted that mobility and swallowing are closely linked and that once patients become immobile, they lose the ability to safely swallow and further increase their risk of respiratory infection as a result.

Social integration and lifestyle

The behavioural and communication issues experienced by patients with AM substantially affects their ability to socialise. The reduced mobility and hearing present in many patients with AM are also likely to affect social interactions.

7.1.3.2 Carers

Overall quality of life

As with other chronic conditions, the impact of AM on carers/family is greatly underestimated. Carers (typically parents) of patients with AM experience a reduced QoL, which worsens over time. Carers are required to take time off work and may experience anxiety and depression. They may also be at risk of injury (e.g. back injuries) due to handling/moving patients. The burden of care differs depending on the age of the patient. For paediatric and adolescent patients, the main aspects of care focus on behaviour management, education and coping with hearing loss. For adult patients, care is increasingly centred around mobility and activities of daily living.

Parents are usually the main provider of care, with one parent often becoming a full-time carer, providing round-the-clock care; siblings of patients with AM may also assist or even lead the organisation of care. Due to the amount of effort required to care for a patient with AM, there is also potential for sibling abandonment, which may impact on the development of the unaffected sibling.

Ability to work

Carers of patients with AM may be unable to work full time, although this depends on the severity of the disease; carers of wheelchair-bound or severely-immobile patients are unlikely to be able to work. They normally have to limit their careers to jobs that are less demanding, which typically provide lower salaries.

Social integration and lifestyle

The lives of carers are focused on the patient and they will generally have a lack of personal time; some carers do not socialise at all.

Out-of-pocket expenses

Caring for a patient with AM generally results in additional out-of-pocket expenses. Examples include non-reimbursable expenses due to travel, additional costs for holidays/excursions, hydrotherapy and supportive services. Families can receive financial assistance for certain elements of care, such as financial aid for wheelchairs and home adaptations; however, home adaptations are means-tested, therefore not all families will receive support.

7.2 *Describe the impact that the technology will have on patients, their families and carers. This should include both short-term*

and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

7.2.1 *Evidence from clinical trials*

Velmanase alfa was shown to positively impact patient QoL throughout the clinical development programme (Section 9.6.1.1 and 9.6.1.2). In rhLAMAN-10, an improvement in the childhood health assessment questionnaire (CHAQ) disability index (a measure of overall disability) from baseline was observed at last observation (12–48 months of treatment with velmanase alfa) in the overall population; the observed mean reduction of –0.13 achieved the established minimal clinically important difference (MCID) for this outcome (see Section 9.4.1.4 for details on adopted MCIDs for AM). Improvements in CHAQ pain (visual analogue scale; VAS) (a measure of pain experienced) were also observed; in particular, adult patients (≥18 years) experienced a 35.3% decrease (improvement) in CHAQ pain (VAS) at last observation, which also exceeds the established MCID for this outcome. The CHAQ also captures the use of aids/assistance required for ambulation. Notably, of the ten patients who required a device or third-party assistance for ambulation at baseline, seven (70%) became independent of assistance at last observation. This included two paediatric patients and one adult who required a wheelchair for long-distance mobility at baseline and discontinued use at last observation. Significant improvements in EuroQol five-dimension questionnaire (EQ-5D) index scores from baseline to last observation were also apparent in the overall population, indicating an improvement in the overall QoL experienced by patients following treatment with velmanase alfa.

The benefit of velmanase alfa on patients' QoL is further demonstrated in the analysis of nine patients who switched from placebo to velmanase alfa (Section 9.6.1.2). During rhLAMAN-05, patients receiving placebo experienced a worsening in QoL, as shown by increased scores from baseline at Month 12 for the CHAQ disability index and CHAQ pain (VAS). These patients then switched to velmanase alfa in either a follow-up trial or compassionate use programme and the CHAQ disability index and CHAQ pain (VAS) was recorded at last observation (12–18 months of treatment with velmanase alfa) in rhLAMAN-10. When compared with the baseline scores recorded in rhLAMAN-05 for the nine patients who switched to velmanase alfa, a reduction (improvement) in CHAQ disability index and CHAQ pain (VAS) scores was observed at last observation.

7.2.2 *Clinical trial KOL feedback*

In order to further understand the impact that velmanase alfa had on patients, feedback was obtained from specialist clinicians/trial investigators who have experience of treating patients with AM using velmanase alfa (14) (Section 12.2.5 [redacted] The clinicians were asked to consider the patient's most meaningful improvements and the impact these had on the patient's life and the lives of their families/carers. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.3 *Key opinion leader testimonials*

Interviews were conducted with four UK KOLs (Section 12.2.5) to gain further understanding on the impact that velmanase alfa may have on the QoL of patients and carers (17). The following is a summary of common themes and key points provided by the KOLs on this topic.

7.2.3.1 Patients

Overall, the KOLs believe that velmanase alfa has the potential to improve mobility, hearing loss, lung function, rates of infections and hospitalisation, and help achieve better outcomes with surgery. The impact of velmanase alfa on mobility may allow patients to be more independent in other activities of daily living, such as using the bathroom, eating and washing. It was also suggested that the improved lung function may reduce the level of mechanical ventilation required by the patient in the later stages of the disease.

Velmanase alfa may also help to reduce the amount of pain experienced by patients with AM. This could improve the quality of sleep and reduce fatigue through a reduction in pain/discomfort at night due to stiff and painful joints. However, the increased mobility that patients may achieve will need to be managed to avoid overexertion, injury, and increased daytime pain.

One KOL highlighted how improvements in simple tasks can be life changing. A specific example was provided for a paediatric patient who may gain greater independence following treatment with velmanase alfa. The patient may now be able to tie their shoe laces and get dressed independently. Additionally, they may be able to play and socialise without having to go to their carer or teacher for assistance. It was suggested that patients take great pride in improvements in their condition, even though they may appear to be relatively small to someone with age-normal cognition.

7.2.3.2 Carers

The improvement in mobility and self-care that velmanase alfa may provide patients is likely to have a beneficial impact on carers. If the patient is able to mobilise and look after themselves more independently, carers will be afforded more time to themselves; therefore, the QoL of carers would likely improve.

7.2.4 *UK MPS Society survey*

7.2.4.1 Overview of methods and objectives

[redacted]

7.2.4.2 Patient and carer interviews

[redacted]

[redacted]

[redacted]

[redacted]

8 Extent and nature of current treatment options

8.1 *Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.*

There are currently no AM-specific guidelines available from NICE, NHS England or expert guidelines.

An NHS England Manual for prescribed specialised services, including lysosomal storage disorder service (adults and children), and a NHS standard contract for lysosomal storage disorders service (adults and children) are available (40, 41). These documents outline the basic organisation and provision of care for patients with LSDs, which is commissioned by NHS England (Section 8.2).

A recent consensus of indications for HSCT in children suggest that allogeneic HSCT can be considered standard of care in AM and is generally indicated for suitable paediatric patients and/or in context of a clinical trial (42); however, the decision to proceed to transplant is ultimately best made between the clinicians and the patient, taking in to account the risks/benefits for the specific patient's circumstances, the evidence base and alternative treatments available. In practice, allogeneic HSCT is rarely performed and usually restricted to young patients aged ≤5 years (see Section 8.3 for further discussion).

8.2 *Describe the clinical pathway of care that includes the proposed use of the technology.*

8.2.1 *Lysosomal storage disorders service*

While there is no formal or specific clinical pathway of care for patients with AM, patients are likely to be cared for under the service specification outlined for LSDs (40).

The service is commissioned directly by NHS England (due to small number of patients and the limited number of expert staff who can provide the service (41)) and the aim of the service is to provide an inclusive, holistic, multi-disciplinary service for patients with LSDs; the service specification does not cover the provision of HSCT. The service specification is divided into children and adults, however, the overall basic care pathway is the same for both adults and children (Figure 2). Importantly, the assessment of the patient and initiation and monitoring of treatments should be conducted by designated LSD specialist centres.

For children with LSDs, the strategic objectives of the service are to provide rapid access to diagnostic testing, assessment and appropriate multi-disciplinary management for their underlying disorder. Children may be managed as outpatients in LSD specialist centres (together with adults) or in children's hospitals.

Overall, the service should provide:

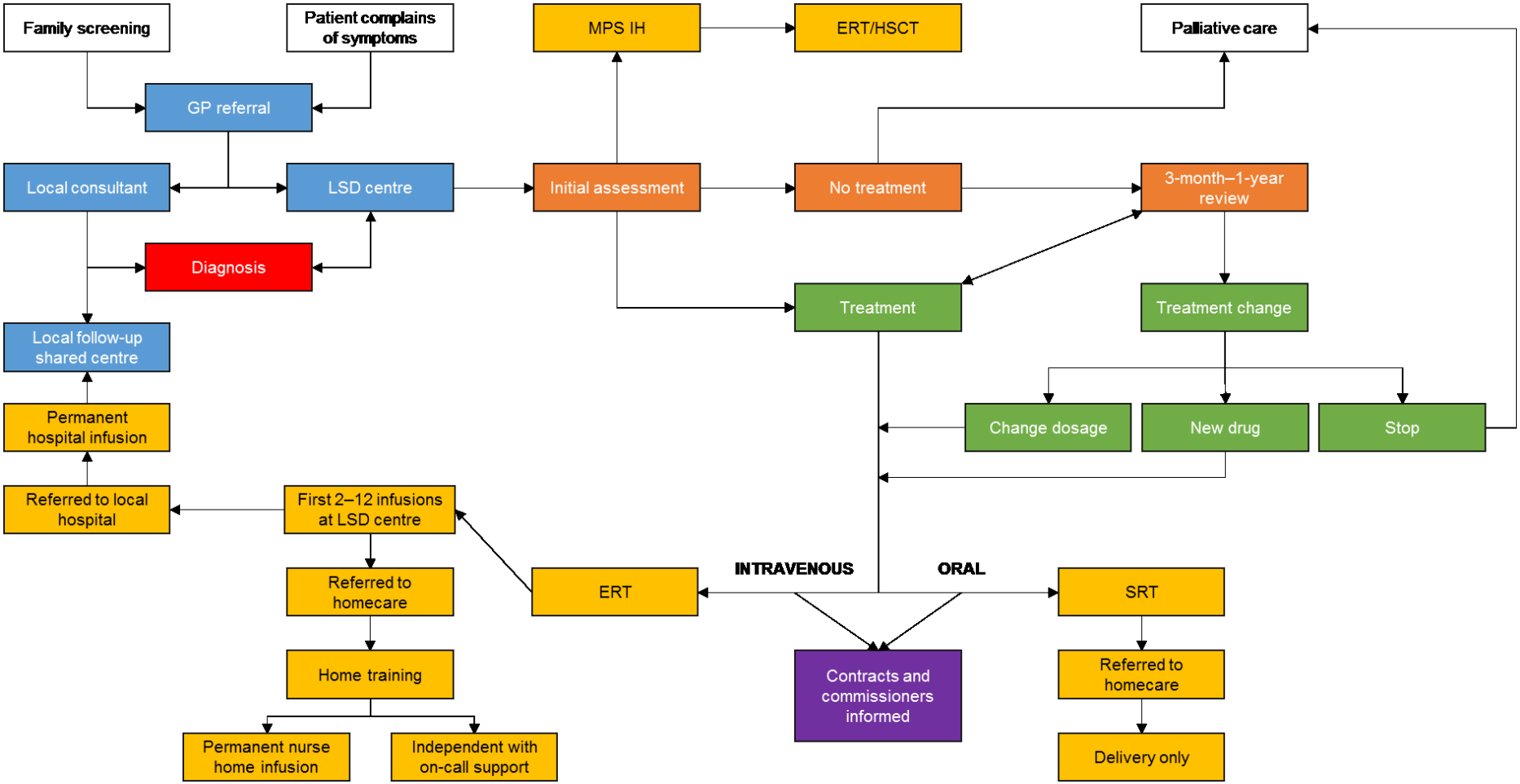
- Prompt and accurate diagnosis

- Assessment and treatment at designated LSD specialist centres by appropriately trained, multi-disciplinary teams (Figure 2)
- Management under shared protocols between designated centres and local hospitals
- Appropriate disease-specific treatment – HSCT, ERT or substrate replacement therapy (SRT)
    - For LSDs untreated with HSCT, ERT or SRT, palliative care should be provided
- Regular monitoring of the condition and response to therapy; patients should be discontinued from therapies where no benefit is received
- Opportunity for patients, parents and advocacy groups to be involved in improving the quality of the service
- Equality of management across centres, treatment protocols, and common quality standards

For adult patients, the designated LSD specialist centres are expected to provide and coordinate the full range of services for the management of LSDs. For patients diagnosed in childhood, a transition process should be in place in order to support the move from paediatric to adult services. The LSD service for adults (delivered by designated LSD specialist centres) is expected to provide:

- Disease-specific treatment where available and the highest possible standard of care for LSDs without a treatment option (i.e. best supportive care [BSC])
    - LSD specialist centres are responsible for the initiation, maintenance and termination of specific LSD therapy (Figure 2)
    - ERT therapy commences at a LSD specialist centre; however, patients can receive home infusions
- Assessment and periodic monitoring of patients
- Specialist input (e.g. cardiology, orthopaedics, ears, nose and throat, etc.), in conjunction with LSD centres, either at specialist units or local to the patient
- Shared care between LSD centres and hospitals local to the patient

Figure 2: Lysosomal storage disorder service care pathway



Source: Adapted from NHS Standard Contract for LSD service (40)
Abbreviations: ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; LSD, lysosomal storage disorder; MPS IH, severe mucopolysaccharidosis I; SRT, substrate replacement therapy.

8.2.2 *Specialist centres for lysosomal storage disorders in the UK*

In England, patients with LSDs (including AM) are managed at designated LSD specialist centres in Birmingham (one adult centre and one paediatric centre), Cambridge (one adult centre), London (two adult centres and one paediatric centre), and Manchester (one adult centre and one paediatric centre). As shown in Figure 2, these designated LSD specialist centres are responsible for the assessment of patients and the initiation and monitoring of treatments.

Wales, Scotland and Northern Ireland have designated specialist hospitals for managing metabolic diseases. The designated specialist hospitals are in Cardiff (Wales), Glasgow and Edinburgh (Scotland) and Belfast (Northern Ireland).

8.2.3 *Diagnosis*

As the clinical features and symptoms of AM overlap with other LSDs (43), diagnosis of AM relies on the use of laboratory measures (2). The methods used to aid diagnosis of AM can include (2):

- Measuring oligosaccharides: elevated levels of oligosaccharides are suggestive of AM but not diagnostic on its own. This is typically measured in the urine (2), but can also be assessed in the serum as performed during the rhLAMAN clinical trial programme; in the rhLAMAN clinical trial programme, values for serum oligosaccharides that were ≥4 µmol/L were considered high (1, 19-22)
- Acid α-mannosidase activity is assessed in leukocytes or fibroblasts. In patients with AM, the activity of α-mannosidase will typically be 5–15% of normal activity (2)
    - This residual activity is actually due to other α-mannosidases found in different sites of the cell and the true activity of lysosomal α-mannosidase ranges from 0.1% to 1.3% of normal activity (2); however, the test for the specific activity of lysosomal α-mannosidase is not routinely performed (2)
- Genetic testing with detection of two copies of an AM-causing mutation in MAN2B1 confirming a diagnosis of AM

In line with the LSD pathway of care, tertiary paediatric centres investigating abnormal development may make the diagnosis and refer the patient to the LSD specialist centre (Figure 2). Patients can also be diagnosed by community paediatricians assessing children with developmental delay. They would typically send the results to a reference laboratory before subsequently referring the patient to a tertiary centre or LSD specialist centre. In adults, a likely route to diagnosis occurs following a suspicion of a genetic/biochemical defect in a patient within a community or outpatient department. A biochemical screen will be requested, which will lead to a definitive genetic diagnosis. The patient will then be referred to an LSD specialist centre.

8.2.4 *Best supportive care*

There is currently no pharmacological disease-modifying therapy available for patients with AM and only a small number of patients may be considered for HSCT (Section 8.3.3). Therefore, the majority of patients with AM will receive BSC, which is typically a symptom-led approach, addressing symptoms and clinical features as they arise (7). In the absence of UK-specific guidelines, Chiesi consulted UK KOLs in structured

interviews (Section 12.2.5) on the definition of BSC for patients with AM. In the UK, BSC was defined by the KOLs as a "needs-based approach to treatment, dealing with symptoms as they arise" (17) and may include a range of treatments such as:

- Provision of walking aids and wheelchairs, and home adaptations
- Aggressive management of infections
- Major surgical interventions (ventriculoperitoneal shunts, cervical spine decompression, joint replacement)
- Minor surgical intervention (tonsillectomy/adenoidectomy, grommet surgery [insertion and removal], umbilical/inguinal hernia repair, carpal tunnel release surgery, feeding tube insertion)
- Physiotherapy, including hydrotherapy
- Ventilation support
- General treatment of comorbidities
- Supportive measurements at home (hoists etc.)

Monitoring and preventative measures are also important to detect or manage emerging problems. These can include:

- MRI of brain and spine
- Skeletal surveys and respiratory function testing (routinely done in paediatric patients)
- Cardiac echo/ECG (typically done in older/adult patients)
- Prophylactic use of antibiotics

Given the range of care required, BSC typically involves a multidisciplinary team. This team includes (but not limited to) metabolic consultants, ear, nose, and throat (ENT) consultants, cardiologists, orthopaedic surgeons, neurologists, paediatricians, ophthalmologists, respiratory specialists, allied-health care teams (physiotherapist, speech and language therapists, occupational therapists), dieticians, dentists and mental health specialists (e.g. counsellors/clinical psychologists/educational psychologists). In the UK, the metabolic consultant (with specialist knowledge of AM) is likely to act as the primary physician for the patient, but will liaise with other specialities in order to manage the patient's care; the consultant may also attend the patient's appointments at specialised clinics in order to provide expert advice on AM. Interaction with the healthcare system is most frequent in paediatric patients and multidisciplinary care is disability-dependent; patients who have progressed to later stages of the disease (i.e. patients with severe immobility who require full time care and transfer support) are typically cared for in the primary care/community healthcare settings or a 24-hour care institution.

As the only pharmacological disease-modifying therapy available, it is anticipated that velmanase alfa will be initiated as soon as clinically possible after a diagnosis of AM is made in patients alongside BSC, taking into consideration the eligibility and 'start and stop' criteria defined in Section 10.1.16.

8.3 *Describe any issues relating to current clinical practice, including any uncertainty about best practice.*

8.3.1 *Standard of care*

For LSDs such as Fabry disease, Gaucher disease, Pompe disease and mucopolysaccharidoses, the LSD service specification for England (Section 8.2) is combined with a number of professional guidelines (UK, European and international) in order to provide a more specific framework for the treatment of these LSDs. In contrast, as there are no AM-specific guidelines available, the LSD service specification only provides a basic framework for the management of AM. Therefore, there is no formal standard of care for AM and the management of patients is largely defined and led by each individual specialist clinician, which may lead to inconsistencies in the care of patients with AM, including the definition of BSC. While the approach to treatment will naturally vary for each patient (due to the heterogeneity of the disease), certain symptoms (such as hearing and cognitive impairment) are consistent findings that may benefit from a defined treatment framework. Furthermore, knowledge of AM remains limited in England and the absence of any formal treatment guideline or framework for AM may lead to the disease being underdiagnosed. This could result in the treatment of patients without specialist coordination, which could increase the use of healthcare resources.

8.3.2 *Provision of paediatric and adult services*

Due to the rarity of the disease, the provision of services to both paediatric and adult patients varies between LSD specialist centres and regions. Similar to that stated by the LSD service specification, a paediatric patient with AM is predominantly treated by an individual paediatrician (with specialist knowledge of AM) in one hospital (18). Adult patients will also have access to a primary point of contact with specialist knowledge of AM. In order to provide multidisciplinary care, both paediatric and adult patients will be referred to a number of different specialists, such as ENT or respiratory consultants (18). While some centres may operate joint clinics (where a patient is seen by several specialists), patients may also be required to travel to several different sites or geographical areas in order to receive holistic care (18).

Patients receiving paediatric services will eventually have to transition to adult services. The LSD service specification provides a general framework for this transition, which includes (40):

- A discussion around transition at least a year before transfer to allow time to resolve concerns the young person may have
- Joint clinics where the young person and family can meet the paediatrician and adult physician together
- Opportunities for the family to meet other members of the adult LSD team

However, the transition between paediatric and adult services may be problematic for patients who require additional services in the community, such as occupational therapy or use of equipment within the home, as the support available to adults is reduced compared with paediatrics (18). For patients with psychological symptoms, access to mental health services (with relevant expertise) is also very limited for adults (18).

8.3.3 *Allogeneic haematopoietic stem cell transplantation*

As stated in the decision problem, allogeneic HSCT may be a treatment option for patients where clinically indicated; however, following discussions (via advisory boards and interviews) with UK KOLs, it is evident that there is a discordance between the population that would be suitable for HSCT and those that would be eligible to receive velmanase alfa (based on the expected licensed indication) (17, 18).

The expert feedback received indicated that allogeneic HSCT is typically reserved for AM patients with extensive disease presenting in early infancy (aged <5 years); a form of disease that is often lethal soon thereafter (18). The ideal age for transplant is <2 years old and only in exceptional circumstances would allogeneic HSCT be considered in patients >5 years old (18). This approach is used because the risk of morbidity and mortality after allogeneic HSCT increases with age – from approximately 1 in 6 in patients aged <5 years to 50% in adults (17, 18). Furthermore, the suitability of allogeneic HSCT also depends on the availability of a matched sibling or matched umbilical cord donor, and the absence of comorbidities/recurrent infections (17, 18).

It is recognised that there may be few instances where allogeneic HSCT is used in those aged >5 years. For example, a delay in diagnosis and the availability of a related, human leukocyte antigen (HLA)-matched donor may contribute to the suitability of allogeneic HSCT. However, as velmanase alfa is positioned in patients with AM alongside BSC for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible, allogeneic HSCT is not considered as a relevant comparator for velmanase alfa.

Overall, there is limited evidence on the safety and efficacy of allogeneic HSCT in the treatment of AM. Following a clinical systematic review (see Appendix 2, Section 17.2.1), only seven studies investigating allogeneic HSCT as a treatment for AM were identified. None of the studies were randomised controlled trials (RCTs) and all studies enrolled a small sample size with a maximum of three patients aged ≥6 years old enrolled in a single study. This is in line with the UK clinical experts (18), which suggests that evidence for the use of allogeneic HSCT in patients aged ≥6 years is scarce. Of note, Broomfield et al, 2010 (44), describes a case report of two siblings with AM in the UK who received allogeneic HSCT. At the time of transplant, one was aged 6 months and the other was aged 13. In the younger sibling, transplantation was performed before any symptoms had manifested. By the age of six, the child had near-normal overall development; however, some minor skeletal and CNS problems were still present. In contrast, although some improvement in speech and a stabilisation of cerebral function was observed in the older sibling, the patient also experienced associated morbidity in the form of graft versus host disease (GVHD; mild) and respiratory distress (mild to moderate bronchiectasis). This case report suggests that the risk-benefit ratio appears to be less favourable in older patients when compared with infants.

The decision to proceed to transplant should also consider the risks/benefits for the specific patient's circumstances, the evidence base and alternative treatments available (42). Furthermore, the effectiveness and morbidity/mortality of allogeneic HSCT is impacted by the availability of a donor and the quality of the HLA matching (for example, related versus unrelated; HLA-matched vs partially HLA mismatched). Therefore, the potential benefits must be weighed against the risk of HSCT-related morbidity and

mortality (2, 5). For patients who received allogeneic HSCT, BSC will also require modification to monitor for the emergence of GVHD and to assess compliance with immunomodulation medications; these patients will also be at a higher risk of infections.

8.4 *Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.*

As the only pharmacological disease-modifying therapy available, it is anticipated that velmanase alfa will be initiated as soon as clinically possible after a diagnosis of AM is made in patients alongside BSC in whom allogenic HSCT is not suitable and/or not possible, taking into consideration the eligibility, 'start' and 'stop' criteria defined in Section 10.1.16.

Due to the once-weekly dosing of velmanase alfa by intravenous (IV) infusion, patients will initially require weekly day case visits to the nearest LSD specialist centre to receive treatment. The LSD service clinical pathway (Figure 2) outlines a minimum of 2–12 infusions before patients are referred to homecare or their local hospital to continue their weekly infusions.

Based on discussions with UK KOLs and their previous experience with ERT in LSDs (17), it is expected that patients will receive their initial infusions of velmanase alfa at an LSD specialist centre. Although the number of infusions received will depend on the individual patient's circumstances (for example, children may receive more infusions at the LSD specialist centre than adults), the maximum number of infusions received at an LSD specialist centre is likely to be 3–12. The KOLs also indicated that 98% of patients would progress to homecare administration; a small number of patients may be required to revert to hospital for treatment administrations following an infusion-related reaction (IRR; before returning to homecare after the IRRs are resolved) or may lack a suitable home setting (e.g. space, cleanliness issues, etc.).

Whilst patients receiving velmanase alfa will continue to receive BSC (i.e. patients will be managed by a multidisciplinary team adopting a symptom-led approach to care) the frequency of some aspects of BSC may differ in the long term.

8.5 *Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.*

There are no licensed pharmacologic, disease-modifying treatments for AM currently available for the population eligible to receive velmanase alfa. Currently, and despite BSC, patients are faced with a progressive condition with no possibility of improving or maintaining their current state. Consequently, the level of burden on patients and carers will only increase over time. Any disease-modifying pharmacological intervention that could help to improve or maintain the patient's condition and prevent/relieve AM-related symptoms would therefore be a meaningful advancement in the management of AM.

Enzyme-replacement therapy is a well-studied approach to the treatment of LSDs including Gaucher's, Fabry's, Pompe disease and the Mucopolysaccharidoses (MPS)

Type I, II, IVA and VI (45-51). In ERT for LSDs, a normal, active version of the impaired enzyme (in the case of AM, α-mannosidase) is introduced into the bloodstream, where it is internalised into cells and subsequently the lysosomes, allowing it to take its place in the lysosomal metabolic pathway (5). Through this, normal cellular function is restored, which may in turn improve or stabilise the symptoms of the disease. Velmanase alfa is a recombinant (genetically engineered) form of human α-mannosidase that moves the treatment of AM from symptomatic management to therapeutic intervention. The evidence base for velmanase alfa is derived from the clinical development programme that includes a Phase III, 12-month, randomised placebo controlled trial (rhLAMAN-05) and up to 48 months of follow-up data from rhLAMAN-10. The programme also represents the first attempt at assessing a pharmacological intervention in the treatment of AM. The data from rhLAMAN-10 demonstrated significant and sustained improvements from baseline to last observation (12–48 months) across a range of clinical outcomes following treatment with velmanase alfa. The clinical value of velmanase alfa was further defined in a post-hoc, multi-domain responder analysis, which demonstrated a high level of response to treatment (88% of patients) at last observation.

Whilst velmanase alfa is not a cure for this disorder, it can significantly modify or attenuate disease progression and it represents a 'step-change' in the management of AM and may deliver valuable benefits in health-related QoL to patients with AM and their carers (Section 7.2). UK KOLs considered velmanase alfa to be a 'step change' in the management of AM on the basis of its potential to change the natural course of the disease by offering improvements to patients' ambulation and/or delaying disease progression in patients (17). They also highlighted that velmanase alfa may reduce the symptom burden (particularly with respects to mobility, pain, lung function and rates of infections) experienced by patients, which in turn should improve their QoL (17). [redacted] Furthermore, the impact of small improvements should not be underestimated. For patients, even improvements in completing simple tasks that increase their independence can be life changing (such as the ability to now tie their shoe laces and get dressed independently) (14, 17). Disease improvement in patients also benefit the carers and the wider family, allowing them more time to focus on other important aspects of their lives that may be neglected through their commitment to care (14, 17). Finally, velmanase alfa will also allow healthcare professionals to offer a treatment, which will encourage pro-active management of patients and help to improve the long-term outcomes of patients.

Given the significant morbidity, mortality and unmet clinical need associated with AM, coupled with the lack of other available treatments for this ultra-rare condition, velmanase alfa was granted orphan medicinal product designation by the EU Committee for Orphan Medicinal Products in January 2005 (EU/3/04/260).

8.6 *Describe any changes to the way current services are organised or delivered as a result of introducing the technology.*

It is not anticipated that the use of velmanase alfa would require any changes to services which already exist for the provision, delivery and administration of other ERTs for other LSD conditions (see Figure 2). Should a patient choose to receive their infusions at home, [redacted] following an appropriate period of administration (3–12 infusions) within the hospital setting.

8.7 *Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.*

For IV administration of velmanase alfa, no additional requirements are anticipated over and above what be required in using a new ERT delivered via IV infusion. The recommended dose of velmanase alfa should be reconstituted as a 2 mg/mL solution and administered using an infusion set equipped with a pump and an in-line low protein-binding 0.22 µm filter. The infusion time should be a minimum of 50 minutes, with a maximum infusion rate of 25 mL/hour. For example, for an average adult weighing 63.6 kg and requiring 31.8 mL of a 2 mg/mL solution (63.6 mg), infusion should take no less than 76:19 minutes (52).

For a patient to start and continue treatment with velmanase alfa, a series of clinical measurements (serum oligosaccharides, 3-MSCT, 6-MWT, FVC, CHAQ disability index, CHAQ pain [VAS]) should be made at baseline and at 12-monthly intervals (Section 10.1.16).

8.8 *Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.*

Velmanase alfa does not require any additional facilities, technologies or infrastructure other than the provision of bed space during initial infusions. Should a patient choose to receive their infusions at home [redacted]

8.9 *Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.*

Evidence from the velmanase alfa clinical development programme suggested that seven out of ten patients (70%), who required a device or third-party assistance for ambulation at baseline, became independent of assistance following treatment with velmanase alfa (Section 9.6.1.2). In particular, two paediatric patients and one adult forced to adopt a wheelchair for long distance mobility/functional capacity at baseline discontinued use at last observation. While three patients became dependent on assistance/aids for ambulation at last observation, one patient (adult) had an amputation and required a walker and a wheelchair post-surgery. For the two remaining patients (paediatric), the rationale for ambulatory assistance from another person was not defined, and both paediatric patients improved in overall function as measured by a

reduction in the CHAQ disability index. Overall, treatment with velmanase alfa may reduce or delay the need for ambulatory assistance/aids, including wheelchairs and modifications to the home, and potentially decrease the burden on the carer and auxiliary NHS services.

UK KOLs suggested that the improvement in lung function following treatment with velmanase alfa may help to reduce the rate of infections (17). [redacted] In particular, a reduction in severe infections may reduce the rate of hospitalisation and time spent in intensive care units (17). The UK KOLs also indicated that improved lung function (as a result of velmanase alfa) would increase the time to ventilatory support and reduce the level of support required (17).

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

Summary of clinical efficacy

- The efficacy and safety of velmanase alfa has been demonstrated in three Phase I/II trials (rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04) and two Phase III trials (rhLAMAN-05 and rhLAMAN-10), with a total patient population of 34
- The results from rhLAMAN-05 and rhLAMAN-10 are the most relevant to the decision problem:
    - rhLAMAN-05 provides data on the relative 12-month efficacy and safety of velmanase alfa (N=15) compared with placebo (N=10)
    - rhLAMAN-10 provides data on the efficacy and safety of velmanase alfa (N=33) for up to 48 months
- In view of the multiple organ systems adversely affected in alpha-mannosidosis (AM), and in response to a request by the European Medicines Agency (EMA), a post-hoc, multi-domain responder analysis combining multiple endpoints into single domains representing clinically important effects was conducted for rhLAMAN-05 and rhLAMAN-10. These data formed part of the EMA regulatory submission for velmanase alfa

rhLAMAN-05 (Phase III)

- rhLAMAN-05 was a 12-month placebo-controlled trial that assessed the efficacy and safety of velmanase alfa in paediatric (aged 6 years to <18 years; n=12) and adult patients (aged ≥18 years; n=13)
- The primary objective of rhLAMAN-05 was to evaluate the efficacy and safety of velmanase alfa compared with placebo in patients with AM. The co-primary endpoints were:
    - change from baseline to Month 12 in serum oligosaccharides
    - change from baseline to Month 12 in the 3-MSCT
- Treatment with velmanase alfa effectively targeted the underlying cause of AM, as demonstrated by statistically significant improvements in serum oligosaccharide clearance compared with placebo: at Month 12, the adjusted mean relative change from baseline was –77.60% (95% confidence interval [CI]:

–81.58, –72.76) in the velmanase alfa group and –24.14% (95% CI: –40.31, –3.59) in the placebo group. The adjusted mean difference (relative change from baseline) for velmanase alfa vs placebo was –70.47% (95% CI: –8.35, –59.72; p<0.001)

- Velmanase alfa demonstrated a trend towards improved symptom control (not statistically significant), as shown by numerical differences in favour of velmanase alfa over placebo for outcomes of mobility/functional capacity (the 3-minute stair climb test [3-MSCT] and the 6-minute walk test 6-MWT) and lung function
- Overall, velmanase alfa was well tolerated. No special safety concerns were raised and the long-term safety profile of velmanase alfa was found to be acceptable

rhLAMAN-10 (Phase III)

- In rhLAMAN-10, long-term data were captured for patients currently enrolled in the compassionate use programme and combined with all available data across the rhLAMAN clinical trial programme (including after-trial studies) as part of an integrated analysis. This analysis was performed to provide as comprehensive a data set as possible given the small potential patient pool for AM. The maximum follow-up time was 48 months (n=9) and the co-primary endpoints for rhLAMAN-10 were:
    - change from baseline in serum oligosaccharides
    - change from baseline in the 3-MSCT
- Overall, treatment with velmanase alfa resulted in a statistically significant and sustained reduction in serum oligosaccharides (–62.8%; 95% CI: –74.7, –50.8; p<0.001) and a statistically significant increase in the 3-MSCT (13.77%; 95% CI: 4.61, 22.92; p=0.004) from baseline to last observation
- Treatment with velmanase alfa also resulted in greater symptom control over time as shown by statistically significant improvements from baseline in mobility/functional capacity, lung, motor and cognitive function, immunological profile (as measured by serum IgG), and quality of life (QoL)
- Of the ten patients who required a device or third-party assistance for ambulation at baseline, seven (70%) became independent of assistance at last observation. In particular, two paediatric patients and one adult who required a wheelchair for long-distance mobility at baseline discontinued use at last observation
- Long-term treatment with velmanase alfa was generally well tolerated. Overall, 19 infusion-related reaction (IRR) events were recorded in three patients, of which 14 occurred in a single patient. All IRRs were mild or moderate in intensity and were resolved

Post-hoc, multi-domain responder analysis

- To further explore the clinical value of velmanase alfa, a post-hoc, multi-domain responder analysis was performed. Key endpoints were grouped into three domains that reflect the pathophysiology and the burden of the disease:

- Pharmacodynamic domain: serum oligosaccharide
- Functional domain: 3-MSCT, 6-MWT and forced vital capacity (FVC) % of predicted
- QoL domain: childhood health assessment questionnaire (CHAQ) disability index and CHAQ pain (visual analogue scale [VAS])

- A patient qualified as a responder to treatment if the response criteria was reached in at least two domains; a patient was considered a responder in a domain if they showed a response for at least one efficacy parameter within that domain by achieving the adopted minimal clinically important difference (MCID) for that outcome
- Overall, 88% (100% of paediatric patients and 71% of adult patients) of patients analysed in the rhLAMAN-10 integrated data set achieved a response to velmanase alfa treatment at last observation
  - At last observation, 46% responded to all three domains, while 42% responded to two domains
- In rhLAMAN-05, 87% of patients in the velmanase alfa group achieved a response to treatment, compared with 30% in the placebo group at 12 months
  - In the velmanase alfa group, 73% responded to 2 domains, while 13% achieved a response to all 3 domains
  - No patient in the placebo group achieved a response to all 3 domains and only three (30%) patients responded to 2 domains
- Overall, the use of a two-domain responder criterion provides enough sensitivity to observe a treatment effect compared with placebo over 12 months. The higher proportion of three-domain responders at last observation in rhLAMAN-10 compared with rhLAMAN-05 (46% vs 13%) may also be indicative of benefit received from long-term treatment with velmanase alfa

Efficacy in paediatric and adult patients

- While both adult and paediatric patients receiving velmanase alfa had improvements across the majority of endpoints:
  - the difference between velmanase alfa and placebo was greater in the paediatric group (6–11 years) and adolescent group (12–17 years) than in adults (≥18 years) after 12 months of treatment with velmanase alfa (rhLAMAN-05)
  - greater changes from baseline to last observation (12–48 months of treatment) were observed in paediatric patients compared with adults (rhLAMAN-10)
- This suggests that velmanase alfa is of particular value in patients who start treatment at <18 years of age; therefore, it may be important to start treatment with velmanase alfa as early as possible, following diagnosis of AM
- Disease improvement with velmanase alfa was observed in adult patients and was most evident in the assessment of serum IgG levels and CHAQ pain (VAS),

which both improved from baseline to last observation in rhLAMAN-10. Furthermore, 71% of adults achieved a response (in the multi-domain responder analysis) to velmanase alfa treatment at last observation in rhLAMAN-10. This provides support for disease improvement with velmanase alfa in adults, as disease stabilisation is not formally captured in the multi-domain responder analysis

9.1 *Identification of studies*

9.1.1 *Published studies*

9.1.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A systematic review was conducted to identify published evidence reporting on the clinical efficacy and safety of available treatments for AM in patients aged ≥6 years.

Original systematic review

An overview of the strategies employed in the original systematic review are outlined below. Full details of the search strategy are provided in Appendix 1.

Databases searched

The following electronic databases were searched via the OVID platform on 25th January 2017:

- MEDLINE® In-Process & Other Non-Indexed Citations
- MEDLINE, 1946 to present
- Embase, 1980 to present
    - The Cochrane Library, incorporating:
    - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - The Database of Abstracts of Reviews of Effects
    - The Cochrane Central Register of Controlled Trials
    - The Health Technology Assessment (HTA) Database
    - The National Health Service Economic Evaluation Database

In addition to these databases:

- Hand-searching was used as a supplementary measure to identify further relevant studies that were not captured in the electronic database search
- Reference lists of included studies were scanned to identify potential relevant publications for inclusion

- To identify any recent studies for which there were currently no full publications, the conference proceedings were examined for relevant abstracts (and posters/slide decks, if available) from the last three years
- Submission documents from HTA agencies (NICE, SMC, Canadian Agency for Drugs and Technologies in Health [CADTH], Institut National d'Excellence en Santé et en Services Sociaux [INESSS] and the Pharmaceutical Benefits Advisory Committee [PBAC]) were reviewed for relevant data. Additional databases, as recommended by NICE, were also hand-searched

Update to systematic review

An update of the search was conducted on 31st October 2017 to identify relevant papers published post-January 2017. The search strategies used for the clinical systematic review (SR) for the updated review are detailed in Appendix 1.

9.1.2 *Unpublished studies*

9.1.2.1 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Please see Section 9.1.1.1 which describes a literature review conducted in line with NICE guidance and therefore describes retrieval of both published and unpublished evidence.

9.2 *Study selection*

Published studies

9.2.1 *Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.*

Table 4: Selection criteria used for published studies

Inclusion criteria	
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age).
Interventions	Not restricted (see Appendix 1, Section 17.1.6 for details on treatments to include).
Outcomes	Aligned to the outcomes presented in the decision problem (Table 2).
Study design	RCTs, non-RCTs, observational/real-world studies, case series and case reports
Language restrictions	Unrestricted
Search dates	Unrestricted
Exclusion criteria	
Population	Patients aged <6 years with AM (all patients were included at first pass regardless of age).
Interventions	Unrestricted
Outcomes	Publications reporting solely on outcomes outside the NICE scope were not considered relevant.
Study design	Studies not meeting the inclusion criteria for study design.
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: AM, alpha-mannosidosis.

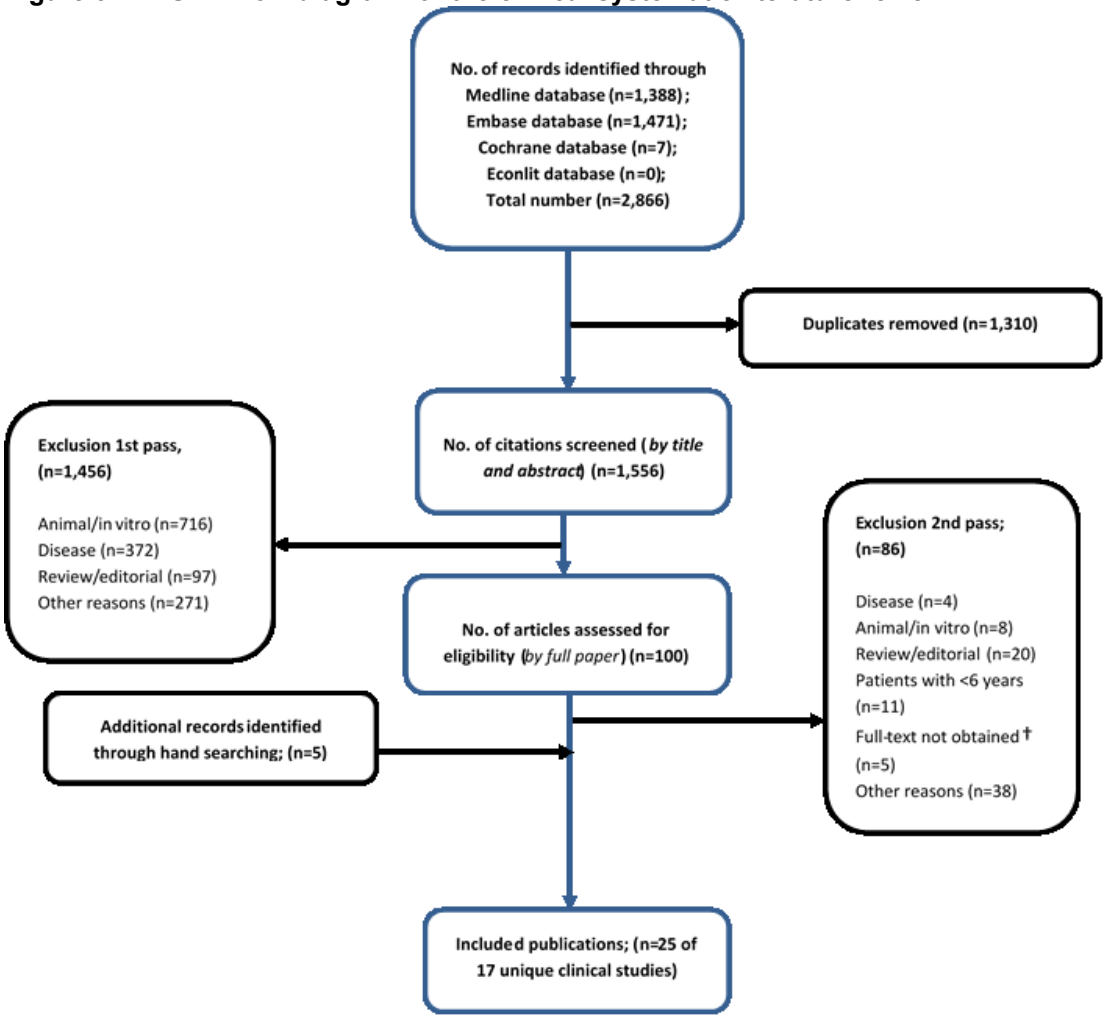
9.2.2 *Report the numbers of published studies included and excluded at each stage in an appropriate format.*

The electronic database searches identified a total of 2,866 citations. After removing duplicate papers, 1,556 titles and abstracts were screened. At this stage, a total of 1,456 articles were excluded, and 100 were deemed to be potentially relevant. Upon review of the full texts, a further 86 articles were excluded. Hand searching yielded an additional five relevant publications for inclusion. This resulted in a total of 19 publications of 16 unique clinical studies that met the eligibility criteria of the review.

In the update, 92 papers were identified through the electronic database searches. Following the removal of 27 duplicate papers, 65 citations were screened on the basis of title and abstract. At this stage, all the studies were excluded based on titles and abstracts. Hand searching yielded six relevant publications for inclusion. Therefore, a total of six publications were identified in the update that met the eligibility criteria of the review.

The overall flow of studies across the original review and the update is reported in the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram in Figure 3. A separate PRISMA for the updated review is also shown in Appendix 1, Section 17.1.7.

Figure 3: PRISMA flow diagram for the clinical systematic literature review



†It was not possible to source these publications from their internal sources or the British Library. Study authors were also contacted to obtain a copy of the full publication wherever contact details were available, but no response was received.
Studies excluded using "Other" exclusion code at 1st pass screening: Genetic/biomarker or diagnostic studies, (n=192); Study reporting only disease characteristics, (n=71); 'Non-relevant' country (Japan), (n=5); Conference abstract superseded by full paper (n=3).
Studies excluded using "Other" exclusion code at 2nd pass screening: Epidemiology/clinical studies, (n=21); Genetic/biomarker or diagnostic studies, (n=10); Study reporting only disease characteristics, (n=4); Treatment for comorbidities, (n=2); Treatment before surgical procedure, (n=1).

In addition, the company provided the clinical study reports (CSRs) for five unique clinical studies. Data from five of these studies have been published in a total of 12 publications which were identified as part of the current SR.

Unpublished studies

9.2.3 *Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.*

Please see Section 9.2.1 which describes the inclusion/exclusion criteria for both published and unpublished evidence.

9.2.4 *Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.*

Please see Section 9.2.2 which describes the flow of studies included and excluded at each stage for both published and unpublished evidence.

9.3 *Complete list of relevant studies*

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 *Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.*

Five trials investigating velmanase alfa were identified in the systematic review or by the provision of the clinical study report (CSR) by the company: A Phase I-II study, which comprised three separate trials (rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04), and two Phase III trials (rhLAMAN-05 and rhLAMAN-10). These trials were part of the velmanase alfa clinical development programme, which is described in Section 9.4. The baseline characteristics, efficacy and safety results reported in the studies identified in the clinical SR are summarised in Appendix 2 (Table 123–Table 125).

At the time of this submission, data from rhLAMAN-02 and rhLAMAN-03 were available in the full publication, Borgwardt et al, 2013 (53), which was used as the primary data source for these studies and supplemented with data from the associated CSRs. Abstracts containing data from rhLAMAN-04 (54), rhLAMAN-05 (55) and rhLAMAN-10 (32, 55-63) were also publicly available; however, as the information within these abstracts were limited, the CSRs for rhLAMAN-04, rhLAMAN-05 and rhLAMAN-10 were used as the primary data source.

Table 5: List of relevant published studies

Primary study reference(s)	Study name (acronym)	Population	Intervention	Comparator
Full text publication Borgwardt et al, 2013 (53)	NCT01268358 (rhLAMAN-02)	10 patients (aged 5–20 years) with AM	• VA 6.25 U/kg • VA 12.5 U/kg • VA 25 U/kg • VA 50 U/kg • VA 100 U/kg	Change from baseline (no active or placebo comparator)
Full text publication Borgwardt et al, 2013 (53)	NCT01285700 (rhLAMAN-03)	10 patients aged 5–20 years) with AM	• VA 25 U/kg • VA 50 U/kg	Change from baseline (no active or placebo comparator)
Abstract Borgwardt et al, 2014 (54)	NCT01681940 (rhLAMAN-04)	Nine patients (aged 5–20 years) with AM	VA 1 mg/kg	Change from baseline (no active or placebo comparator)
Abstract Guffon et al, 2017 (55)	NCT01681953 (rhLAMAN-05)	25 patients with AM • VA (n=15) ○ 7 paediatrics (aged 5–<18 years) ○ 8 adults • Placebo (n=10) ○ 5 paediatrics (aged 5–<18 years) 5 adults	VA 1 mg/kg	Placebo
Abstract Guffon et al, 2017 (55) Borgwardt 2017 (56) Borgwardt 2017 (32) Borgwardt 2017 (57)	NCT02478840 (rhLAMAN-10)	33 patients with AM: • 19 paediatrics 14 adults	VA 1 mg/kg	Change from baseline (no active or placebo comparator)

Primary study reference(s)	Study name (acronym)	Population	Intervention	Comparator
Lund 2017 (58) Harmatz 2017 (59) Borgwardt 2017 (60) Cattaneo 2016 (61) Ardigo 2016 (62) Borgwardt 2016 (63)				

Abbreviations: AM, alpha-mannosidosis; CSR, clinical summary report; VA, velmanase alfa.

Table 6: List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
CSR (19)	NCT01268358 (rhLAMAN-02)	10 patients (aged 5–20 years) with AM	• 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)
CSR (20)	NCT01285700 (rhLAMAN-03)	10 patients aged 5–20 years) with AM	• VA 25 U/kg • VA 50 U/kg	Change from baseline (no active or placebo comparator)
CSR (21)	NCT01681940 (rhLAMAN-04)	Nine patients (aged 5–20 years) with AM	VA 1 mg/kg	Change from baseline (no active or placebo comparator)
CSR (22)	NCT01681953 (rhLAMAN-05)	25 patients with AM • VA (n=15) ○ 7 paediatrics (aged 5–<18 years) ○ 8 adults • Placebo (n=10) ○ 5 paediatrics (aged 5–<18 years) ○ 5 adults	VA 1 mg/kg	Placebo
CSR (1)	NCT02478840 (rhLAMAN-10)	33 patients with AM: • 19 paediatrics • 14 adults	VA 1 mg/kg	Change from baseline (no active or placebo comparator)

Abbreviations: AM, alpha-mannosidosis; CSR, clinical summary report; VA, velmanase alfa.

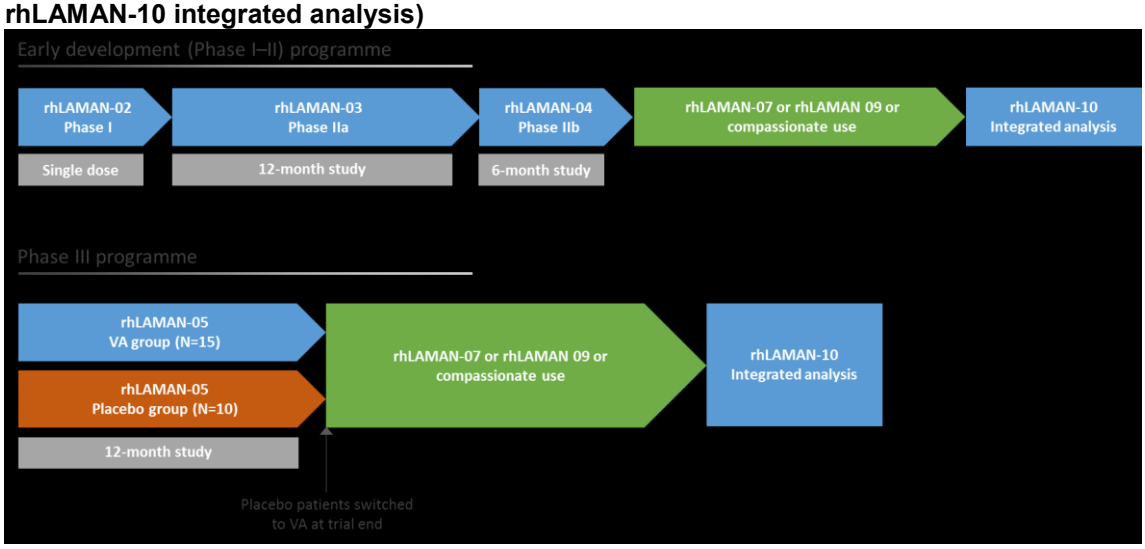
9.3.2 *State the rationale behind excluding any of the published studies listed in tables C3 and C4.*

None of the relevant studies have been excluded.

9.4 *Summary of methodology of relevant studies*

The clinical development programme for velmanase alfa comprised a series of Phase I, II and III clinical trials in patients with AM. All patients were enrolled in one of two parental clinical trials: Phase I/II trial (rhLAMAN-02/03/04) or rhLAMAN-05 (a 12-month Phase III trial). Figure 4 shows a schematic of the velmanase alfa clinical development programme.

Figure 4: Schematic of the velmanase alfa clinical development programme (Phase I to rhLAMAN-10 integrated analysis)



Abbreviations: VA, velmanase alfa.

Patients enrolled in rhLAMAN-02 were assigned to one of five dose groups (6.25 U/kg, 12.5 U/kg, 25 U/kg, 50 U/kg or 100 U/kg), where they would receive a minimum of one dose. Infusions commenced with the lowest dose (6.25 U/kg), with patients in the next dose group (12.5 U/kg) receiving their first dose of velmanase alfa a week (± two days) later and so on. Patients continued receiving weekly doses of velmanase alfa until patients in the highest dose group (100 U/kg) had received their first dose. Therefore, the maximum number of doses received in rhLAMAN 02 was five; up to five additional infusions were allowed if the following study (rhLAMAN-03) was delayed. Patients then progressed to the 6-month (with a 6-month extension period) Phase IIa trial (rhLAMAN-03) and subsequently the 6-month Phase IIb trial (rhLAMAN-04). Together, rhLAMAN-03 (25 U/kg and 50 U/kg of velmanase alfa) and rhLAMAN-04 (1 mg/mL [31.25 U/kg)] of velmanase alfa) covered 18 months of active treatment. At the end of rhLAMAN-04, patients were eligible to receive velmanase alfa in either an after-trial study (rhLAMAN-07 or rhLAMAN-09) or in the compassionate use programme as per requirements from national authorities in the different European countries. The after-trial studies rhLAMAN-07 and rhLAMAN-09 involved annual centralised efficacy assessments, whereas no efficacy assessments were collected in the compassionate use programme. Patients who were enrolled in the rhLAMAN-05 Phase III trial were randomised 3:2 to receive active treatment (1 mg/kg) or placebo. After 12 months,

patients in both the active and placebo arm were eligible to receive velmanase alfa in rhLAMAN 07, rhLAMAN-09 or the compassionate use programme. Overall, 34 patients (with 35 patient identifiers) were enrolled in these rhLAMAN trials – one patient (patient 403) withdrew from rhLAMAN-03 and was subsequently enrolled in rhLAMAN-05 as patient 520; consequently, this patient has two patient identifiers.

To address the need for long-term data, patients receiving velmanase alfa in the compassionate use programme were enrolled in rhLAMAN-10. A one-week clinical evaluation visit (CEV) was scheduled per the time point the patient attended the last assessment visit in the previous trial. At the same time, patients enrolled in rhLAMAN-07 and rhLAMAN-09 undertook a CEV as part of their respective studies. Data from the CEVs (database of rhLAMAN-10) were integrated with the databases of rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-07 and rhLAMAN-09 to form the rhLAMAN-10 integrated data set. As the rhLAMAN-07 and rhLAMAN-09 trials were ongoing at the time of analysis in rhLAMAN-10, the cut-off date was defined as “the end date of the CEV in rhLAMAN 07, rhLAMAN-09 and rhLAMAN-10”. At the time of analysis, patients included in the rhLAMAN-10 integrated data set analysis were expected to have follow-up times ranging from a minimum of 1 year to a maximum of 4 years.

While a data cut from rhLAMAN-07 and 09 was included in the rhLAMAN-10 integrated data set, these studies are currently ongoing and are not reported individually in the timeframe of this HST evaluation.

Description of clinical assessments

The lack of α-mannosidase activity results in impaired cellular function and organ toxicity due to reduced oligosaccharide clearance, which manifests as a wide range of symptoms affecting multiple systems (5). Accordingly, a range of tests were employed as endpoints throughout the rhLAMAN clinical trial programme, which assessed the key systems affected in AM. These tests were selected on the basis of the literature from other similar indications and also informed from the natural history study (12) and via agreement with the EMA. An overview of these tests (including the relevance to the decision problem) are provided in Table 7 and in the following section.

Table 7: Overview of tests used in the rhLAMAN clinical trial programme

Relevance to decision problem	Test used and description	Relation to AM	Direction of effect
Assessment of serum oligosaccharides	The levels of oligosaccharides in serum are measured to evaluate VA activity and its efficacy in clearing oligosaccharides.	Patients with AM have increased levels of oligosaccharides due to the lack of activity of α-mannosidase (10). Enzyme replacement therapy with VA may restore oligosaccharide clearance.	A decrease in values represents an improvement.
Infection (biomarker)	Assessment of serum IgG.	AM is associated with immunodeficiency which leads to an increase in infections (33). Treatment with VA may restore levels of serum IgG, which may improve the immune function of patients.	An increase in values represents an improvement.
Mobility/functional capacity	3-MSCT – evaluation of the number of steps climbed in 3 minutes to assess mobility/functional capacity. 6-MWT – evaluation of the distanced walked in 6 minutes to assess mobility/functional capacity.	Due to the array of symptoms present (including skeletal abnormalities and impaired motor function), patients with AM have reduced mobility/functional capacity (5). This includes an ability to walk (7). Treatment with VA may help to restore mobility/functional capacity.	An increase in 3-MSCT scores and an increase in 6-MWT scores represents an improvement.
Lung function	Assessment of FVC (L and % of predicted), FEV_1 (L and % of predicted) and PEF (L/s) to evaluate lung function.	α-mannosidase is highly expressed in the lungs and repeated lung infections are thought to contribute to the impaired lung function observed in AM patients (32). Treatment with VA may help to restore normal lung function; improvement in lung function may also result from improvements in skeletal damage.	An increase in age- and height-adjusted values represents an improvement.
Quality of life	Evaluation of QoL using CHAQ and EQ-5D (assessments were completed by parent/caregiver on behalf of patient, i.e. indirect measures only).	Patients with AM may have a reduced QoL. If treatment with VA reduces symptom burden, patients may experience a better QoL.	A decrease in CHAQ values represents an improvement. An increase in EQ-5D values represents an improvement.
Motor function	BOT-2 assessment to evaluate motor skills.	AM is known to affect areas of the brain involved in motor function and muscle coordination (7). Treatment	An age-adjusted increase in values

Relevance to decision problem	Test used and description	Relation to AM	Direction of effect
		with VA may help improve these faculties.	represents an improvement.
Cognitive function	Leiter-R test to assess cognitive ability.	Patients with AM typically have mild to moderate cognitive impairment (7). Treatment with VA may result in improvements in cognitive ability.	An age-adjusted increase in values represents an improvement.
Hearing	PTA to assess hearing loss.	Hearing loss is seen in all patients with AM and is caused by a combination of conductive hearing loss (due to recurrent infections) and sensorineural hearing loss (due to damage to the middle ear) (5). Treatment with VA may help to improve hearing.	A decrease in values represents an improvement.

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AM, alpha-mannosidosis; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, Childhood health assessment questionnaire; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; PTA, pure tone audiometry; QoL, quality of life; VA, velmanase alfa.

Biomarkers – serum oligosaccharides and serum IgG

Due to the loss of α-mannosidase activity, patients with AM accumulate mannose-rich oligosaccharides throughout the body, including the serum. Therefore, a reduction of serum oligosaccharide content in serum after treatment with velmanase alfa is an important biomarker that can be used to assess the efficacy of velmanase alfa in AM patients. In the natural history study of AM (12), low oligosaccharide levels (measured in the urine) corresponded to a longer walking distance (6-MWT) and more steps climbed (3-MSCT), suggesting that the level of oligosaccharides may be clinically relevant. Change in serum oligosaccharides, rather than urine oligosaccharides, was used as a primary endpoint in the rhLAMAN trials. It was considered logistically easier to measure serum oligosaccharides in the context of centralised visits, as the collection of 24-hour urine samples was not reliable and associated with low quality data (18).

Patients with AM also suffer from recurrent infections, suggestive of immunodeficiency (33). Immunoglobulins play a major role in adaptive immunity (64). In particular, serum IgG levels comprise 70–80% of the total serum immunoglobulin content and low levels of serum IgG are associated with an increased risk of infections (64). Serum IgG levels were measured to assess the level of immunodeficiency, with an increase in levels representing an improvement. The biomarker of serum IgG is well accepted as a surrogate for humoral deficiency, and for patients with hypogammaglobulinaemia, and the standard therapy is replacement with immunoglobulins (65).

Mobility/functional capacity – 3-MSCT and 6-MWT

Patients with AM have reduced mobility/functional capacity, as demonstrated in a natural history study using the 3-MSCT and 6-MWT (5, 12). The 3-MSCT and 6-MWT have been

widely adopted to assess endurance in other lysosomal storage disorders (66, 67) and results have been used as clinical endpoints to support the approval of ERT products for mucopolysaccharidosis type 1 (MPS I), MPS II, MPS VI, and MPS IVA (68).

The 3-MSCT is an endurance test that evaluates the number of steps climbed in three minutes. Advantages of the 3-MSCT include the ability to measure effects on multiple systems and highlight the interactions between limiting factors such as the musculoskeletal, neurological and cardiorespiratory systems (69). Stairs are also an excellent functional assessment measure as they are relevant to people's activities of daily living and have been related to independence and community participation (69). In addition, stair climbing requires a greater range of motion from the joints of the lower limbs and greater muscle strength, when compared with walking (69). The 3-MSCT was administered in the rhLAMAN trials in accordance with trial protocol guidelines (Bolton et al, 1987 and Holden et al, 1992 (70, 71)) by a trained physiotherapist and an increase in the number of stairs climbed represents an improvement. Two tests were performed on different days, and the better result of the two tests was used.

The 6-MWT is another frequently used indicator of functional exercise capacity which measures the distance that a patient can walk on a flat, hard surface (back and forth in a 50 m hospital hall) in six minutes. It evaluates the global and integrated responses of all systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. The 6-MWT was administered to all patients by a trained physiotherapist and an increase in the distance walked represented an improvement. Two tests were performed on different days and the better result of the two tests was used. The test was performed in accordance with American Thoracic Society standards (72).

Both the 3-MSCT and 6-MWT have limitations. In particular, the assessments are effort-dependent, which could be problematic in paediatric or cognitively-impaired patients whose performance is often influenced by their developmental stage, understanding of the instructions, and willingness to cooperate. Furthermore, while verbal encouragement is allowed for both tests, no physical assistance may be provided to patients during the 3-MSCT; for the 6-MWT, evaluators do not normally walk with the patient to avoid setting a walking pace (73, 74). The level of experience that patients have with stairs may also differ, depending on whether there are stairs in their home; the 3-MSCT would therefore be biased towards patients with more experience of stairs. The same walking track or stair case is used for all patients and the evaluator conducting either the 3-MSCT or the 6-MWT should be the same throughout (73, 74).

Lung function – PFT endpoints

Patients with AM may have reduced lung function, typically due to a restrictive ventilatory defect (5). To evaluate lung function, pulmonary function tests (PFTs) were completed for all patients using spirometry in accordance with the American Thoracic Society and European Respiratory Society Statement (75). Lung function measurements are related to body size and age, and reference values are important for interpreting PFT results and distinguishing between healthy and impaired lungs (76). As over half the population in the rhLAMAN clinical trial programme were paediatric patients at enrolment, a reference value for growing lungs was used. This use of reference values helps to assist

the interpretation of PFT results in the context of natural improvements in lung function due to growth during childhood; lung function increases 20-fold during the first 10 years of life (76, 77). The parameters measured were FVC, forced expiratory volume in 1 second (FEV_1; both as a percentage of predicted and in litres) and peak expiratory flow (PEF; L/s). The best result of three tests was used. An age- and height-adjusted increase in values represents an improvement in lung function. All spirometry curves were reviewed blind by a pulmonologist for quality evaluation. PFT values judged as not reliable due to poor quality were excluded from the analysis.

Quality of life – CHAQ and EQ-5D

All patients' legally authorised guardian(s) were asked to complete the following CHAQ topics: dressing and personal care, getting up, eating, walking, hygiene, reach, grip, activities, pain (VAS), and general evaluation (VAS). The score for each question in the CHAQ was based on the following validated scoring system:

0. Without any difficulty
1. With some difficulty
2. With much difficulty
3. Unable to do

For each category the 2–5 items within the category were averaged for the summary tabulation. Discomfort is determined by the presence of pain measured on a 100 mm long visual analogue scale (VAS) with 'no pain' or 0 at one end and 'very severe pain' or 100 at the other end.

The CHAQ is normally used to assess QoL in children and has been previously used for assessing QoL in patients with LSDs (66). The CHAQ is also frequently used to assess physical function and activities of daily living in rheumatology; the challenges faced by children with arthritis or other chronic musculoskeletal conditions may be similar to patients with AM. Although the majority of patients were aged <18 years at the time of enrolment in the rhLAMAN trials, approximately 40% of patients were adults. However, the CHAQ was still considered appropriate for use, as all patients were expected to have a low equivalent age; ultimately, the equivalent age of the trial population was <18 years old. As such, the CHAQ was considered suitable for adult patients with AM. Additional advantages that support the use of the CHAQ in the rhLAMAN clinical trial programme include easy administration, minimal respondent burden and a strong correlation between parent and child responses (78). This correlation is important given the role of parents/caregivers in completing the questionnaire. For CHAQ disability index and CHAQ Pain (VAS), a decrease in scores represents an improvement.

The EQ-5D questionnaire was also completed by the patients' legally authorised guardian(s). The topics were mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A visual analogue scale (EQ VAS) score for general evaluation of health was also used. The EQ-5D questionnaire is a simple, well-validated, generic measure of health and is used frequently for both clinical and economic assessments (79). The EQ-5D questionnaire has also been previously used in the assessment of LSDs, including the effect that ERT has on QoL (80). While the questionnaire can provide

a broad overview of patient QoL, it is less sensitive to smaller changes, which may be clinically relevant depending on the disease (80). Additionally, as four of the five domains focus on physical attributes (79), the questionnaire is less valuable in assessing the effect of cognitive impairment on QoL, which is important in AM. For EQ-5D (Index and EQ VAS), an increase in scores represents an improvement.

Motor function – BOT-2

The Bruininks-Oseretsky test of motor proficiency 2nd edition (BOT-2) is a widely used test for evaluating motor deficits in children and adolescents with disabilities such as cognitive impairment, developmental coordination disorder, autism spectrum disorder, attention deficit hyperactivity disorder, and cerebral palsy (81-83). In particular, BOT-2 was used because it measures key impairments that are found in AM. The test is divided into four domains, with each domain comprising two subtests (Table 8).

Table 8: BOT-2 domains and subtests

Domain	Subtest	
Fine manual control	Fine motor precision	Fine motor integration
Manual coordination	Manual dexterity	Upper limb coordination
Body coordination	Bilateral coordination	Balance
Strength and agility	Running speed and agility	Strength†

Abbreviations: BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition.
†Not collected in the rhLAMAN trials.

Composite point scores can be calculated from the subtest point scores for each domain and the total point score is derived from the composite point scores from the four domains. Due to the characteristics of the patient population, scores for the subtest 'strength' were not collected during the rhLAMAN trials; therefore, the domain 'strength and agility' is represented by the 'running speed and agility' subtest only. The BOT-2 was administered to all patients by a trained physiotherapist and an occupational therapist. An age-adjusted increase in total and/or domain point scores represents an improvement in skill acquisition.

Subtest total point scores can also be converted to age equivalent scores, which indicate the average age at which healthy children typically achieve the raw score, and to scale scores which reflect the patient's performance relative to healthy, same-aged peers (presented in rhLAMAN-10). The normative mean (standard deviation [SD]) for the BOT-2 scaled scores is 15 (5). Normative data for comparison are only available on the BOT-2 until 21 years of age. An increase in age equivalent values indicates skill acquisition. A stable or increasing scale score also indicates skill acquisition because the children in the normative comparison sample are continuing to gain skills and the reference skill set for comparison is different at every age. An increase in scale score indicates a reduction in the delay or difference between the treated group and normal healthy peers. A stable scale score indicates continued skill acquisition at a rate similar to children in the same age group in the normative sample and no progression in the level of developmental delay relative to normal healthy peers.

Cognitive function

Almost all patients with AM develop cognitive impairment (10). Typically, patients show cognitive impairment, with IQs of 30–81 (5). To assess cognitive impairment, the Leiter-R test was used. The Leiter-R test is a non-verbal measure designed to assess intellectual ability, memory and attention. The Leiter-R consists of two standardised batteries:

1. Visualisation and reasoning (VR) subtests: Design Analogies, Figure-Ground, Form Completion, Paper Folding, Repeated Pattern and Sequential Order
2. Attention and memory (AME) subtests: Associated Pairs, Attention Divided, Attention Sustained, and Forward Memory

The Leiter-R VR battery provides an estimate of global intelligence and the AME battery is used in the interpretation of the global IQ. For both, an increase in scores represent an improvement in cognitive ability.

Hearing

Hearing loss is seen in nearly all of patients with AM and is a combination of conductive hearing loss (due to recurrent infections) and sensorineural hearing loss (due to damage to the middle ear) (5). To assess changes in hearing during treatment hearing was measured by a pure tone audiometry (PTA) test, which was performed in all patients while not wearing hearing aids. PTA was carried out using audiometer earphones in a sound-proof room. Bone conduction was used as a combined measurement for each ear and air conduction was also measured. For all PTA measures, a decrease in values represent an improvement.

9.4.1 *Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.*

9.4.1.1 Phase I-II study (rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04)

The Phase I-II study comprised three individual trials and covered 18 months of active treatment with velmanase alfa. The individual methodology for rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04 are presented in Table 9–Table 11.

Table 9: Summary of methodology for rhLAMAN-02

Study name	NCT01268358 – rhLAMAN-02
Objectives	To evaluate the safety and determine the PK profile of VA when administered to patients with AM.
Location	Single centre in Denmark
Design	Phase I, open-label, dose-escalation, single centre study The study consisted of a screening and baseline visit followed by a treatment phase.
Duration of study	Patients received 1–5 doses before the end of the trial†
Sample size	10 patients
Inclusion criteria	• Confirmed diagnosis of AM as defined by α-mannosidase activity <10% of normal activity in blood leukocytes • Aged ≥5 year and ≤20 years • Physical ability to perform 6-MWT, 3-MSCT and PFTs • Ability to mentally cooperate in the cognitive and motor function tests • Ability to hear and follow a request. Hearing aids can be worn Patient or patient's legally authorised guardian(s) must provide signed, informed consent prior to performing any trial-related activities; both must have the ability to comply with the protocol
Exclusion criteria	• The patient cannot walk without support • Presence of known chromosomal abnormality and syndromes affecting psychomotor development, other than AM • History of HSCT • Presence of known clinically significant cardiovascular, hepatic, pulmonary or renal disease or other medical conditions that would preclude participation in the trial • Presence of an echocardiogram with abnormalities within half a year that would preclude participation in the trial • Any other medical condition or serious intercurrent illness, or extenuating circumstance that would preclude participation in the trial • Pregnancy • Psychosis within the last 3 months
Method of randomisation	Patients were allocated to one of five dose groups in a 1:1:1:1:1 ratio by stratification. Patients were stratified based on gender and age, to obtain homogenous pairs in each group.
Method of blinding	The study was open-label.

Intervention(s) (n=) and comparator(s) (n=)	Once weekly IV dosing of (N=2 in each group): • Group 1: 6.25 U/kg • Group 2: 12.5 U/kg • Group 3: 25 U/kg • Group 4: 50 U/kg • Group 5: 100 U/kg
Baseline differences	See full details of baseline characteristics in 9.4.3.
Duration of follow-up, lost to follow-up information	Infusions commenced with Group 1, where patients received their first dose at Day 0. One week later (7 days ± 2 days) Group 2 received their first infusion, while Group 1 received their second dose and so on until Group 5 who would have only one infusion before entering rhLAMAN 03.
Statistical tests	No statistical testing was performed.
Primary outcomes (including scoring methods and timings of assessments)	There were no efficacy endpoints in this study. Safety endpoints were AEs, vital signs, safety laboratory data (haematology, biochemistry and urinalysis) and ADAs.
Secondary outcomes (including scoring methods and timings of assessments)	N/A

Abbreviations: 3-MSCT, 3-minute walk test; 6-MWT, 6-minute walk test; ADA, anti-drug antibody; AE, adverse event; AM, alpha-mannosidosis; HSCT, haematopoietic stem cell transfer; IV, intravenous; PFT, pulmonary function test; PK, pharmacokinetic; VA, velmanase alfa.
[†]Patients could receive up to five additional doses if the following study (rhLAMAN-03) was postponed.

Table 10: Summary of methodology for rhLAMAN-03

Study name	NCT01285700 – rhLAMAN-03
Objectives	To evaluate the efficacy and long-term safety of VA and to define the effective dose of VA in patients with AM.
Location	Single centre in Denmark
Design	Phase IIa, single centre, randomised, open-label, multiple dose trial The trial consisted of a screening visit and a treatment phase. The baseline visit was performed in rhLAMAN-02.
Duration of study	The trial was conducted over 12 months: • Efficacy evaluation was carried out at Month 6 • A continuation phase was added, which extended the trial from 6 months to 12 months. This approach was to avoid the discontinuation of patients before they enrolled in rhLAMAN-04
Sample size	Ten patients were included in the trial, enrolled from the previous Phase I trial, rhLAMAN-02.
Inclusion criteria	As presented in Table 9.
Exclusion criteria	As presented in Table 9.
Method of randomisation	Patients were randomised to one of two dose groups in a 1:1 ratio. The dose levels were handled as blocks, i.e. one patient from each dose level in this trial was randomised to 25 U/kg and 50 U/kg, respectively.
Method of blinding	The study was open-label.
Intervention(s) (n=) and comparator(s) (n=)	Once weekly IV dosing of VA (N=5 in each group): • Group 1: 25 U/kg • Group 2: 50 U/kg
Baseline differences	See full details of baseline characteristics in 9.4.3.
Duration of follow-up, lost to follow-up information	Patients were followed until Month 12, at which patients were invited to enrol in rhLAMAN-04. One patient discontinued treatment (from the 25 U/kg arm) during rhLAMAN-03.
Statistical tests	Baseline data from the rhLAMAN-02 trial were treated as baseline in all analyses. All statistical tests were performed using a two-sided test at a 5% significance level; however, as no sample size was calculated, p-values should be treated with caution. For log-transformed analyses, the estimate was transformed back to the original scale for presentation. For each efficacy endpoint, two types of comparisons were made: • The change from baseline to Month 6 was compared between the two treatment groups in a linear model with treatment as factor and baseline values as a covariate

	• The change from baseline for both treatment groups combined, i.e. the Month 6 values were compared with the baseline value as a paired t-test
Primary outcomes (including scoring methods and timings of assessments)	**Efficacy endpoints measured at interim (Month 3) and Month 6 evaluations:** Change from baseline in: • oligosaccharide concentrations in serum, urine and CSF • CSF neurodegeneration biomarkers • Brain MRS of white matter, grey matter and centrum semiovale (standard), including estimation of the mannose complex level • functional capacity • cognitive development • pulmonary function • hearing **Pharmacokinetics** The PK profile of VA in patients with AM. **Safety** Patients were evaluated for AEs, vital signs, safety laboratory tests (haematology, blood chemistry and urinalysis) and ADAs.
Secondary outcomes (including scoring methods and timings of assessments)	N/A

Abbreviations: ADA, anti-drug antibody; AE, adverse event; AM, alpha-mannosidosis; CSF, cerebrospinal fluid; IV, intravenous; MRS, magnetic resonance spectroscopy; PK, pharmacokinetic; VA, velmanase alfa.

Table 11: Summary of methodology for rhLAMAN-04

Study name	NCT01681940 – rhLAMAN-04
Objectives	To evaluate the efficacy and long-term safety of VA and to define the effective dose of VA in patients with AM.
Location	Five sites in EU. The primary site was Denmark, where the screening and efficacy assessments were performed. The weekly infusions and ongoing safety monitoring were performed in Denmark, UK, France, Spain, and Belgium.
Design	Phase IIb, multi-centre, open-label trial The rhLAMAN-04 trial was planned to cover 6 months of treatment (Month 12 to Month 18) in continuation of the 12 months of treatment in the rhLAMAN-02 and rhLAMAN-03 trials. The baseline visit was performed in rhLAMAN-02.
Duration of study	The trial was conducted over 6 months. Patients had previously received VA treatment for 12 months.
Sample size	Nine patients enrolled from the previous rhLAMAN-03 trial.
Inclusion criteria	As presented in Table 9 with the following addition: • Patient must have participated in rhLAMAN-02 and rhLAMAN-03
Exclusion criteria	As presented in Table 9 with the following additions: • Participation in other interventional trials testing investigational medicinal product except for studies with VA • Planned major surgery that would preclude participation in the trial
Method of randomisation	All patients were enrolled into one group.
Method of blinding	The study was open-label.
Intervention(s) (n=) and comparator(s) (n=)	All nine patients were treated at the established minimum effective dose of 1 mg/kg (31.25 U/kg) of VA once weekly (IV).
Baseline differences	See full details of baseline characteristics in 9.4.3.
Duration of follow-up, lost to follow-up information	Patients were followed for 6 months until study end, at which patients were invited to enrol in an after-trial study (rhLAMAN-07 or rhLAMAN-09) or the compassionate use programme.
Statistical tests	Data were presented combined for the complete period of the rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04 trials. Baseline data were recorded in the rhLAMAN-02 trial. Month 6 data was recorded in the rhLAMAN-03 trial. These data were included as part of the analysis database for rhLAMAN-04. For each efficacy endpoint, the change (absolute and relative) from baseline at each time point was analysed using a paired t-test. In addition, for key efficacy endpoints, change from baseline was compared between the rhLAMAN-03 treatment groups (25 or 50 U/kg) in a linear model with treatment as factor and baseline values as a covariate. The relative change was based on log-transformation and transformed back for presentation.

	All statistical tests were performed using a two-sided test at a 5% significance level; however, as no sample size was calculated, p-values should be treated with caution.
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline to Month 18 in serum and CSF oligosaccharides, 3-MSCT, 6-MWT and pulmonary function
Secondary outcomes (including scoring methods and timings of assessments)	Change from baseline to Month 18 in: • mannose-rich oligosaccharides in brain tissue as measured by MRS visual score and reduction of MRI diffusion coefficient in white matter, grey matter and centrum semiovale • CSF neurodegeneration biomarkers (tau, NFLp, GFAp) • BOT-2 and hearing loss • age equivalence with Leiter-R • CHAQ score

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; ADA, anti-drug antibody; AE, adverse event; AM, alpha-mannosidosis; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; GFAp, glial fibrillary acidic protein; IV, intravenous; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NFLp, neurofilament protein; PK, pharmacokinetic; VA, velmanase alfa.

9.4.1.2 rhLAMAN-05

The methodology of the rhLAMAN-05 Phase III, placebo-controlled, 12-month study is summarised in Table 12.

Table 12: Summary of methodology for rhLAMAN-05

Study name	NCT01681953 – rhLAMAN-05
Objectives	To evaluate the efficacy and safety of VA compared with placebo in patients 5–35 years of age (at the time of treatment initiation) with AM.
Location	The trial was conducted across seven sites in six countries in the European Union: Denmark, France, Spain, Belgium, Germany and Sweden. The assessments were centralised in Denmark.
Design	The rhLAMAN-05 clinical trial was a Phase III, multi-centre, double-blind, randomised, placebo-controlled, parallel group trial.
Duration of study	12 months
Sample size	25 patients
Inclusion criteria	• AM confirmed by α-mannosidase activity <10% of normal activity in blood leucocytes • Aged 5–35 years (inclusive) at screening • Ability to physically and mentally cooperate in the tests • The patient must have an echocardiogram without abnormalities that would preclude participation in the trial • The patient and his/her guardian(s) must have the ability to comply with the protocol
Exclusion criteria	• The patient cannot walk without support • Presence of known chromosomal abnormality and syndromes affecting psychomotor development, other than AM • History of allogeneic HSCT • Presence of known clinically significant cardiovascular, hepatic, pulmonary, or renal disease or other medical conditions that would preclude participation in the trial • Any other medical condition or serious intercurrent illness, or extenuating circumstance that would preclude participation in the trial • Pregnancy • Psychosis; any psychotic disease, also in remission • Participation in other interventional trials testing IMP (including VA) within the last three months • Adult patients who would be unable to give consent, and who do not have any legal protection or guardianship • Total IgE >800 IU/ml • Known allergy to the IMP or any excipients (sodium-phosphate, glycine, mannitol)
Method of randomisation	Randomisation (in a 3:2 ratio) into active and placebo groups was stratified by age and was used to allocate the

	patients into blocks. Within the blocks, a standard randomisation into active and placebo was performed.
Method of blinding	Patients and investigators remained blinded to treatment assignment during the study. The blinding for a particular patient could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the patient.
Intervention(s) (n=) and comparator(s) (n=)	Once weekly VA (N=15) or placebo (N=10) by IV at a dose level of 1 mg/kg body weight.
Baseline differences	See full details of baseline characteristics in 9.4.3.
Duration of follow-up, lost to follow-up information	Patients were followed for 12 months until study end, at which patients were invited to enrol in an after-trial study (rhLAMAN-07 or rhLAMAN-09) or the compassionate use programme. Patients who were receiving placebo in rhLAMAN-05 could initiate treatment with VA.
Statistical tests	No formal sample size calculation was performed for this trial. The total of 25 patients represents a compromise between availability of patients who can fulfil the admission criteria and the minimum amount of data that can support an assessment of efficacy and safety of the treatment regimen. The primary analysis of the co-primary endpoints (serum oligosaccharides and 3-MSCT) and prioritised secondary endpoints (FVC [% of predicted] and 6-MWT) was performed on the relative change from baseline to Month 12. Data were log-transformed and then submitted to an ANCOVA with treatment as a fixed factor and corresponding baseline values and age as continuous covariates. The adjusted means in each treatment group, the adjusted mean difference between VA and placebo, their 95% CIs and associated p-values were estimated by the model; however, as no sample size was calculated, p-values should be treated with caution. The absolute change from baseline to Month 12, log-transformed relative change from baseline to Month 6 and absolute change from baseline to Month 6 were also assessed for these endpoints. For primary endpoints, demonstration of efficacy was defined as: • a statistically significant improvement in the two primary endpoints (at significance levels of 0.025 [serum oligosaccharides] and 0.05 [3-MSCT]) at the interim analysis (Month 6), or; • a statistically significant reduction in serum oligosaccharides (at a significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis For the ANCOVA models used in the primary and secondary endpoints, in case of missing data a multiple imputation method was applied before performing the analysis. This approach assumes that measures for withdrawn patients follow the pattern of patients who remained in the study. Imputation was performed by PROC multiple imputation using the Markov Chain Monte Carlo approach by treatment. Each record included

	baseline, Month 6, Month 12 and the baseline age. One thousand imputations were created and the imputed data sets were then analysed with PROC MIANALYSE.
Primary outcomes (including scoring methods and timings of assessments)	The co-primary endpoints for rhLAMAN-05 were: • Change from baseline to Month 12 in serum oligosaccharides • Change from baseline to Month 12 in the 3-MSCT
Secondary outcomes (including scoring methods and timings of assessments)	The prioritised secondary endpoints for rhLAMAN-05 were: • Change from baseline to Month 12 in 6-MWT • Change from baseline to Month 12 in FVC as a percentage of predicted normal value Additional secondary efficacy endpoints for rhLAMAN-05 were: • Change from baseline to other visits in PFTs (FEV_1 [L], FEV_1 [% of predicted value], FVC [L] and PEF [L/s]) • Change from baseline to other visits in BOT-2 (total score and domain scores) • Change from baseline to other visits in the Leiter-R • Change from baseline to other visits in CSF oligosaccharides and CSF biomarkers (tau, NFLp and GFAp) • Change from baseline to other visits in PTA (air conduction left and right ear and bone conduction for the best ear) • Change from baseline to other visits in CHAQ and EQ-5D (total score and domain scores)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AM, alpha-mannosidosis; ANCOVA, analysis of covariance; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GFAp, glial fibrillary acidic protein; IV, intravenous; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NFLp, neurofilament protein; PEF, peak expiratory flow; PK, pharmacokinetic; PTA, pure tone audiometry; VA, velmanase alfa.

9.4.1.3 rhLAMAN-10

At the end of rhLAMAN-02/03/04 and rhLAMAN-05, patients were invited to enrol in an after-trial study (rhLAMAN-07 or rhLAMAN-09) or the compassionate use programme. While data were collected for patients enrolled in rhLAMAN-07 and 09 (these trials are currently ongoing), no efficacy measurements were performed for patients enrolled in the compassionate use programme (N=20). Therefore, patients in the compassionate use programme were invited to enrol in rhLAMAN-10, where a single long-term data point was collected for a range of outcomes, to obtain long term data. These data were integrated with the databases of the Phase I/II trial (rhLAMAN-02/03/04), rhLAMAN-05, rhLAMAN-07 and rhLAMAN-09 to form the rhLAMAN-10 integrated data set (N=33). As the rhLAMAN-07 and rhLAMAN-09 trials were ongoing at the time of analysis in rhLAMAN-10, the cut-off date was defined as “the end date of the CEV in rhLAMAN-07, rhLAMAN-09 and rhLAMAN-10”. At the time of analysis, patients included in the

rhLAMAN-10 integrated data set analysis were expected to have follow-up times ranging from a minimum of 1 year to a maximum of 4 years. The methodology for rhLAMAN-10 is summarised in Table 13.

Table 13: Summary of methodology for rhLAMAN-10

Study name	NCT02478840 – rhLAMAN-10
Objectives	The overall objective of the trial was the evaluation of the long-term efficacy of VA treatment in patients with AM who were previously enrolled in trials with VA and were currently receiving VA in the compassionate use programme. These data were combined with all available data across the rhLAMAN clinical development programme, as part of an integrated data set analysis.
Location	Single centre in Denmark
Design	rhLAMAN-10 was an open-label, Phase III study. The study comprised a CEV (data collection for patients enrolled in the compassionate use programme) and an integrated data set analysis.
Duration of study	A one-week assessment visit (the CEV) for patients in the compassionate use programme.
Sample size	18 patients currently enrolled in the compassionate use programme attended the CEV. 33 patients included in the final integrated data set analysis.
Inclusion criteria	• The patient must have participated in rhLAMAN-02/03/04 or rhLAMAN-05 • The patient had to still be receiving weekly IV infusions of VA according to the after-trial studies or compassionate use programme • The patient's legally authorised guardian(s) had to provide signed, informed consent prior to performing any trial-related activities • The patient and his/her guardian(s) had to have the ability to comply with the protocol
Exclusion criteria	• History of allogeneic HSCT • Presence of known clinically significant cardiovascular, hepatic, pulmonary or renal disease or other medical conditions that would have precluded participation in the trial. Patients unable to perform the motor tests independently from support were permitted to participate in the trial and were to be evaluated for the remnant non-motor endpoints • Any other medical condition or serious intercurrent illness, or extenuating circumstance that would have precluded participation in the trial • Pregnant and/or lactating women • Participation in other interventional trials testing IMP, including rhLAMAN-07 and rhLAMAN-09

	○ The data from patients enrolled in rhLAMAN-07 or rhLAMAN-09 were combined with patients enrolled in rhLAMAN-10 • Pause of the IMP for two consecutive weeks during the last month. Patients were allowed to be re-screened
Method of randomisation	No randomisation of patients was required.
Method of blinding	The study was open label.
Intervention(s) (n=) and comparator(s) (n=)	A single dose of VA was given to patients attending the CEV (n=18) by IV at 1 mg/kg body weight.
Baseline differences	See full details of baseline characteristics in 9.4.3.
Duration of follow-up, lost to follow-up information	rhLAMAN-10 data collection – a one-week assessment visit (the CEV) for patients in the compassionate use programme. • Patients enrolled in the compassionate use programme were not assessed for efficacy. Therefore, patients were invited to enrol in rhLAMAN-10 and undergo a CEV, to obtain long-term efficacy data for these patients. • Patients attended a screening visit (Visit 0) on Day 1, at which eligibility was checked and informed consent was signed. After consent was obtained, patients attended the CEV (also on Day 1), at which they underwent pre-infusion evaluations, and then received their infusion of VA. This infusion was the weekly infusion for that week as part of the compassionate use programme. Further evaluations were then carried out over Days 1–6 (Visit 1). Visit 3 (final visit) was held on Day 6 after the evaluations had been completed and before the patient left the trial site. rhLAMAN-10 integrated data set analysis • As patients enrolled in rhLAMAN-07 and -09 were subject to annual efficacy evaluations as part of the trial protocol, they were not enrolled in the rhLAMAN-10 data collection (as defined by the exclusion criteria). In order to obtain long-term follow-up data, rhLAMAN 07 and 09 were amended to include a CEV. • CEV data from rhLAMAN-07, rhLAMAN-9 and the rhLAMAN-10 data collection were pooled and analysed with data from rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, and pre-CEV rhLAMAN-07 and 09 data points. For the integrated data set, details on how the data were aligned to the designated efficacy time points is discussed below this table.
Statistical tests	For each outcome, the absolute and relative changes from baseline to each time point were estimated and analysed using the paired t-test and presented with their p-value and 95% CI; however, as no sample size was calculated, p-values should be treated with caution. Unless otherwise specified, baseline values were defined as the last non-missing value before the first dose of VA (derived from parental Phase I/II and rhLAMAN-05

	studies). For patients in rhLAMAN-05 who were randomised to placebo, the baseline for all scheduled evaluations was the last non-missing value recorded in rhLAMAN-05. Unless otherwise specified, last observation values were defined as the last available value at the end of rhLAMAN trials (derived from the last trial the patient participated in). As such, last observation values presented comprise a range of follow-up times. As the rhLAMAN-07 and rhLAMAN-09 trials were ongoing at the time of the rhLAMAN-10 integrated data set, the cut-off date was defined as "the end date of the CEV in rhLAMAN-07, rhLAMAN-09 and rhLAMAN-10". Missing data was not imputed. Unless otherwise specified, missing values were included in the denominator count when computing percentages. When continuous data were summarised, only non-missing values were evaluated for computing summary statistics
Primary outcomes (including scoring methods and timings of assessments)	The co-primary endpoints for rhLAMAN-10 were: • Change from baseline in serum oligosaccharides • Change from baseline in the 3-MSCT
Secondary outcomes (including scoring methods and timings of assessments)	• Change from baseline in the 6-MWT (metres and % of predicted) • Change from baseline in PFTs (FEV_1 [L], FEV_1 [% of predicted value], FVC [L], FVC [% of predicted value], and PEF [L/s]) • Change from baseline in BOT-2 (total score and domain scores) • Change from baseline in the Leiter-R • Change from baseline in CSF oligosaccharides and CSF biomarkers (tau, NFLp and GFAp) • Change from baseline in PTA (air conduction left and right ear and bone conduction for the best ear) • Change from baseline in CHAQ and EQ-5D (total score and domain scores)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AM, alpha-mannosidosis; ANCOVA, analysis of covariance; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CEV, comprehensive evaluation visit; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GFAp, glial fibrillary acidic protein; IV, intravenous; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NFLp, neurofilament protein; PEF, peak expiratory flow; PK, pharmacokinetic; PTA, pure tone audiometry; VA, velmanase alfa.

rhLAMAN-10 integrated data set efficacy windowing

Efficacy assessments were assigned to a time point based on the calculated study day to create the rhLAMAN-10 integrated data set. The date of the assessment and the date of the first velmanase alfa dose were used to calculate the study day and a window was built around a target day (e.g. Day 183 for Month 6 with a window of Day 1–274). Any study day within the window was assigned to the associated time point.

The following time points were used: Baseline, Month 6, Month 12, Month 18, Month 24, Month 36 (due to the sparseness of the data, Month 30, Month 36 and Month 42 were

combined) and Month 48. The number of patients with data for each time point is presented by parental study in Table 14.

Table 14: Number of patients with available data per time point – overall, Phase I/II and rhLAMAN-05

Study contribution, n (% of total rhLAMAN-10)	Total N=33						
	Baseline	Month 6	Month 12	Month 18	Month 24	Month 36	Month 48
rhLAMAN-10	33 (100.0)	24 (72.7)	31 (93.9)	11 (33.3)	10 (30.3)	7 (21.2)	9 (27.3)
Parental study contribution, n (% of total rhLAMAN-10)							
Phase I/II‡	9 (27.3)	9 (27.3)	9 (27.3)	9 (27.3)	0	3 (9.1)	9 (27.3)
rhLAMAN-05							
Active	15 (45.5)	15 (45.5)	15 (45.5)	0	10 (30.3)	4 (12.1)	N/A
Placebo→Active	9 (27.3)†	0	7 (21.2)	2 (6.0)	N/A	N/A	N/A

Key: blue cells indicate data derived from rhLAMAN-07 and 09 (baseline to CEV), or rhLAMAN-10 data collection.
Abbreviations: N/A, time point not available; VA, velmanase alfa.
†Although 10 patients were included in the rhLAMAN-05 placebo group, patient 502 discontinued VA treatment shortly after starting the compassionate use programme. As this patient had no data collected during the active treatment, the patient was excluded from all analyses. ‡Phase I/II trial comprised rhLAMAN-02/03/04.

9.4.1.4 Post-hoc, multi-domain responder analysis

Background

In view of the multiple organ systems adversely affected in AM, and in response to a request from the EMA (23), it was considered clinically relevant and methodologically sound to conduct a multi-domain responder analysis that combines multiple endpoints into single domains representing clinical important effects.

In an ultra-rare and heterogeneous disease setting such as AM, a responder analysis approach is more reflective of the overall impact of the disease; measuring the treatment effect using single parameters is confounded by large variability in baseline values and small patient numbers. As AM is an ultra-rare disease, aggregating multiple clinically relevant endpoints for generating an overall response rate is considered to provide evidence of treatment response (and be sensitive enough to show lack of response between treatment and placebo groups) that may not be captured using a single measure across patients variably afflicted.

This approach is supported by recent studies in Duchenne muscular dystrophy (DMD), MPS IVA, and MPS VII. Studies assessing patients with DMD have shown that the use of a combination of outcome measures is an effective approach that could provide information on different aspects of motor function, which may not be detected by a single measure (84). In studies of MPS VII, response has been measured using an index of aggregated scores for 6-MWT, FVC, shoulder flexion, visual acuity and BOT-2 (85). Within the regulatory landscape, the provision of a domain response rate approach using multiple endpoints supported the approval of elosulfase alfa as therapy for MPS IVA (68). Methodologically, this approach may mitigate the limitations in sample size and the

potential loss of statistical power to detect a treatment effect, especially in heterogeneous populations where 'ceiling effects' should also be considered.

Methodology

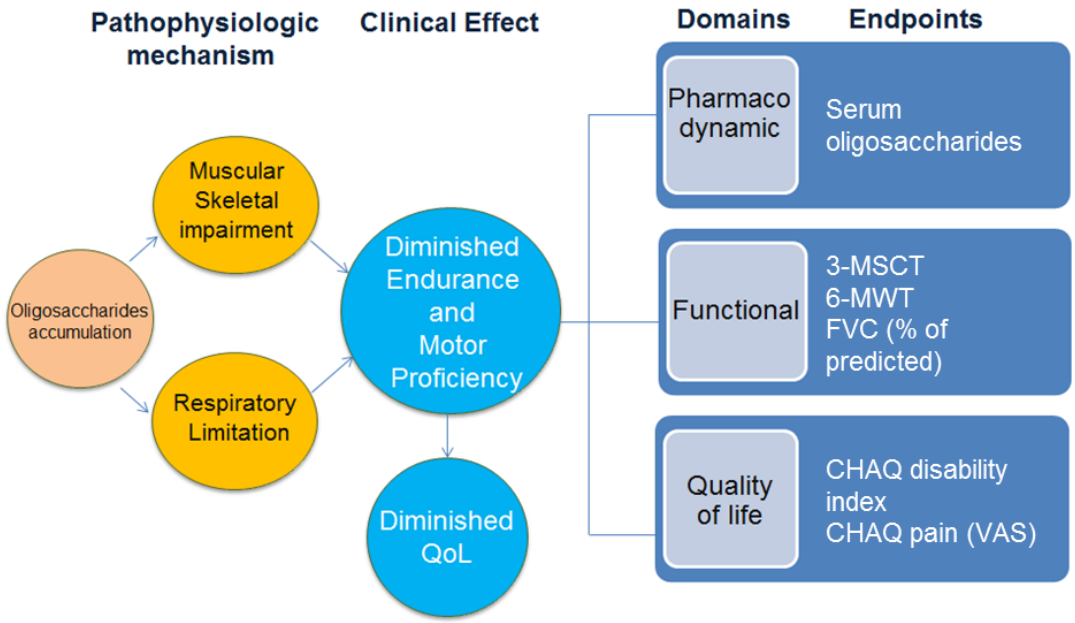
Physical impairments in the form of muscular skeletal impairment and respiratory limitation adversely affect endurance and motor proficiency, which manifests clinically as limited mobility, diminished activities of daily living and reduced QoL. These effects are measured through the key clinical endpoints of 3-MSCT, 6-MWT, FVC (% of predicted), CHAQ disability index, and CHAQ pain (VAS).

These endpoints (measured in rhLAMAN-05 and rhLAMAN-10) were grouped into three domains, together reflecting the pathophysiology and the burden of the disease. The domains were identified as:

- Pharmacodynamic: serum oligosaccharide response
- Functional: 3-MSCT, 6-MWT and FVC (% of predicted)
    - As muscular weakness is a key symptom of the disease, FVC is included within the functional domain as representative of muscular effort
- Quality of life: CHAQ disability index and CHAQ pain (VAS)

The overall AM response model is presented in Figure 5.

Figure 5: AM response model



Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AM, alpha-mannosidosis; CHAQ, childhood health assessment questionnaire; FVC, forced vital capacity; QoL, quality of life; VAS, visual analogue scale.

For the aggregated multi-domain responder analysis, a patient qualified as a responder to treatment if the response criteria were reached in at least two domains. Requiring a response in two domains provides treatment-effect sensitivity, whereas a single response domain does not. A patient was considered a responder in a domain if they

showed a response for at least one efficacy parameter within that domain by achieving the adopted MCID for that outcome.

Minimal clinically important differences

The MCID is the smallest difference in score for an efficacy endpoint of interest that patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management (86). Two main components are included under the umbrella of the MCID concept:

- the evaluation of the magnitude of change produced by the treatment; and
- clinical implications or importance of that change, or lack there-of, which are related to both patient and/or clinician expectations

The MCIDs for the clinical endpoints used in the trials of velmanase alfa have not previously been defined for patients with AM, which is typical of an orphan condition. Uncertainty remains in the scientific and clinical community regarding MCID thresholds in AM and the level of response required to define a "responder" given the heterogeneity of the disease and severity across the different measurement parameters.

In order to define MCIDs de novo for AM, a literature review was conducted and experts within the field were consulted (see Appendix 7, Section 17.7.3.1 for methodology) in an attempt to define MCIDs for serum oligosaccharide, 6-MWT, 3-MSCT, and FVC and QoL endpoints (CHAQ disability index and CHAQ VAS pain). Based on the evidence obtained from the literature review and clinical experts, the following MCIDs were defined.

Serum oligosaccharides

The adopted MCID for patients with AM was defined as a cut off of ≤4 µmol/L.

This was based on the data from rhLAMAN-05, in which all patients had pre-treatment serum oligosaccharide levels >4.0 µmol/L. The lower limit of quantification of the assay was 0.5 µmol/L and the patient value at baseline ranged from 4.4 µmol/L to 10.2 µmol/L.

3-MSCT

The adopted MCID for patients with AM was defined as an increase in ≥7 steps/min.

The use of the 3-MSCT as a measure of efficacy is limited in the context of LSDs. The 3-MSCT has been previously used in a study (MOR-004) assessing the effect of elosulfase alfa in patients with MPS IVA over 6 months (68). An attempt was made to define a pre-specified MCID for each of the outcomes of interest using a combination of literature review and a Delphi consensus panel prior to the unblinding of the trial; however, these efforts proved unsuccessful, such that the responder analyses that were ultimately carried out were conducted post hoc. In MOR-004, there was a mean change (SD) from baseline of 4.8 (8.1) steps/min in the elosulfase alfa group compared with 3.6 (8.5) steps/min in the placebo group (least squares [LS] mean difference: 1.1 [95% CI –2.1 to 4.4]). In MPS IVA, a 20% of change from baseline was adopted for the threshold in the relative risk. With a baseline in MPS IVA of 27–35 steps/min, 20% was approximately 7 steps/minute.

In the absence of any existing MCID, an absolute change of ≥7 steps/minute can be considered appropriate to apply to AM patients, based on the clinical plausibility claimed with other LSDs. No additional references emerged from a literature search and consultation with the experts in the field.

6-MWT

The adopted MCID for patients with AM was defined as an absolute increase of ≥30 meters.

This endurance test was originally developed to measure the submaximal level of functional capacity in adult patients with moderate to severe heart or lung diseases, and is a predictor of morbidity and mortality in these patients. The test has been adopted to assess functional outcome in other patient populations, such as cystic fibrosis, obesity, and MPS. The 6-MWT results are associated with pulmonary function, health related QoL, maximum exercise capacity, and mortality, and the MCID for the 6-MWT has been reported as 54–80 metres in chronic lung disease patients (87, 88), as 33 metres in patients with pulmonary hypertension (89) and as 30.1 metres in patients with chronic heart failure (90). In DMD, the MCID for the 6-MWT was reported as 28.5 to 31.7 metres based on two statistical distribution methods (91). A literature-based combined predictive model of the 6-MWT in healthy subjects was used to derive 6-MWT as percentage of predicted normative value (adjusted for age, height and gender).

For elosulfase alfa in the treatment of MPS IVA, an increase in the 6-MWT was considered clinically significant where the magnitude of change from baseline over 24 weeks compared with placebo was 22.5 metres (68). As the baseline functional status of patients with AM was better (466 metres) compared with MPS IVA (200 metres), this makes a definition of MCID more challenging given the confounding ceiling effect, i.e. as patients with AM were generally well functioning at baseline, there is limited ability to observe further improvement; consequently, demonstrating that treatment with velmanase alfa results in a significant improvement in 6-MWT compared with placebo is challenging. Furthermore, a longer treatment duration is required in higher-functioning patients in order to observe a meaningful effect; the variable progression of physical function in AM also requires the assessment of efficacy over a prolonged period when considering a single efficacy measure.

When Lachmann and Schoser (2013 (92)) analysed the MCID for endpoints in Pompe disease, they conducted a literature search on the MCID for the 6-MWT in different diseases. When these absolute and relative MCIDs for the 6-MWT were applied to clinical trials of late-onset Pompe disease, the majority of studies (9 out of 10) reported absolute changes from baseline in 6-MWT that lay within or above the absolute MCID level (24–54 meters). As Pompe disease is a rare LSD associated with progressive proximal myopathy, causing a gradual loss of muscular function and respiratory insufficiency, Pompe disease is considered a proxy disease for understanding of clinical endpoints and their relevance in AM. The results from the Lachmann and Schoser review support the assumption that an absolute MCID of 30 meters is also applicable to AM; the distance of 30 meters may have real-world significance in terms of keeping up with peers and traversing the distances required to perform activities of daily living.

Notably, when accepted MCID relative thresholds of other diseases (as low as 5% change) are applied to the mean baseline 6-MWT, a 23.35-meter change would be considered clinically meaningful for AM. This further emphasises that ≥30 meters would be a robust measure of clinical meaningfulness in evaluation of 6-MWT and would exceed the MCID for 6-MWT from multiple accepted methodologies in other diseases.

FVC percentage of predicted

The adopted MCID for patients with AM was an absolute increase of ≥10% of FVC (% of predicted).

When FVC is used as a measure of respiratory function, predicted FVC values >80% are considered to be within normal range. In patients with chronic lung diseases, change in FVC over time is a valid outcome measure. Guidelines for the assessment of patients with systemic scleroderma cite that an improvement or reduction of 10% from baseline values is required to ensure that the variation in lung capacity can be ascribed to a change in disease severity rather than measurement error (93). In a large study of 1,156 patients with idiopathic pulmonary fibrosis, the MCID in FVC (% of predicted) was defined as an absolute change of 2–6% of predicted (equivalent to a 3–9% relative change from baseline) and changes from baseline in FVC (% of predicted) reflected changes in global health status (94). However, the definition of a relevant change from baseline in FVC in late-onset Pompe disease is variable compared with the MCID described for idiopathic pulmonary fibrosis; despite an observed change below the MCID, patients still reported feeling either “somewhat better” or “much better” in their overall health. In two-thirds of the studies in which late-onset Pompe patients were treated with alglucosidase alfa, the changes from baseline in FVC (% of predicted) were above or within the MCID established in respiratory diseases aforementioned (absolute MCID 2–6%; or 3–9% relative MCID), and the difference was perceived as either an improvement or stabilisation by patients.

The MCID adopted for patients with AM is a challenging target given that the overall study population had predominantly normal values at baseline (mean values were 85% of predicted). Therefore, the study population may be subject to a ceiling effect, where the ability to observe further improvement is limited. Consequently, demonstrating that treatment with velmanase alfa results in a significant improvement in FVC (% of predicted) compared with placebo is challenging.

CHAQ disability index

The adopted MCID for patients with AM was a reduction of ≥0.13.

Disability index scores range from 0 to 3 with higher scores indicating greater disability and the MCID has been reported as -0.13 in Juvenile Arthritis (95). Similarly, AM patients with arthritis present with pain, muscle weakness, skeletal abnormalities and challenges with activities of daily living; 35.7% of the adult patients included in the rhLAMAN-10 integrated data set presented with arthralgia at baseline.

CHAQ pain (VAS)

The adopted MCID for patients with AM was a reduction of ≥0.246.

The MCID for Pain (VAS) has been reported as a reduction of magnitude ≥8.2% (0.82 cm on a 10 cm VAS, (96)) in patients with juvenile arthritis, which is a disease with physical impact on the musculoskeletal system and joints similar to that experienced in AM; this corresponds to a reduction of ≥0.246 on the 0–3 scale. Similar to patients with AM, patients with arthritis present with pain, muscle weakness, skeletal abnormalities and challenges with activities of daily living.

9.4.2 *Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).*

An overview of the clinical development programme for velmanase alfa is provided in Section 9.4. Briefly, rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04 are considered as a single Phase I-II trial spanning 18 months of active treatment. At the end of the Phase I-II study (end of rhLAMAN-04) and rhLAMAN-05 (Phase III), patients were invited to enrol in an after-trial study (rhLAMAN-07 or rhLAMAN-09) or the compassionate use programme. Efficacy assessments were included in rhLAMAN-07 and -09, but not during the compassionate use programme. To obtain a long-term data set, patients in the compassionate use programme were invited to enrol in rhLAMAN-10 and attend a CEV. The data from this CEV were combined with the databases from the Phase I-II trial, rhLAMAN-05, rhLAMAN-07 and rhLAMAN-09 to form the rhLAMAN-10 integrated data set.

9.4.3 *Highlight any differences between patient populations and methodology in all included studies.*

The key differences between the included studies are as follows:

- rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04 were Phase I and II studies, while rhLAMAN-05 and rhLAMAN-10 were Phase III
- rhLAMAN-05 is the only double-blind, placebo-controlled study. The Phase I-II study and rhLAMAN-10 were open-label trials with no comparator. Therefore, rhLAMAN-05 is the only trial designed to evaluate the efficacy of velmanase alfa relative to a comparator. The remaining studies were designed to evaluate the effect of velmanase alfa on a range of efficacy outcomes by assessing change from baseline
- In contrast to the Phase I-II and Phase III studies, rhLAMAN-10 comprised two parts:
    - A CEV where patients were enrolled from the compassionate use programme
    - An analysis of an integrated data set which included data from the Phase I-II study, rhLAMAN-05, rhLAMAN-07, rhLAMAN-09 and the data collected from the rhLAMAN-10 CEV

The baseline characteristics of the patients included in each trial are shown in Sections 9.4.3.1–9.4.3.3. The inclusion criteria for the Phase I-II study allowed patients up to the age of 20, however, only paediatric patients (<18 years old) were enrolled. In contrast, both adult and paediatric patients were enrolled in rhLAMAN-05. Overall,

patients enrolled in both the Phase I-II study and rhLAMAN-05 were similar in functional capacity; however, patients in the Phase I-II study had a higher average (mean) baseline level of serum oligosaccharides (9.4 µmol/L) than patients in rhLAMAN-05 (6.6–6.8 µmol/L).

9.4.3.1 Phase I-II study (rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04)

The key baseline characteristics of patients in the Phase I-II study are summarised in Table 15.

Table 15: Baseline characteristics of rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04

Characteristic	Combined (N=10)
Age, years	
Mean (SD)	11.8 (3.7)
Median (range)	12.5 (7.0–17.0)
Female, n (%)	3 (30.0)
Male, n (%)	7 (70.0)
Race (white)	10 (100.0)
Weight, kg	
Mean (SD)	48.0 (17.2)
Height, metres	
Mean (SD)	1.44 (0.19)
BMI, kg/m^2	
Mean (SD)	22.2 (3.6)
3-MSCT, steps	
Mean (SD)	157 (40.5)
6-MWT, metres	
Mean (SD)	444 (104)
FVC	
% of predicted, mean (SD)	79.1 (15.8)
L, mean (SD)	2.1 (0.9)
FEV_1	
% of predicted, mean (SD)	79.1 (15.8)
L, mean (SD)	1.9 (0.8)
PEF, L/s	
Mean (SD)	3.7 (1.5)
Leiter-R, years	
Total equivalence age, mean (SD)	5.6 (1.2)
Serum oligosaccharides, µmol/L	
Mean (SD)	9.40 (2.88)
CSF oligosaccharides, µmol/L	
Mean (SD)	10.70 (4.55)

Characteristic	Combined (N=10)
BOT-2, points	
Manual dexterity, mean (SD)	14.90 (6.3)
Bilateral Coordination, mean (SD)	11.40 (5.1)
Running Speed and Agility, mean (SD)	13.70 (7.2)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CSF, cerebrospinal fluid; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation.

9.4.3.2 rhLAMAN-05

The characteristics of patients in rhLAMAN-05 are summarised in Table 16. Overall, the demographic characteristics were similar between the two groups. In terms of functional capacity (by categorical values arbitrary adopted for 3-MSCT and 6-MWT), PFTs and BOT-2, the two groups were less balanced, with a higher proportion of more compromised patients randomised to the velmanase alfa group. However, patients were generally at the more mobile end of the AM functional impairment axis at baseline, as patients were required to have the ability to physically and mentally cooperate in the tests; with respect to the 3-MSCT and 6-MWT, this suggests that no patients were wheelchair bound or severely disabled. It should be noted that one patient was not naïve to velmanase alfa at the start of rhLAMAN-05 (see Section 9.4.6 for details of this patient). The patient was subsequently randomised to the velmanase alfa group in rhLAMAN-05 after a treatment gap of approximately 18 months. Therefore, it is possible that this patient may not receive the same level of benefit (from baseline) as the other patients in the velmanase alfa group, who were treatment naïve prior to study entry, and this may reduce the mean treatment effect of the velmanase alfa group as a whole across the endpoints.

Table 16: Baseline characteristics of rhLAMAN-05

Characteristic	VA (N=15)	Placebo (N=10)
Age, n (%)		
<12	4 (26.7)	2 (20.0)
12–<18	3 (20.0)	3 (30.0)
≥18	8 (53.3)	5 (50.0)
Female, n (%)	6 (40.0)	5 (50.0)
Male, n (%)	9 (60.0)	5 (50.0)
Race (white)	15 (100.0)	10 (100.0)
Weight, kg		
Mean (SD)	60.2 (21.5)	64.2 (12.2)
Height, metres		
Mean (SD)	1.51 (0.19)	1.61 (0.14)
BMI, kg/m^2		
Mean (SD)	25.1 (4.9)	24.7 (2.7)

Characteristic	VA (N=15)	Placebo (N=10)
3-MSCT, steps/min		
Mean (SD)	52.9 (11.2)	55.5 (16.0)
35–45, n (%)	1 (6.7)	3 (30.0)
45–55, n (%)	9 (60.0)	2 (20.0)
55–65, n (%)	3 (20.0)	1 (10.0)
≥65, n (%)	2 (13.3)	4 (40.0)
6-MWT, metres		
Mean (SD)	460 (72.3)	466 (140)
200–400, n (%)	2 (13.3)	3 (30.0)
400–500, n (%)	11 (73.3)	3 (30.0)
≥500, n (%)	2 (13.3)	2 (40.0)
FVC		
% of predicted, mean (SD)	81.7 (20.7)	90.4 (10.4)
L, mean (SD)	2.5 (1.1)	3.3 (0.9)
FEV_1		
% of predicted, mean (SD)	80.3 (19.6)	85.9 (18.2)
L, mean (SD)	2.3 (1.0)	2.9 (0.9)
PEF, L/s		
Mean (SD)	4.6 (2.2)	5.7 (1.6)
Leiter-R, years		
TEA-AME mean (SD)	6.3 (2.6)	6.6 (1.8)
TEA-VR mean (SD)	5.7 (1.7)	6.1 (1.6)
Serum oligosaccharides, µmol/L		
Mean (SD)	6.8 (1.2)	6.6 (1.9)
CSF oligosaccharides, µmol/L		
Mean (SD)	11.4 (3.0)	10.3 (2.9)
BOT-2 Total Score, points		
Mean (SD)	94.93 (41.68)	109.2 (51.84)
CHAQ disability index, score		
Mean (SD)	1.37 (0.82)	1.59 (0.64)
EQ-5D index, score		
Mean (SD)	0.61 (0.19)	0.61 (0.18)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation; TEA-AME, total equivalence age for attention and memory; TEA-VR, total equivalence age for visualisation and reasoning; VA, velmanase alfa.

9.4.3.3 rhLAMAN-10

The baseline characteristics of patients included in the rhLAMAN-10 integrated data set are summarised in Table 17. Overall, patients were generally at the more mobile end of the AM functional impairment axis at baseline, as patients were required to have the ability to physically and mentally cooperate in the tests; with respect to the 3-MSCT and 6-MWT, this suggests that no patients were wheelchair bound or severely disabled. At the time of analysis, all patients had been receiving velmanase alfa for a period of ≥12 months. Patients from the Phase I/II studies had been receiving velmanase alfa for the longest time (48 months), while patients in the active treatment group of rhLAMAN-05 will have received a maximum of 36 months of treatment. Similar to ERT in other LSDs (97), it was expected that (for certain endpoints) much of the benefit of velmanase alfa will have already been achieved in these patients; therefore, the long-term follow up would most likely establish the sustainability of the early response to velmanase alfa. However, patients from the placebo group of rhLAMAN-05 were exposed to velmanase alfa for relatively shorter time periods (via rhLAMAN-07, rhLAMAN-09 or the compassionate use programme) prior to inclusion in rhLAMAN-10 integrated data set. For these patients, the initial benefit(s) of velmanase alfa may be observed for the first time during rhLAMAN-10.

Table 17: Baseline characteristics of patients included in the rhLAMAN-10 integrated data set, overall, by age and by parental study

Characteristic	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)	Phase I/II trial (N=9)	rhLAMAN-05 (N=24)
Age of starting treatment, years					
Mean (SD)	17.1 (7.8)	11.6 (3.7)	24.6 (5.3)	12.4 (3.8)	18.9 (8.3)
Female, n (%)	13 (39.4)	6 (31.6)	7 (50.0)	2 (22.2)	11 (45.8)
Male, n (%)	20 (60.6)	13 (68.4)	7 (50.0)	7 (77.8)	13 (54.2)
Race (white)	33 (100.0)	19 (100.0)	14 (100.0)	9 (100.0)	24 (100.0)
Weight, kg					
Mean (SD)	58.8 (18.6)	49.8 (19.7)	70.9 (6.2)	49.5 (17.5)	62.3 (18.1)
Height, metres					
Mean (SD)	1.53 (0.18)	1.46 (0.20)	1.63 (0.08)	1.46 (0.19)	1.55 (0.17)
BMI, kg/m^2					
Mean (SD)	24.3 (4.3)	22.4 (4.2)	26.9 (2.9)	22.2 (3.9)	25.1 (4.3)
3-MSCT, steps/min					
Mean (SD)	53.60 (12.53)	54.04 (13.34)	53.00 (11.82)	52.63 (14.25)	53.96 (12.14)
6-MWT, metres					
Mean (SD)	466.6 (90.1)	454.2 (86.3)	483.4 (95.6)	452.8 (106.7)	471.8 (85.0)
FVC					
n	29	17	12	9	20
% of predicted, mean (SD)	84.9 (18.6)	79.6 (16.4)	92.5 (19.4)	81.7 (14.1)	86.4 (20.4)
L, mean (SD)	2.65 (1.08)	2.24 (0.93)	3.23 (1.05)	2.20 (0.87)	2.86 (1.13)

Characteristic	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)	Phase I/II trial (N=9)	rhLAMAN-05 (N=24)
FEV_1					
n	29	17	12	9	20
% of predicted, mean (SD)	83.8 (17.6)	79.0 (15.0)	90.5 (19.3)	82.2 (12.8)	84.5 (19.6)
L, mean (SD)	2.44 (1.00)	2.06 (0.83)	2.98 (1.00)	2.05 (0.79)	2.62 (1.05)
PEF, L/s					
n	29	17	12	9	20
Mean (SD)	4.85 (2.04)	3.90 (1.58)	6.20 (1.90)	3.89 (1.50)	5.29 (2.14)
Leiter-R TEA-VR, years					
Mean (SD)	5.88 (1.57)	5.40 (1.40)	6.53 (1.59)	5.69 (1.29)	5.95 (1.68)
Leiter-R TEA-AME, years					
n	24	10	14	-	24
Mean (SD)	6.51 (2.18)	5.93 (2.11)	7.03 (1.92)	-	6.514
Serum oligosaccharides, µmol/L					
Mean (SD)	6.90 (2.30)	7.63 (2.52)	5.91 (1.54)	9.00 (2.74)	6.11 (1.53)
CSF oligosaccharides, µmol/L					
Mean (SD)	10.64 (3.53)	10.65 (3.84)	10.62 (3.20)	10.33 (4.66)	10.75 (3.11)
BOT-2 total score, points					
Mean (SD)	107.0 (47.6)	101.9 (53.8)	113.9 (38.6)	120.7 (54.1)	101.9 (45.1)
CHAQ disability index, score					
Mean (SD)	1.36 (0.77)	1.22 (0.89)	1.55 (0.55)	0.97 (0.80)	1.51 (0.73)

Characteristic	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)	Phase I/II trial (N=9)	rhLAMAN-05 (N=24)
EQ-5D index, score					
n	24	10	14	-	24
Mean (SD)	0.62 (0.17)	0.70 (0.18)	0.57 (0.14)	-	0.62 (0.17)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five dimension; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation; TEA-AME, total equivalence age for attention and memory; TEA-VR, total equivalence age for visualisation and reasoning.

9.4.4 *Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.*

9.4.4.1 rhLAMAN-05

Patients were analysed according to age class (<18 vs ≥18 years) as part of a post-hoc analyses; this classification is the age of patients at the time of starting treatment. This was to investigate whether the efficacy of velmanase alfa was impacted by the age of the patient at time of initiation.

9.4.4.2 rhLAMAN-10

The pre-planned subgroup analyses performed in rhLAMAN-10 were:

- Age group (<18 years vs ≥18 years); this classification is the age of patients at the time of starting treatment
- Parental study (Phase I/II vs rhLAMAN-05)
- Anti-drug antibody (ADA) status (positive or negative) for the following outcomes: cerebral spinal fluid (CSF) oligosaccharides, 6-MWT, 3-MSCT and serum IgG

In order to characterise the general patient status, a performance status analysis was performed on the following outcomes: 6-MWT, FVC (% of predicted), FEV_1 (% of predicted), CSF oligosaccharides, serum IgG, PTA and CHAQ disability index.

The patient status was categorised for each parameter at each time point, in one of the following three classes:

1. Not impaired/slightly impaired
2. Impaired
3. Seriously impaired

The corresponding value for each level impairment for the endpoints is shown in Table 18.

A subsequent post-hoc analysis was performed that assessed patients according to the following age classes: 6–11, 12–17 and ≥18 years old.

Table 18: Criteria for level of impairment per outcome

Outcome	Not/slightly impaired	Impaired	Seriously impaired
Serum oligosaccharide, µmol/L	0–1.5	>1.5–4.9	≥5
CSF oligosaccharides, µmol/L	0–2	2–7	≥7
Serum IgG, mg/mL	Reference range according to reference range in Cassidy (1974) (98)	4 to normal range	<4
3-MSCT, steps/min	>55	45–55	<45
6-MWT, % of predicted	>80–120	>50–80	≤50
FVC, % of predicted	>80–120	>50–80	≤50
FEV_1, % of predicted	>80–120	>50–80	≤50
PTA air conduction left ear, dBHL	≤25	26–55	≥56
PTA air conduction right ear, dBHL	≤25	26–55	≥56
PTA bone conduction best ear, dBHL	≤25	26–55	≥56
CHAQ disability index, score	0–1	>1–2	>2–3
CHAQ pain (VAS), score	0–1	>1–2	>2–3

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PTA, pure tone audiometry.

9.4.5 *If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.*

9.4.5.1 Phase I-II study (rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04)

The disposition of patients in rhLAMAN-02 and rhLAMAN-03 is shown in Figure 6 and Figure 7. All patients from rhLAMAN-02 progressed to rhLAMAN-03. Overall, nine patients completed rhLAMAN-03 and progressed to rhLAMAN-04; one patient withdrew due to an AE (this patient later enrolled in rhLAMAN-05, see Section 9.4.5.2). No patients failed screening or withdrew from the rhLAMAN-04 trial.

Figure 6: rhLAMAN-02 patient disposition

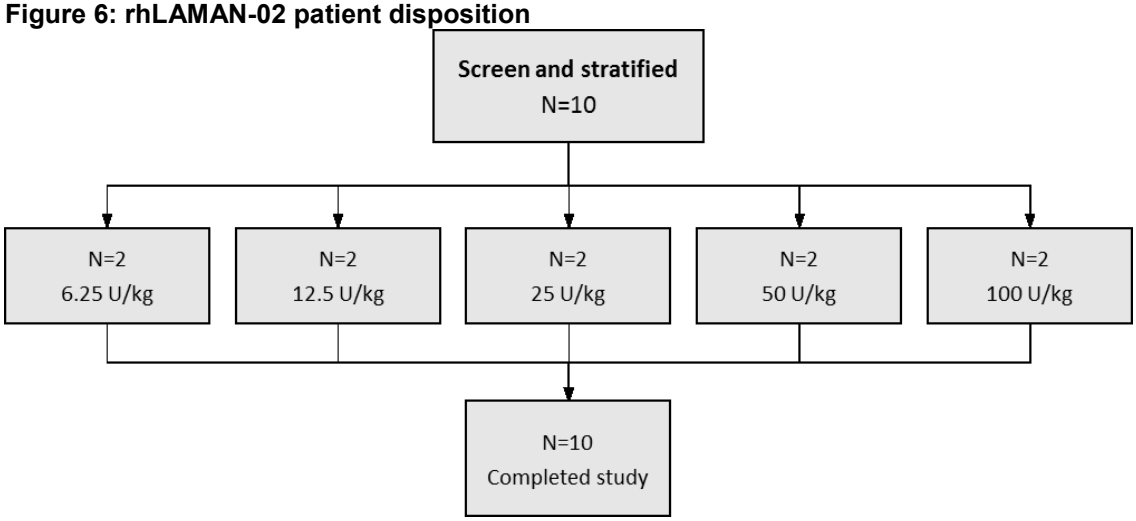
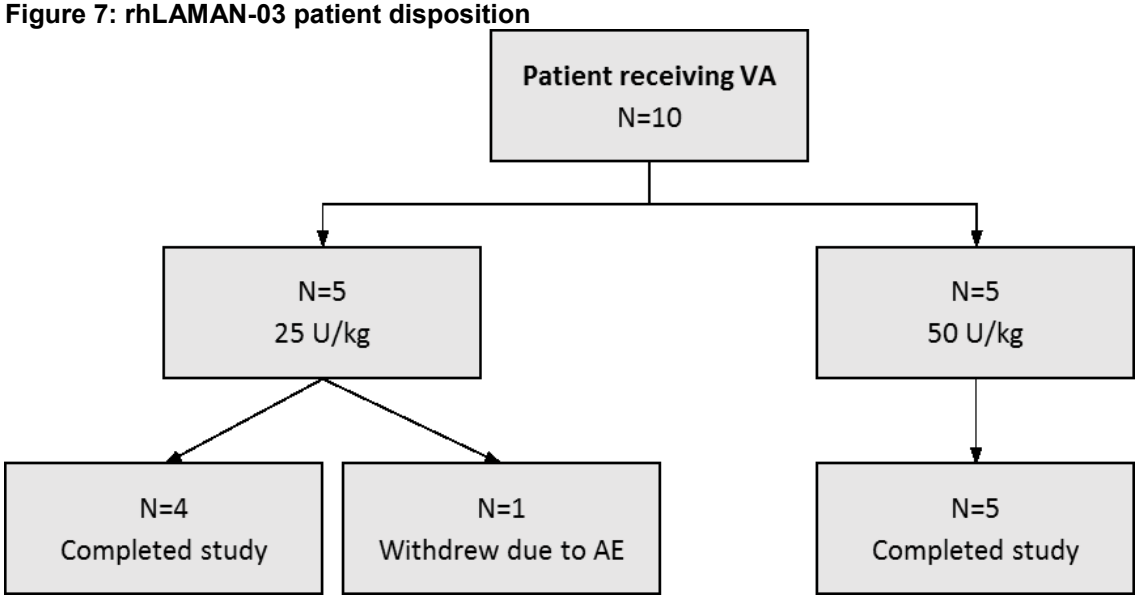


Figure 7: rhLAMAN-03 patient disposition



Abbreviations: AE, adverse event; VA, velmanase alfa.

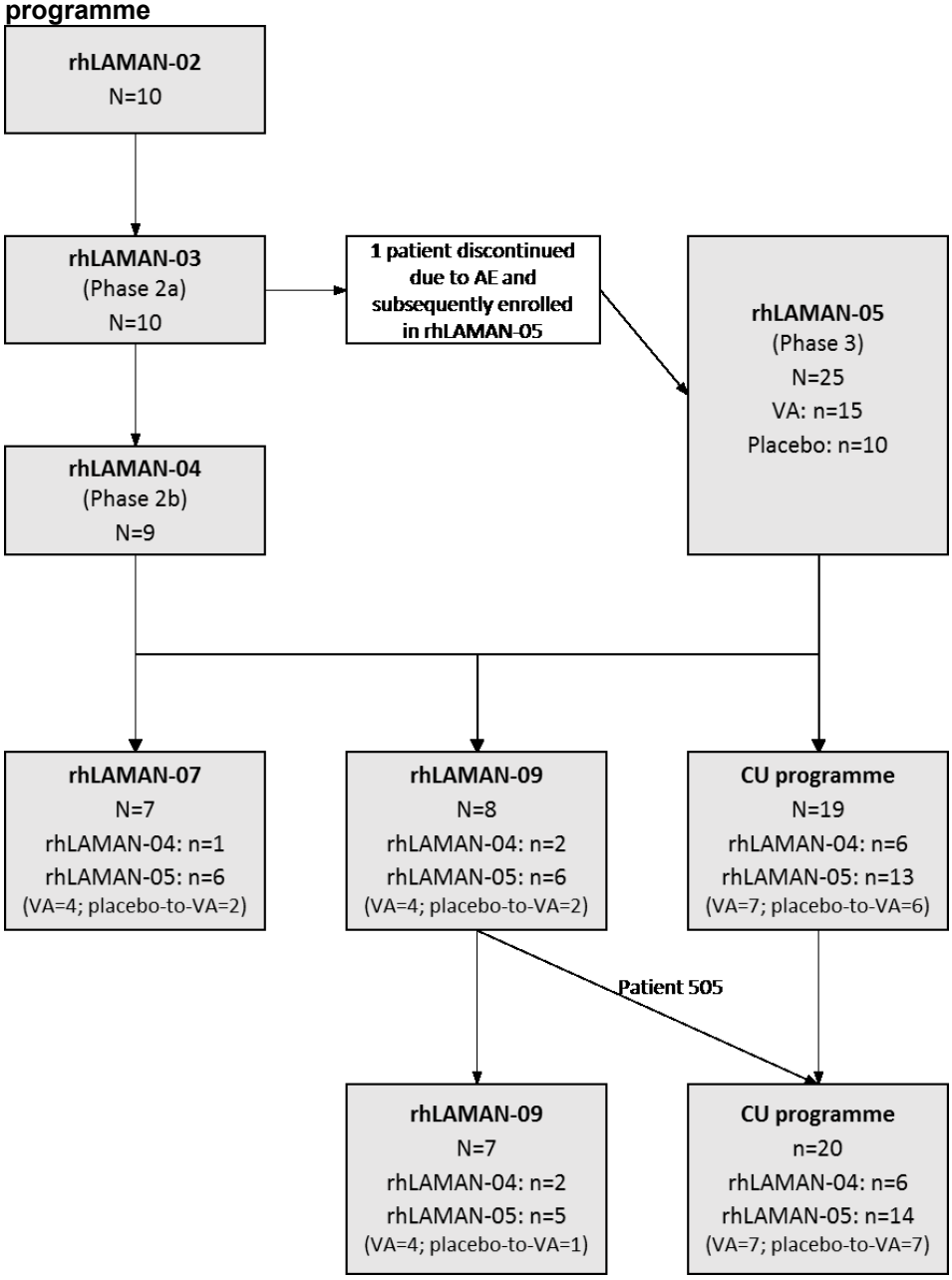
9.4.5.2 rhLAMAN-05

A total of 26 patients were screened in the rhLAMAN-05 trial. There was one screening failure due to a level of immunoglobulin E (IgE) compatible with exclusion criteria. One patient had previously received velmanase alfa in rhLAMAN-03 (patient discontinued rhLAMAN-03 due to an AE and subsequently enrolled in rhLAMAN-05). Twenty-five patients were randomised to velmanase alfa (N=15) or placebo (N=10). No patients withdrew from the rhLAMAN-05 trial.

9.4.5.3 Patient disposition following the Phase I-II study and rhLAMAN-05

At the end of the Phase I-II study (rhLAMAN-04) and rhLAMAN-05, patients were invited to enrol in an after-trial study (rhLAMAN-07 or rhLAMAN-09) or the compassionate use programme. The disposition of patients from the Phase I-II study or rhLAMAN-05 to the after-trial studies/compassionate use programme is shown in Figure 8. One patient (patient 505) initially enrolled in rhLAMAN-09, but switched to the compassionate use programme.

Figure 8: Patient disposition from Phase I to after-trial studies and compassionate use programme



Abbreviations: AE, adverse event; CU, compassionate use.

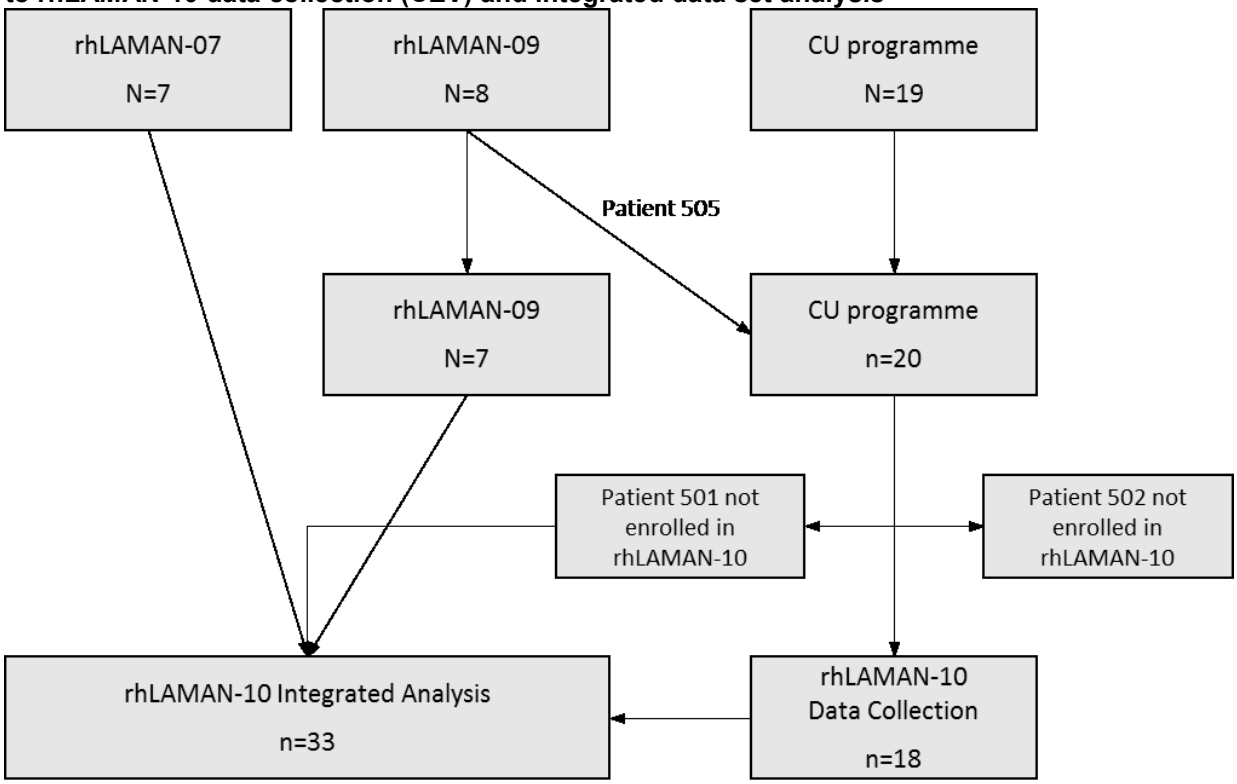
9.4.5.4 rhLAMAN-10

The patient disposition from the after-trial studies and compassionate use programme to rhLAMAN-10 data collection and rhLAMAN-10 integrated data set is shown in Figure 9. A CEV to obtain a long-term data point was performed on all patients (except one; patient 501) included in the integrated data set, either in rhLAMAN-07 and 09 or the rhLAMAN-10 data collection. Overall, a total of 33 patients were included in the integrated data set.

Patient 501, who previously received velmanase alfa in rhLAMAN-05, did not progress from the compassionate use programme to the rhLAMAN-10 data collection as no CEV was performed on this patient; however, the 12-month data obtained from this patient

during rhLAMAN-05 was included in the integrated data set. Patient 502, who previously received placebo in rhLAMAN-05, also did not progress from the compassionate use programme to the rhLAMAN-10 data collection. As this patient had no data collected while receiving velmanase alfa, they were excluded from the integrated data set.

Figure 9: Patient disposition from after-trial studies and compassionate use programme to rhLAMAN-10 data collection (CEV) and integrated data set analysis



Abbreviations: CU, compassionate use.
Note: See text for description.

9.4.6 *If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.*

One patient withdrew from the Phase I-II study during rhLAMAN-03. The patient had received nine doses of velmanase alfa at 25 U/kg in rhLAMAN-03 and withdrew following a long-term interruption of treatment due to repeated (three events) IRR (mild, treatment-related, anaphylactoid reaction) and the patient's desire not to receive premedication. The patient was subsequently randomised to the velmanase alfa group in rhLAMAN-05 after a treatment gap of approximately 18 months.

Two patients (patient 501 and 502) from the compassionate use programme did not enrol in rhLAMAN-10. As described in Section 9.4.5.4, patient 501 had previously received velmanase alfa for 12 months in rhLAMAN-05; therefore, these data were included in the rhLAMAN-10 integrated data set. Patient 502 had previously received placebo in rhLAMAN-05 and withdrew from the compassionate use programme shortly after initiating velmanase alfa. Neither patient withdrew from the clinical development programme due to an AE.

9.5 *Critical appraisal of relevant studies*

9.5.1 *Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.*

Table 19: Critical appraisal of trials – rhLAMAN-02 (non-randomised)

Study name	rhLAMAN-02	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients were allocated to one of five dose groups by stratification (rather than randomisation) in a 1:1:1:1:1 ratio. Patients were stratified based on gender and age, to obtain homogenous pairs in each group. Patients with the lowest and highest age were allocated to the higher dose arm.
Was the concealment of treatment allocation adequate?	N/A	The study was open-label.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Patients were balanced between dose groups. The safety and efficacy results are presented as the whole population (N=10) in this submission.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	The study was open-label.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	While baseline clinical data are not presented in the rhLAMAN-02 CSR, they are presented in the subsequent trial CSR, rhLAMAN-03.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	This was a Phase I study where the main objectives were safety and pharmacodynamic profile. The study did not involve randomisation; therefore, the ITT principle was not relevant.

Abbreviations: CSR, clinical study report; ITT, intention-to-treat.

Table 20: Critical appraisal of trials – rhLAMAN-03 (randomised)

Study name	rhLAMAN-03	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients from rhLAMAN-02 were randomised to one of two dose groups in a 1:1 ratio. The dose levels were handled as blocks, i.e. one patient from each dose level in rhLAMAN-02 was randomised to 25 U/kg and 50 U/kg, respectively.
Was the concealment of treatment allocation adequate?	N/A	The study was open-label.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The two persons receiving each of the previous rhLAMAN-02 treatments (6.25 U/kg through 100 U/kg) were randomised prior to treatment: one to the 25 U/kg group and one to the 50 U/kg group. Therefore, there was a balance between the treatment groups of 25 U/kg and 50 U/kg with respect to the previous treatment. The safety and efficacy results are presented as the whole population (N=10) in this submission.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	The study was open-label.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety evaluation was based on a modified ITT analysis and included all patients exposed to at least one dose of trial drug.

Abbreviations: ITT, intention-to-treat.

Table 21: Critical appraisal control trials – rhLAMAN-04 (non-randomised)

Study name	rhLAMAN-04	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients were enrolled from the previous study, rhLAMAN-03.
Was the concealment of treatment allocation adequate?	N/A	The study was open-label.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	N/A	Only one treatment group was included in the study.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	The study was open-label.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Only one treatment group was included in the study.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety evaluation was based on a modified ITT analysis and included all patients exposed to at least one dose of trial drug.

Abbreviations: ITT, intention-to-treat.

Table 22: Critical appraisal of trials – rhLAMAN-05 (randomised and controlled)

Study name	rhLAMAN-05	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomisation (in a 3:2 ratio) into active and placebo groups was stratified by age and was used to allocate the patients into blocks. Within the blocks, a standard randomisation into active and placebo was performed.
Was the concealment of treatment allocation adequate?	Yes	rhLAMAN-05 was double-blind study.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Overall, the demographic characteristics were similar between the two groups. In terms of functional capacity (by categorical values arbitrary adopted for 3-MSCT and 6-MWT), PFTs and BOT-2, the two groups were less balanced, with a higher proportion of more compromised patients randomised to the active treatment group.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Patients and investigators remained blinded to treatment assignment during the study. The blinding for a particular patient could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the patient.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety evaluation was based on a modified ITT analysis and included all patients who received ≥1 dose of trial drug and whose efficacy was evaluated post-baseline.

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency, 2nd edition; ITT, intention-to-treat; PFT, pulmonary function test.

Table 23: Critical appraisal of trials – rhLAMAN-10 (non-randomised)

Study name	rhLAMAN-10	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients who were receiving active treatment as part of the compassionate use programme (after-trial study following the Phase I-II and rhLAMAN-05 trials) were invited to attend a CEV in order to obtain a long-term data point. These data were combined with the data bases of the Phase I-II trial, rhLAMAN-05, rhLAMAN-07 and rhLAMAN-09 to form the integrated data base (see Section 9.4.1.3 for details)
Was the concealment of treatment allocation adequate?	N/A	The study was open-label.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	N/A	Only one treatment group was included in the study.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	The study was open-label.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety evaluation was based on a modified ITT analysis and included all patients who received ≥1 dose of trial drug and whose efficacy was evaluated post-baseline.

Abbreviations: ITT, intention-to-treat.

9.6 *Results of the relevant studies*

Of the studies identified in Section 9.1, the results from rhLAMAN-05 and rhLAMAN-10 are the most relevant to the decision problem; rhLAMAN-05 provides data on the relative 12-month efficacy of velmanase alfa compared with placebo, while rhLAMAN-10 provides up to 48 months of follow-up data. Efficacy data were also recorded in the Phase I-II trial (during rhLAMAN-03 and rhLAMAN-04); as these data are represented in rhLAMAN-10, the results are presented in Appendix 7, Section 17.7.4.

In view of the multiple organ systems adversely affected in AM, and in response to a request by the EMA, a post-hoc, multi-domain responder analysis combining multiple endpoints into single domains representing clinical effects was conducted for rhLAMAN-05 and rhLAMAN-10; this also included the establishment of a range of MCIDs de novo for AM (Section 9.6.1.3). These data formed part of the pivotal evidence base for velmanase alfa in the EMA submission.

9.6.1 *Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.*

9.6.1.1 rhLAMAN-05

The efficacy analysis was carried out on the FAS, which was defined as all patients who received ≥1 dose of velmanase alfa and whose efficacy was evaluated post-baseline. Results of the outcomes relevant to the decision problem are presented as the adjusted (for age and baseline value) mean relative change from baseline to Month 12 in Table 24. While p-values are shown for endpoints where calculated, these should be interpreted with caution as no formal sample size calculation was performed.

Table 24: rhLAMAN-05 results

Endpoints	VA (N=15)	Placebo (N=10)
Co-primary endpoints – biomarker (serum oligosaccharides) and mobility/functional capacity (3-MSCT)		
Change from baseline to Month 12 in serum oligosaccharide (µmol/L)		
Adjusted† mean relative change, % (95% CI)	−77.60 (−81.58, −72.76)	−24.14 (−40.31, −3.59)
Adjusted mean difference from placebo, % (95% CI)	−70.47 (−78.35, −59.72)	-
p-value for difference from placebo	<0.001	-
Change from baseline to Month 12 in the 3-MSCT (steps/min)		
Adjusted mean relative change, % (95% CI)	−1.07 (−9.05, 7.61)	−3.97 (−13.38, 6.47)
Adjusted mean difference from placebo, % (95% CI)	3.01 (−9.86, 17.72)	-
p-value for difference from placebo	0.648	-

Endpoints	VA (N=15)	Placebo (N=10)
Prioritised secondary endpoints – mobility/functional capacity and lung function		
Change from baseline to Month 12 in the 6-MWT (metres)		
Adjusted mean relative change, % (95% CI)	0.64 (−4.74, 6.32)	−1.20 (−7.63, 5.68)
Adjusted mean difference from placebo, % (95% CI)	1.86 (−6.63, 11.12)	-
p-value for difference from placebo	0.664	-
Change from baseline to Month 12 in FVC percent of predicted normal value		
Adjusted mean relative change, % (95% CI)	10.11 (1.31, 19.67)	1.58 (−9.48, 13.99)
Adjusted mean difference from placebo, % (95% CI)	8.40 (−6.06, 25.08)	-
p-value for difference from placebo	0.269	-
Secondary endpoint: CHAQ and EQ-5D– quality of life (descriptive statistics only)		
Change from baseline to Month 12 in CHAQ disability index score		
Mean absolute change (SD)	-0.01 (0.32)	0.18 (0.36)
Change from baseline to Month 12 in CHAQ pain (VAS) score		
Mean absolute change (SD)	0.19 (0.69)	0.15 (0.71)
Change from baseline to Month 12 in EQ-5D index score		
Mean absolute change (SD)	0.04 (0.09)	0.03 (0.16)
Change from baseline to Month 12 in EQ-5D VAS score		
Mean absolute change (SD)	2.00 (17.95)	3.70 (15.71)
Secondary endpoint: BOT-2 – motor function		
Change from baseline to Month 12 in BOT-2 total score (points)		
Adjusted mean relative change, % (95% CI)	9.99 (3.89, 16.45)	3.73 (–3.39, 11.37)
Adjusted mean difference from placebo, % (95% CI)	6.04 (–3.21, 16.17)	-
p-value for difference from placebo	0.208	-
Secondary endpoint: Leiter R – cognition		
Change from baseline to Month 12 in TEA-VR (years)		
Adjusted mean relative change, % (95% CI)	4.18 (–0.93, 9.56)	3.89 (–2.33, 10.51)
Adjusted mean difference from placebo, % (95% CI)	0.28 (–7.43, 8.62)	-
p-value for difference from placebo	0.943	-

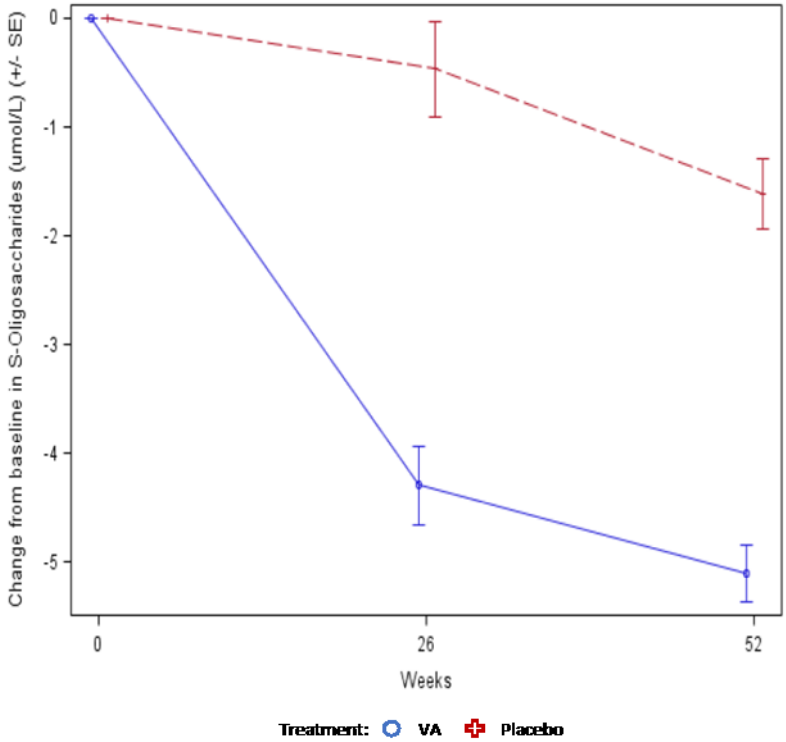
Endpoints	VA (N=15)	Placebo (N=10)
Change from baseline to Month 12 in TEA-AME (years)		
Adjusted mean relative change, % (95% CI)	2.10 (–6.61, 11.62)	4.64 (–6.20, 16.74)
Adjusted mean difference from placebo, % (95% CI)	–2.43 (–15.33, 12.43)	-
p-value for difference from placebo	0.722	-
Secondary endpoint: PTA – hearing		
Change from baseline to Month 12 in bone conduction best ear (dBHL)		
Adjusted mean relative change, % (95% CI)	6.31 (0.16, 12.83)	–1.94 (-8.62, 5.24)
Adjusted mean difference from placebo, % (95% CI)	8.40 (–1.17, 18.90)	-
p-value for difference from placebo	0.087	-
Change from baseline to Month 12 in air conduction left ear (dBHL)		
Adjusted mean relative change, % (95% CI)	3.44 (–3.70, 11.10)	0.34 (–8.10, 9.56)
Adjusted mean difference from placebo, % (95% CI)	3.09 (–8.05, 15.57)	-
p-value for difference from placebo	0.586	-
Change from baseline to Month 12 in air conduction right ear (dBHL)		
Adjusted mean relative change, % (95% CI)	4.42 (–4.47, 14.12)	-5.20 (–15.01, 5.74)
Adjusted mean difference from placebo, % (95% CI)	10.15 (–4.42, 26.93)	-
p-value for difference from placebo	0.171	-

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AME, attention and memory; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CI, confidence interval; dBHL, decibel hearing loss; EQ-5D, EuroQol five-dimension questionnaire; FVC, forced vital capacity; PTA, pure tone audiometry; SD, standard deviation; TEA, total equivalence age; VA, velmanase alfa; VAS, visual analogue scale; VR, visualisation and reasoning.
[†]Values were adjusted for baseline value and age (applicable for all adjusted means).

Biomarkers – serum oligosaccharides (co-primary endpoint)

At Month 12, serum oligosaccharide clearance was significantly (statistically) improved in the velmanase alfa group compared with the placebo group. The adjusted mean relative change is presented in Table 24. The adjusted mean absolute change from baseline to Month 12 was −5.11 µmol/L (95% CI: −5.66, −4.56) in the velmanase alfa group vs −1.61 µmol/L (95% CI: −2.28, −0.94) in the placebo group; adjusted mean difference: −3.50 µmol/L (95% CI: −4.37; −2.62; p<0.001). The absolute mean change from baseline in serum oligosaccharides by visit and treatment is presented in Figure 10.

Figure 10: Serum oligosaccharides (µmol/L) – absolute mean change from baseline

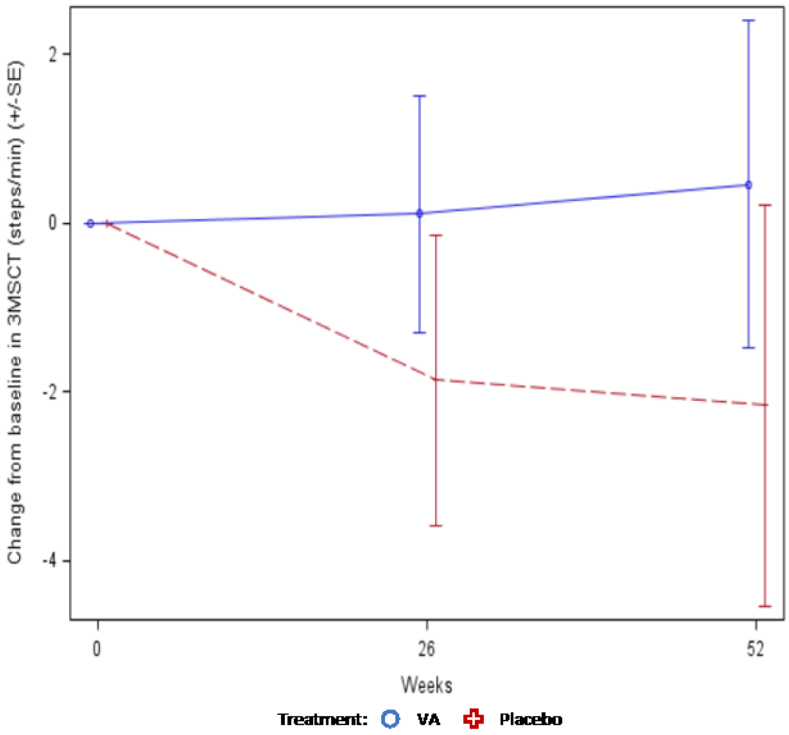


VA, n=15; placebo, n=10. P-value for between-group difference: <0.001.
Abbreviations: SE, standard error; VA, velmanase alfa.

Mobility/functional capacity – 3-MSCT (co-primary endpoint) and 6-MWT (prioritised secondary endpoint)

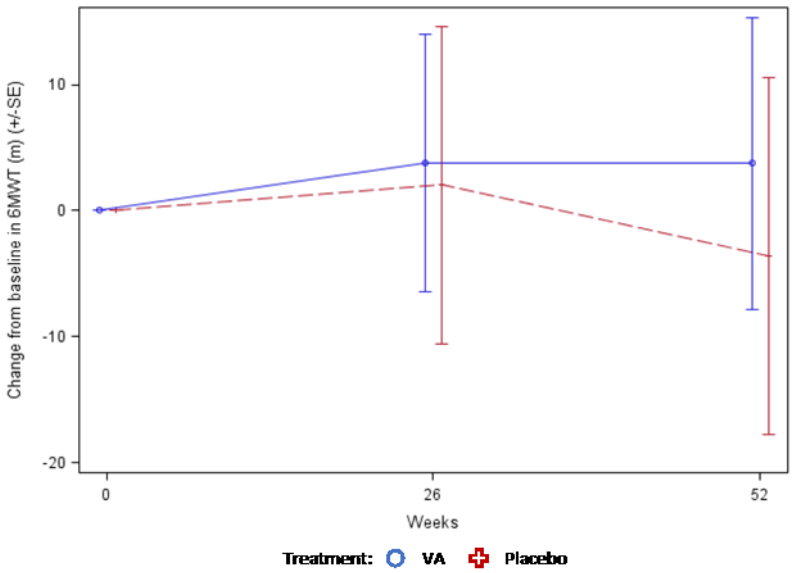
A trend towards improved mobility/functional capacity (not statistically significant) was observed at Month 12, as shown by numerical differences in favour of velmanase alfa compared with placebo for the 3-MSCT and the 6-MWT. The adjusted mean relative changes for the 3-MSCT and 6-MWT are presented in Table 24. For the 3-MSCT (velmanase alfa vs placebo), the adjusted mean absolute change from baseline to Month 12 was 0.46 steps/min (95% CI: −3.58, 4.50) vs −2.16 steps/min (95% CI: −7.12, 2.80); adjusted mean difference: 2.62 steps/min (95% CI: −3.81, 9.05; p=0.406). For the 6-MWT (velmanase alfa vs placebo), the adjusted mean absolute change from baseline to Month 12 was 3.74 m (95% CI: −20.32, 27.80) vs −3.61 m (95% CI: −33.10, 25.87); adjusted mean difference: 7.35 m (95% CI: −30.76; 45.46; p=0.692). The absolute mean change from baseline in the 3-MSCT and 6-MWT by visit and treatment is presented in Figure 11 and Figure 12, respectively. Both the 3-MSCT and the 6-MWT scores appeared to be stable in the velmanase alfa group over 12 months, potentially reflecting improved disease control. In contrast, patients in the placebo group experienced a decrease in scores; however, the difference between the velmanase alfa and placebo group was not statistically significant.

Figure 11: 3-MSCT (steps/min) – absolute mean change from baseline



VA, n=15; placebo, n=10. P-value for between-group difference: 0.406
Abbreviations: 3-MSCT, 3-minute stair climb test; SE, standard error; VA, velmanase alfa.

Figure 12: 6-MWT (metres) – absolute mean change from baseline



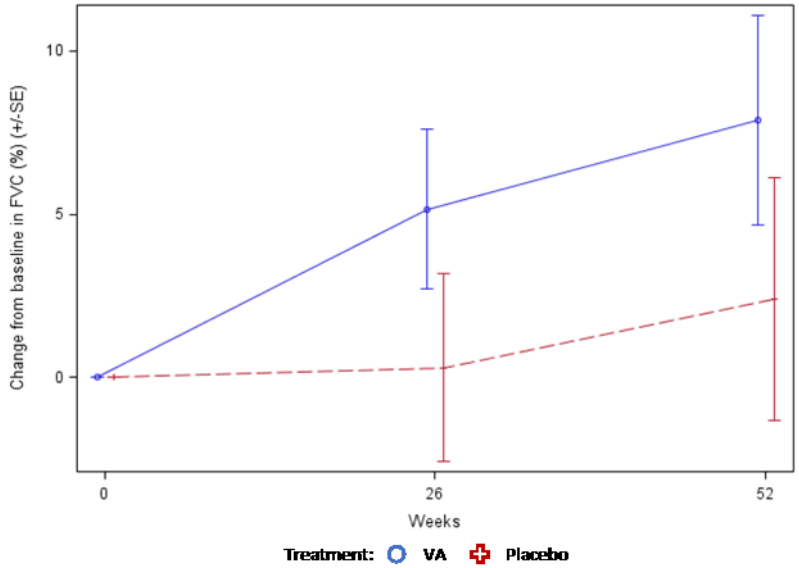
VA, n=15; placebo, n=10. P-value for between-group difference: 0.692
Abbreviations: 6-MWT, 6-minute walk test; SE, standard error; VA, velmanase alfa.

Lung function – FVC (% of predicted) (prioritised secondary endpoint)

At Month 12, a trend for improved lung function, as measured by FVC % of predicted, was observed in the velmanase alfa group compared with the placebo group, although the difference did not reach statistical significance. The adjusted mean relative change

is presented in Table 24. The adjusted mean absolute change from baseline to Month 12 was 8.21 % of predicted (95% CI: 1.79, 14.63) in the velmanase alfa group vs 2.30 % of predicted (95% CI: −6.19, 10.79) in the placebo group; adjusted mean difference: 5.91 % of predicted (95% CI: −4.78; 16.60; p=0.278). The absolute mean change from baseline in the FVC (% of predicted) by visit and treatment is presented in Figure 13.

Figure 13: FVC (% of predicted) – absolute mean change from baseline



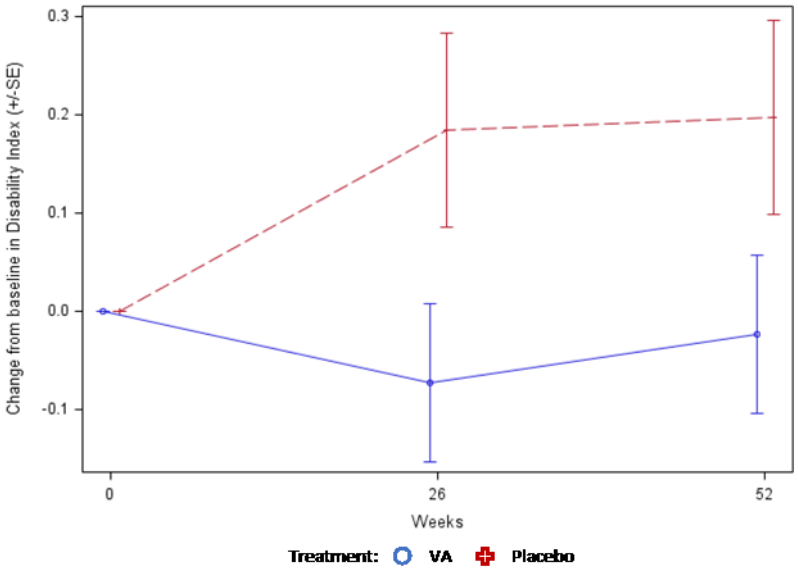
VA, n=15; placebo, n=10. P-value for between-group difference: 0.278
Abbreviations: FVC, forced vital capacity; SE, standard error; VA, velmanase alfa.

In addition to FVC (% of predicted), lung function was also measured by FVC (L), FEV_1 (% of predicted), FEV_1 (L) and PEF (L/s); these results are presented in Appendix 7 (Section 17.7.1, Table 129). Overall, a trend for improved lung function compared with placebo was apparent in the velmanase alfa group for all additional PFT endpoints. While patients in both the velmanase alfa and placebo group experienced an improvement in pulmonary function, velmanase alfa demonstrated a numerical advantage over placebo for all PFT secondary endpoints, although no statistically significant differences were observed.

Quality of life – CHAQ and EQ-5D

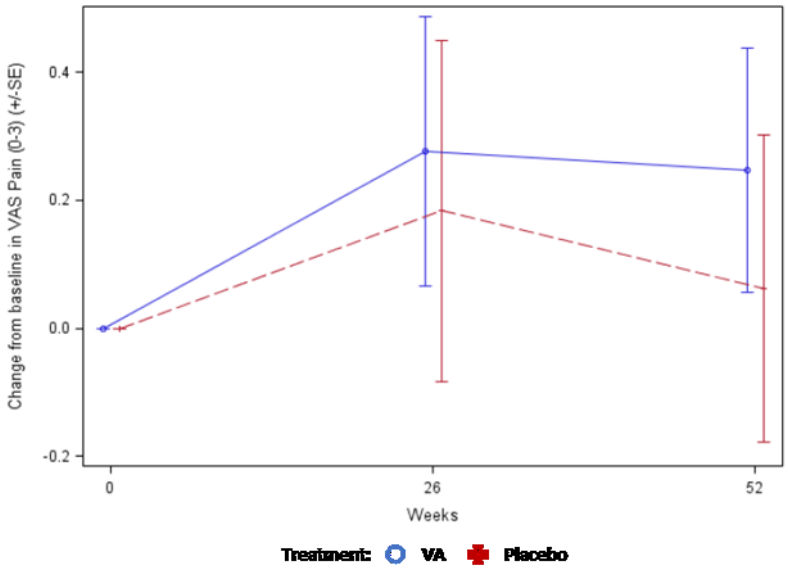
A trend for improved QoL with velmanase alfa was observed; however, change from baseline in CHAQ and EQ-5D scores were analysed using descriptive statistics only. Changes in CHAQ disability index and pain (VAS) scores are presented in Table 24, Figure 14 and Figure 15. Changes in EQ-5D index and VAS scores are presented in Table 24, Figure 16 and Figure 17.

Figure 14: CHAQ disability index (score) – mean change from baseline



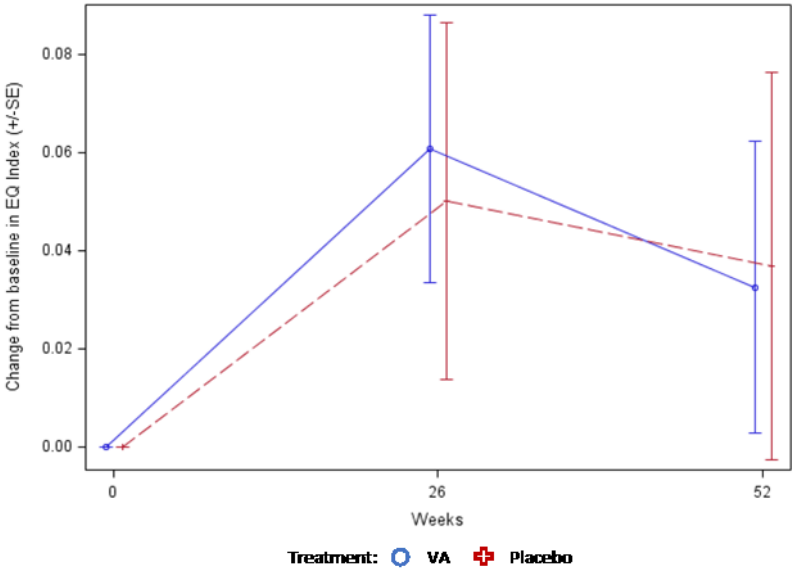
VA, n=15; placebo, n=10.
Abbreviations: CHAQ, childhood health assessment questionnaire; SE, standard error; VA, velmanase alfa.

Figure 15: CHAQ pain (VAS) – mean change from baseline



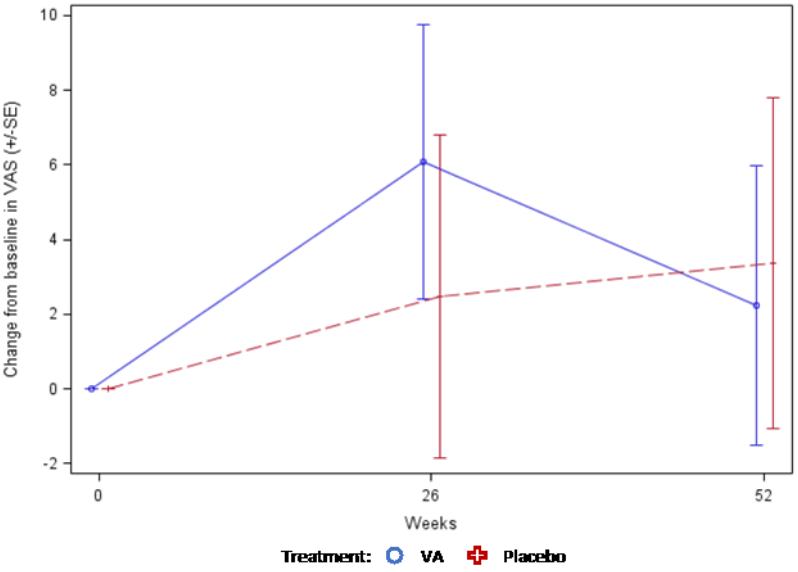
VA, n=15; placebo, n=10.
Abbreviations: CHAQ, childhood health assessment questionnaire; SE, standard error; VA, velmanase alfa; VAS, visual analogue scale.

Figure 16: EQ-5D Index (score) – absolute mean change from baseline



VA, n=15; placebo, n=10.
Abbreviations: EQ-5D, EuroQol five-dimension questionnaire; SE, standard error, VA, velmanase alfa.

Figure 17: EQ-5D VAS (score) – absolute mean change from baseline



VA, n=15; placebo, n=10.
Abbreviations: EQ-5D, EuroQol five-dimension questionnaire; SE, standard error, VA, velmanase alfa; VAS, visual analogue scale.

Motor function – BOT-2

Overall, a trend for improved motor function was observed in the velmanase alfa group compared with the placebo group (Table 24). The Month-12 results for the four composite (domain) point scores are presented in Appendix 7 (Section 17.7.1, Table 130). With the exception of running speed and agility, velmanase alfa demonstrated a numerical advantage over placebo for the composite (domain) point scores, although no statistically significant differences were observed.

Cognition – Leiter R

Overall, no significant difference in cognitive ability (as measured by the Leiter-R test) was observed between the velmanase alfa and placebo groups at Month 12 (Table 24)

Hearing – PTA

Overall, hearing loss as measured by PTA tests (bone conduction [best ear] and air conduction [left and right ear]) was statistically similar between the velmanase alfa and placebo groups at Month 12; however, the results numerically favoured the placebo group (Table 24).

Additional secondary outcomes

Although less relevant to the decision problem, the results for the change from baseline in CSF oligosaccharides, tau, neurofilament protein (NFLp) and glial fibrillary acidic protein (GFAp) at Month 12 are presented in Appendix 7 (Section 17.7.1, Table 131) for completeness.

Post-hoc analysis – results by age class

Patients were analysed according to age class (<18 vs ≥18 years) as part of a post-hoc analyses; this classification is the age of patients at the time of starting treatment. The change from baseline to Month 12 for serum oligosaccharides, 3-MSCT, 6-MWT, and FVC (% of predicted) is presented by age class in Table 25.

While both adult and paediatric patients receiving velmanase alfa had favourable changes from baseline in serum oligosaccharides compared with placebo, the difference between velmanase alfa and placebo was greater (more improved) in the paediatric group (–63.4 percentage points in favour of velmanase alfa) than in adults (–46.9 percentage points in favour of velmanase alfa). Similarly, for the 3-MSCT, the 10.2 percentage point difference between the paediatric velmanase alfa and placebo groups (in favour of velmanase alfa) was greater than the percentage point difference observed in the adult population (–1.3 percentage points in favour of placebo). In contrast, the 6-MWT difference between velmanase alfa and placebo was greater in adult patients (3.2 percentage points in favour of velmanase alfa) compared with paediatric patients (0.8 percentage points in favour of velmanase alfa). However, this was largely due to a decrease in scores in the adult placebo group, while scores increased in the paediatric placebo group. For FVC (% of predicted), the difference between velmanase alfa and placebo was greater (more improved) in the paediatric group (11.0 percentage points in favour of velmanase alfa) than in adults (6.4 percentage points in favour of velmanase alfa).

Results of additional PFT endpoints and BOT-2 (total and domain score) by age class are shown in Appendix 7 (Section 17.7.1, Table 132 and Table 133)

Overall, the difference between velmanase alfa and placebo was greater (more improved) in the paediatric group than in adults for all PFT secondary outcomes. The difference between velmanase alfa and placebo was also greater (more improved) in the paediatric group than in adults for BOT-2 total and domain scores.

Table 25: Primary and prioritised secondary endpoints by age class

Outcome	Mean change from baseline to Month 12 (SD)			
	<18 years		≥18 years	
	VA (n=7)	Placebo (n=5)	VA (n=8)	Placebo (n=5)
Serum oligosaccharides (µmol/L)				
Relative change, %	−70.6 (14.6)	−7.2 (19.3)	−80.3 (4.4)	−33.4 (22.2)
VA - placebo†	-63.4	-	-46.9	-
3-MSCT (steps/min)				
Relative change, %	5.8 (18.0)	−4.4 (10.8)	−4.1 (13.7)	−2.8 (16.4)
VA - placebo†	10.2	-	-1.3	-
6-MWT (metres)				
Relative change, %	2.0 (7.8)	1.2 (9.4)	0.4 (11.7)	–2.8 (12.8)
VA - placebo†	0.8	-	3.2	-
FVC (% of predicted)				
n	6	4	6	5
Relative change, %	20.5 (11.2)	9.5 (5.6)	2.3 (7.5)	–4.1 (18.7)
VA - placebo†	11.0	-	6.4	-

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; FVC, forced vital capacity; SD, standard deviations; VA, velmanase alfa.
†The differences between the VA and placebo group are provided for descriptive purposes only. For serum oligosaccharides, positive values indicate a treatment effect in favour of placebo. For 3-MSCT, 6-MWT and FVC (% of predictive) negative values indicate a treatment effect in favour of placebo.

Post-hoc analysis – serum IgG (biomarker)

The absolute changes from baseline to Month 12 in serum IgG (g/L) were analysed by analysis of covariance (ANCOVA) with treatment as a fixed factor, and baseline values and age as continuous covariates. An increase in serum IgG represented an improvement.

Serum IgG mean (SD) values at baseline were 9.00 g/L (5.02) and 7.27 g/L (1.64) for the velmanase alfa and placebo groups, respectively. At Month 12, treatment with velmanase alfa resulted in a statistically significant increase in serum IgG levels compared with placebo. The adjusted (for baseline value and age) mean change from baseline was 3.59 g/L (95% CI: 2.75, 4.43) in the velmanase alfa group and 0.12 g/L (95% CI: –0.91, 1.16) in the placebo group; the adjusted mean difference was 3.47 g/L (95% CI: 2.12, 4.81; p<0.001).

When expressed in terms of normal range, 5/15 patients in the velmanase alfa group and 3/10 in the placebo group had low serum IgG levels, comparable with hypogammaglobulinaemia, at baseline. At Month 12, 3/5 patients in the velmanase alfa group reverted to normal serum IgG levels, while the other two patients experienced substantial improvements. In contrast, no patients in the placebo group reverted to normal serum IgG levels after 12 months.

Conclusion

- The biological activity of velmanase alfa was confirmed through statistically significant improvements in serum oligosaccharide clearance compared with placebo: the adjusted mean difference (relative change from baseline) for velmanase alfa vs placebo was –70.47% (95% CI: –78.35, –59.72; p<0.001)
- Treatment with velmanase alfa demonstrated a numerical advantage over placebo in the 3-MSCT, suggesting a more favourable effect on mobility/functional capacity: the adjusted mean difference (relative change from baseline) for velmanase alfa vs placebo was 3.01% (95% CI: –9.86, 17.72; p=0.648)
- Analysis of prioritised secondary endpoints showed trends in favour of velmanase alfa for measures of mobility/functional capacity and lung function:
    - For the 6-MWT, the adjusted mean difference (relative change from baseline) for velmanase alfa vs placebo was 1.86% (95% CI: –6.63, 11.12; p=0.664)
    - For the FVC (% of predicted), the adjusted mean difference (relative change from baseline) for velmanase alfa vs placebo was 8.40% (95% CI: –6.06, 25.08; p=0.269)
- The 3-MSCT and 6-MWT results may be confounded by the lack of patient selection at baseline according to motor performance and a potential unbalance in the severity of patients in favour of placebo. In addition, these tests are dependent upon a patient's motivation and understanding to complete the task, which may present a problem in paediatric and/or cognitively-impaired patients
- The ability to observe a large treatment effect in the 3-MSCT and 6-MWT may have also been limited, as patients were generally well functioning at baseline. This limitation is known as a 'ceiling effect' and suggests that improvement is more difficult to observe in patients who have baseline values approaching the normal range
- A trend for improved lung function compared with placebo was apparent in the velmanase alfa group for all additional PFT endpoints (FVC [L], FEV_1 [L and % of predicted] and PEF [L/s]), suggesting that velmanase alfa may help to prevent deterioration of lung function
- While both adult and paediatric patients receiving velmanase alfa had favourable changes from baseline in serum oligosaccharides, the 6-MWT, FVC (L and % of predicted) and BOT-2 total score compared with placebo, the difference between velmanase alfa and placebo was greater in the paediatric group than in adults. Velmanase alfa may therefore be of particular value in patients aged <18 years at the time of starting treatment

9.6.1.2 rhLAMAN-10

The results presented in this section are from the analysis of the rhLAMAN-10 integrated data set, which comprised data from the Phase I-II trial, rhLAMAN-05, rhLAMAN-07, rhLAMAN-09 and the rhLAMAN-10 CEV. The efficacy analysis was carried out on the FAS, which consisted of all patients who were dosed and whose efficacy was evaluated post-baseline. Results of the outcomes relevant to the decision problem are presented as the adjusted (for age and baseline value) mean absolute and relative change from baseline to last observation in Table 26. Last observation is a composite value comprising a range of follow-up times (12–48 months of active treatment). While p-values are shown for endpoints where calculated, these should be interpreted with caution as no formal sample size calculation was performed.

Table 26: rhLAMAN-10 results

Endpoints	Overall (N=33)	P-value vs baseline
Co-primary endpoints – biomarker (serum oligosaccharides) and mobility/functional capacity (3-MSCT)		
Change from baseline to last observation in serum oligosaccharide (µmol/L)		
Absolute mean change (95% CI)	–4.59 (–5.74, –3.45)	<0.001
Relative mean change, % (95% CI)	–62.8 (–74.7, –50.8)	<0.001
Change from baseline to last observation in 3-MSCT (steps/min)		
Absolute mean change (95% CI)	6.38 (2.65, 10.12)	0.001
Relative mean change, % (95% CI)	13.77 (4.61, 22.92)	0.004
Secondary endpoint: 6-MWT – mobility/functional capacity		
Change from baseline to last observation in the 6-MWT (metres)		
Absolute mean change (95% CI)	22.4 (0.0, 44.8)	0.050
Relative mean change, % (95% CI)	7.1 (–0.7, 14.9)	0.071
Secondary endpoint: FVC (% of predicted) – lung function		
Change from baseline to last observation in FVC percent of predicted normal value		
n	29	-
Absolute mean change (95% CI)	8.1 (2.4, 13.7)	0.007
Relative mean change, % (95% CI)	10.5 (2.6, 18.5)	0.011

Endpoints	Overall (N=33)	P-value vs baseline
Secondary endpoint: CHAQ and EQ-5D – quality of life		
Change from baseline to last observation in CHAQ disability index score		
n	33	-
Absolute mean change (95% CI)	–0.13 (–0.29, 0.02)	0.095
n	31	-
Relative mean change, % (95% CI)	–2.41 (–18.9, 14.11)	0.768
Change from baseline to last observation in CHAQ pain (VAS) score		
n	32	-
Absolute mean change (95% CI)	–0.17 (–0.41, 0.06)	0.139
n	21	-
Relative mean change, % (95% CI)	–17.0 (–67.0, 32.94)	0.485
Change from baseline to last observation in EQ-5D index score		
n	24	
Absolute mean change (95% CI)	0.05 (–0.01, 0.11)	0.080
Relative mean change, % (95% CI)	11.23 (0.79, 21.67)	0.036
Change from baseline to last observation in EQ-5D VAS score		
n	24	
Absolute mean change (95% CI)	3.3 (–4.5, 11.1)	0.391
Relative mean change, % (95% CI)	11.5 (–3.1, 26.1)	0.117
Secondary endpoint: BOT-2 – motor function		
Change from baseline to last observation in BOT-2 total score (points)		
Absolute mean change (95% CI)	5.1 (–3.4, 13.6)	0.230
Relative mean change, % (95% CI)	13.0 (1.0, 25.0)	0.035
Secondary endpoint: Leiter R – cognition		
Change from baseline to last observation in TEA-VR (years)		
Absolute mean change (95% CI)	0.27 (0.04, 0.49)	0.023
Relative mean change, % (95% CI)	5.34 (1.63, 9.04)	0.006
Change from baseline to last observation in TEA-AME (years)		
n	24	-
Absolute mean change (95% CI)	0.16 (–0.49, 0.80)	0.619
Relative mean change, % (95% CI)	9.35 (–4.37, 23.06)	0.172

Endpoints	Overall (N=33)	P-value vs baseline
Secondary endpoint: PTA – hearing		
Change from baseline to last observation in bone conduction best ear (dBHL)		
n	32	-
Absolute mean change (95% CI)	–0.49 (–2.86, 1.88)	0.674
Relative mean change, % (95% CI)	–0.72 (–5.96, 4.52)	0.782
Change from baseline to last observation in air conduction left ear (dBHL)		
Absolute mean change (95% CI)	–2.83 (–5.36, –0.29)	0.030
Relative mean change, % (95% CI)	–3.79 (–7.58, 0.00)	0.050
Change from baseline to last observation in air conduction right ear (dBHL)		
Absolute mean change (95% CI)	–1.41 (–5.06, 2.25)	0.438
Relative mean change, % (95% CI)	0.54 (–6.62, 7.70)	0.878
Secondary endpoint: serum IgG – biomarker		
Change from baseline to Month 12 in CHAQ disability index score		
n	24	-
Absolute mean change (95% CI)	3.05 (2.39, 3.71)	<0.001
Relative mean change, % (95% CI)	44.07 (32.58, 55.57)	<0.001

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AME, attention and memory; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CI, confidence interval; dBHL, decibel hearing loss; FVC, forced vital capacity; PTA, pure tone audiometry; SD, standard deviation; TEA, total equivalence age; VAS, visual analogue scale; VR, visualisation and reasoning.

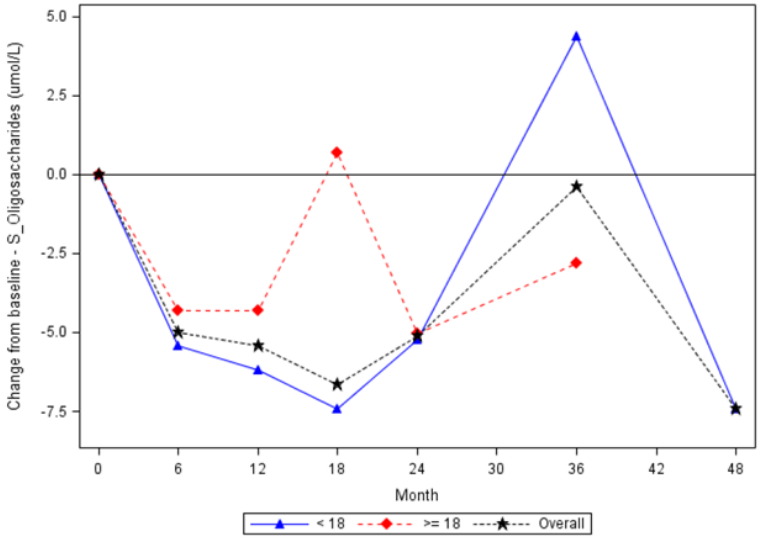
Biomarkers – serum oligosaccharides (co-primary endpoint) and serum IgG

Serum oligosaccharides

In the overall population, treatment with velmanase alfa resulted in a statistically significant and sustained reduction in serum oligosaccharide concentration, reflecting the effect that velmanase alfa has at the cellular level (Table 26).

The analysis of serum oligosaccharides by time point and age of starting treatment with velmanase alfa is presented in Figure 18. This analysis confirms that velmanase alfa can reduce serum oligosaccharides in both paediatric and adult patients. The relative mean (SD) change from baseline to last observation was similar in both age groups: –66.6% (36.09%) for patients aged <18 years and –57.6% (30.46%) for patients aged ≥18 years. The absolute mean (SD) changes from baseline were –5.26 µmol/L (3.74 µmol/L) and –3.68 µmol/L (2.20 µmol/L), respectively. The analysis of serum oligosaccharides by time point and parental study is presented in Appendix 7 (Section 17.7.2.2, Figure 49) and showed that patients from the Phase I/II trial and rhLAMAN-05 demonstrated a similar trend for reduction in serum oligosaccharides.

Figure 18: Serum oligosaccharides (µmol/L) – absolute mean change from baseline by time point and age of starting treatment with velmanase alfa



	Overall	<18	≥18
BL	N=33	N=19	N=14
M6	n=24	n=15	n=9
M12	n=31	n=18	n=13
M18	n=11	n=10	n=1
M24	n=10	n=4	n=6
M36	n=3	n=1	n=2
M48	n=9	n=9	n=0

P-value for change from baseline to last observation for overall population: <0.001.
Abbreviations: BL, baseline; M, month.

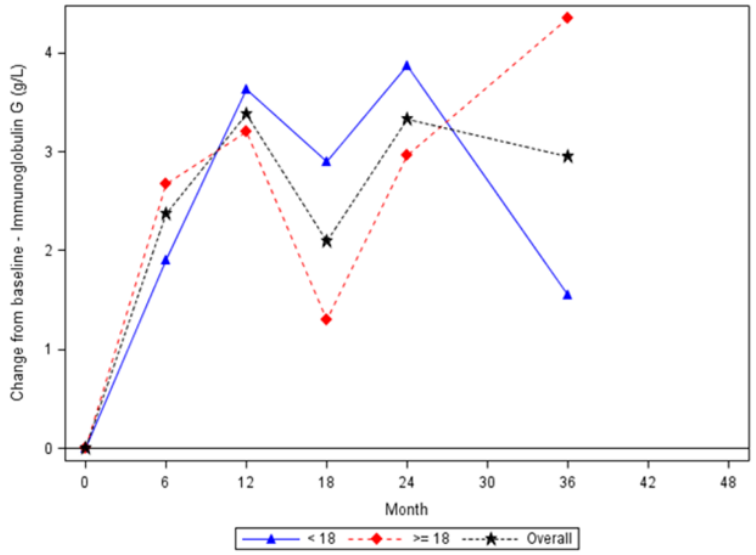
The analysis of serum oligosaccharides by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in an improvement in patient status; only 9.1% were considered to be seriously impaired for serum oligosaccharides at last observation, compared with 81.8% at baseline Appendix 7 (Section 17.7.2.3). When the ADA status of patients was taken into account, both ADA positive and negative patients experienced a reduction in serum oligosaccharides from baseline to last observation (Appendix 7, Section 17.7.2.4).

Serum IgG

In the overall population, treatment with velmanase alfa resulted in a statistically significant and sustained improvement in serum IgG levels, which may indicate an overall improvement in immune function (Table 26).

The analysis of serum IgG by time point and age of starting treatment with velmanase alfa is presented in Figure 19. While both paediatric and adult patients improved from baseline, there was a trend for a greater improvement in serum IgG in paediatric patients compared with adults. The relative mean (SD) change from baseline to last observation was 51.72% (33.28%) for patients aged <18 years and 38.61% (21.62%) for patients aged ≥18 years; the absolute mean (SD) changes from baseline were 3.24 g/L (1.92 g/L) and 2.91 g/L (1.31 g/L), respectively.

Figure 19: Serum IgG (g/L) – absolute mean change from baseline by time point and age of starting treatment with velmanase alfa



	Overall	<18	≥18
BL	N=24	N=10	N=14
M6	n=15	n=6	n=9
M12	n=22	n=9	n=13
M18	N=2	n=1	n=1
M24	n=10	n=4	n=6
M36	n=4	n=2	n=2
M48	n=0	n=0	n=0

P-value for change from baseline to last observation for overall population: <0.001.
Abbreviations: BL, baseline; M, month.

The analysis of serum IgG by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in a notable reduction in the number of patients considered to be impaired (29.2% at baseline to 12.5% at last observation) and seriously impaired (8.3% at baseline to 0% at last observation) for serum IgG levels, with the majority of patients (87.5%) considered to have no or minor impairment at last observation (Appendix 7, Section 17.7.2.3). When the ADA status of patients was taken into account, improvements in serum IgG levels were observed in both ADA negative and positive patients (Appendix 7, Section 17.7.2.4).

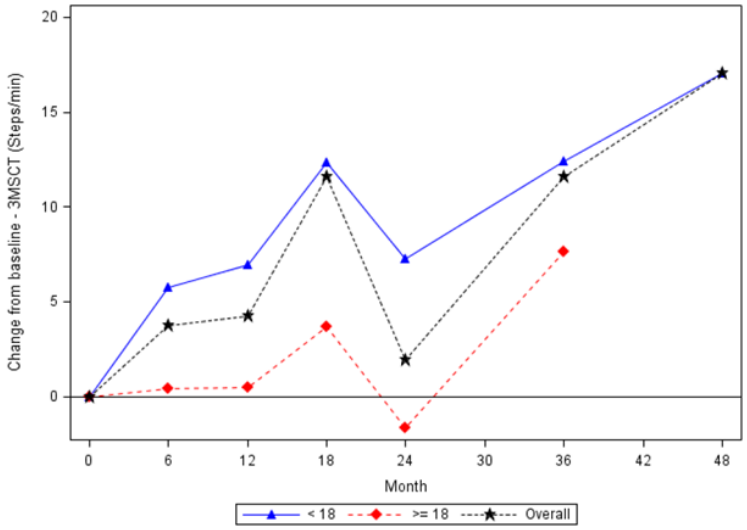
Mobility/functional capacity – 3-MSCT (co-primary endpoint) and 6-MWT

3-MSCT

In the overall population, treatment with velmanase alfa resulted in a statistically significant and sustained improvement in mobility/functional capacity as measured by the 3-MSCT (Table 26).

The analysis of the 3-MSCT by time point and age of starting treatment with velmanase alfa is also presented in Figure 20. While both paediatric and adult patients improved from baseline, there was a trend for a greater improvement in the 3-MSCT in paediatric patients compared with adults. The relative mean (SD) change from baseline to last observation was 23.11% (27.27%) for patients aged <18 years and 1.08% (17.65%) for patients aged ≥18 years; the absolute mean (SD) changes from baseline were 10.65 steps/min (10.32 steps/min) and 0.60 (7.97 steps/min), respectively. The analysis of the 3-MSCT by time point and parental study is presented in Appendix 7 (Section 17.7.2.2, Figure 50) and showed that while improvements were observed in both groups, there was a trend for a greater improvement in the 3-MSCT in patients from the Phase I/II trial compared with patients from rhLAMAN-05; this is in line with the age subgroup analysis, as the Phase I/II trial only included paediatric patients.

Figure 20: 3-MSCT (steps/min) – absolute mean change from baseline by time point and age of starting treatment with velmanase alfa



	Overall	<18	≥18
BL	N=33	N=19	N=14
M6	n=24	n=15	n=9
M12	n=31	n=18	n=13
M18	n=11	n=10	n=1
M24	n=10	n=4	n=6
M36	n=6	n=5	n=1
M48	n=9	n=9	n=0

P-value for change from baseline to last observation for overall population: 0.001.
Abbreviations: 3-MSCT, 3-minute stair climb test; BL, baseline; M, month.

The analysis of 3-MSCT by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in an increase in the proportion of patients considered to have no or minor impairment at last observation (60.6%) compared with baseline (39.4%) (Appendix 7, Section 17.7.2.3). When the ADA status of patients was taken into account, improvements in the 3-MSCT were observed in both ADA negative and positive patients (Appendix 7, Section 17.7.2.4).

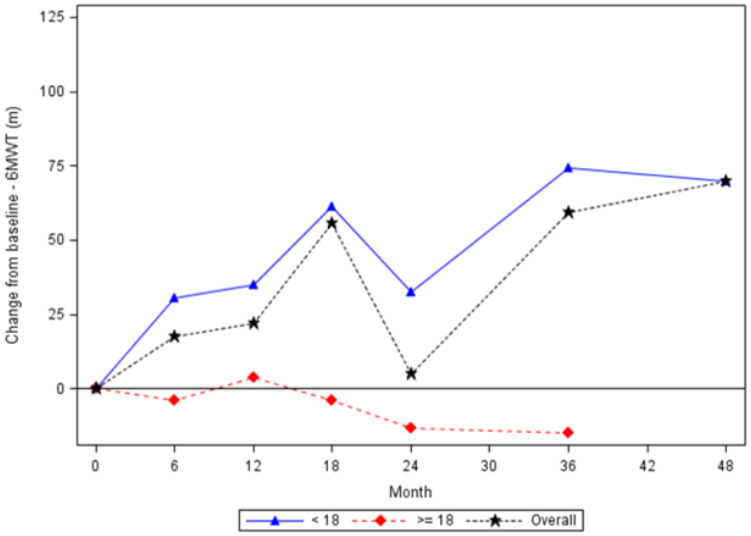
6-MWT

Mobility was also assessed using the 6-MWT. Overall, treatment with velmanase alfa resulted in a statistically significant (absolute change only) and sustained improvement in mobility/functional capacity as measured by the 6-MWT (Table 26). The results of the analysis of 6-MWT (% of predicted) did not show any statistically significant changes from baseline at any time point. Mean 6-MWT (% of predicted) was relatively high at baseline and showed a small increase from baseline to last observation in patients overall; the absolute mean change was 1.16 % of predicted (95% CI: –2.13, 4.46; p=0.478) and the relative change was 3.6% (95% CI: –2.94, 10.04; p=0.273).

The analysis of the 6-MWT (m) by time point and age of starting treatment with velmanase alfa is also presented in Figure 21, which shows that the benefit of velmanase alfa treatment was predominantly in paediatric patients compared with adults. The relative mean (SD) change from baseline to last observation was 11.9% (26.6%) for patients aged <18 years and 0.7% (11.6%) for patients aged ≥18 years; the absolute mean (SD) changes from baseline were 39.1 m (67.6 m) and –0.3 m (50.5 m), respectively. The results of the analysis of 6-MWT (% of predicted) demonstrated a small increase from baseline to last observation in patients age <18 years old. The absolute mean (SD) change was 1.87 % of predicted (10.56 % of predicted) and the relative mean (SD) change was 5.37% (22.04%). No change was observed in patients aged ≥18 years. The analysis of the 6-MWT (m) by time point and parental study is presented in Appendix 7 (Section 17.7.2.2, Figure 51), which again demonstrates that the benefit of velmanase

alfa treatment was predominantly in patients from the Phase I/II trial compared with patients from the rhLAMAN-05. This observation is in line with the age subgroup analysis, as the Phase I/II trial only enrolled paediatric patients.

Figure 21: 6-MWT (metres) – absolute mean change from baseline by time point and age of starting treatment with velmanase alfa



	Overall	<18	≥18
BL	N=33	N=19	N=14
M6	n=24	n=15	n=9
M12	n=31	n=18	n=13
M18	n=11	n=10	n=1
M24	n=10	n=4	n=6
M36	n=6	n=5	n=1
M48	n=9	n=9	n=0

P-value for change from baseline to last observation for overall population: 0.050.
Abbreviations: 6-MWT, 6-minute walk test; BL, baseline; M, month.

The analysis of 6-MWT (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in modest reductions in the number of patients considered to be seriously impaired based on the 6 MWT (% of predicted; 6.1% at baseline to 0% at last observation) (Appendix 7, Section 17.7.2.3). When the ADA status of patients was taken into account, improvements in the 6-MWT (metres and % of predicted) were observed in both ADA negative and positive patients (Appendix 7, Section 17.7.2.4).

Lung function – FVC (% of predicted)

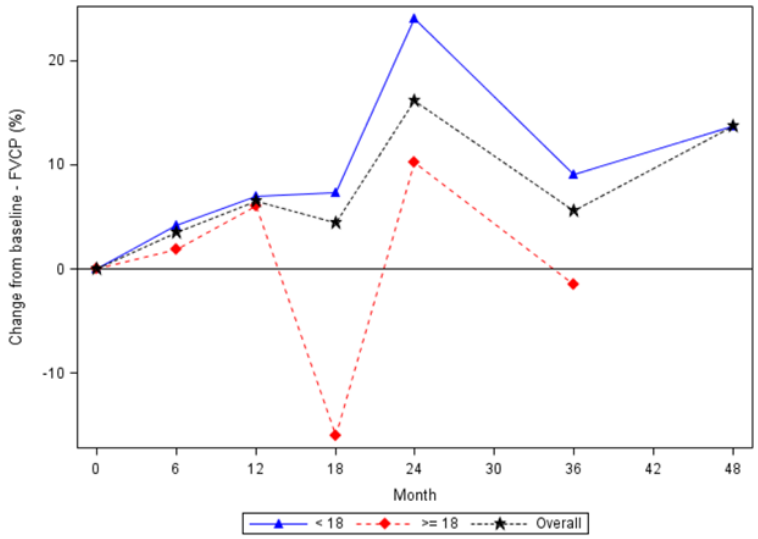
In the overall population, the analysis of FVC (% of predicted) revealed a statistically significant improvement in lung function from baseline with velmanase alfa (Table 26).

The analysis of FVC (% of predicted) by time point and age of starting treatment with velmanase alfa is presented in Figure 22. While both paediatric and adult patients showed improvements from baseline, there was a trend for a greater improvement in FVC (% of predicted) in paediatric patients compared with adults. At baseline, FVC (% of predicted) was lower in patients aged <18 years compared with those aged ≥18 years. For FVC (% of predicted), the relative mean (SD) change from baseline to last observation was 16.4% (22.0%) for patients aged <18 years and 2.1% (16.7%) for patients aged ≥18 years; the absolute mean (SD) changes from baseline were 11.6 % of predicted (15.7 % of predicted) and 3.0 % of predicted (12.4 % of predicted), respectively. The analysis of FVC (% of predicted) by time point and parental study is presented in Appendix 7 (Section 17.7.2.2, Figure 52) and showed that while improvements were observed in both groups, there was a trend for a greater improvement in FVC (% of predicted) in patients from the Phase I/II trial compared with

patients from the rhLAMAN-05; this is in line with the age subgroup analysis, as the Phase I/II trial only enrolled paediatric patients.

In addition to FVC (% of predicted), lung function was also measured by FVC (L), FEV_1 (% of predicted), FEV_1 (L) and PEF (L/s); these results are presented in Appendix 7 (Section 17.7.2.1 for overall results and by age class; Section 17.7.2.2 for results by parental study). Together, the results from the PFT secondary endpoints demonstrate that velmanase alfa can produce statistically significant improvements in lung function in patients with AM.

Figure 22: FVC (% of predicted) – absolute mean change from baseline by time point and age of starting treatment with velmanase alfa



	Overall	<18	≥18
BL	N=29	N=17	N=12
M6	n=20	n=14	n=6
M12	n=28	n=17	n=11
M18	n=8	n=7	n=1
M24	n=7	n=3	n=4
M36	n=6	n=4	n=2
M48	n=7	n=7	n=0

P-value for change from baseline to last observation for overall population: 0.050.
Abbreviations: BL, baseline; FVC, forced vital capacity; M, month.

The analysis of FVC (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in a small increase in the number of patients considered to have no or some impairment based on FVC (% of predicted; 58.6% at baseline to 67.7% at last observation); similar results were observed when the analysis was based on FEV_1 (% of predicted) (Appendix 7, Section 17.7.2.3).

Quality of life – CHAQ disability index, CHAQ pain (VAS), assistance required for ambulation and EQ-5D

CHAQ disability index and pain (VAS)

In the overall population, treatment with velmanase alfa resulted in an improvement in QoL, as measured by a numerical improvement in the CHAQ scores (Table 26).

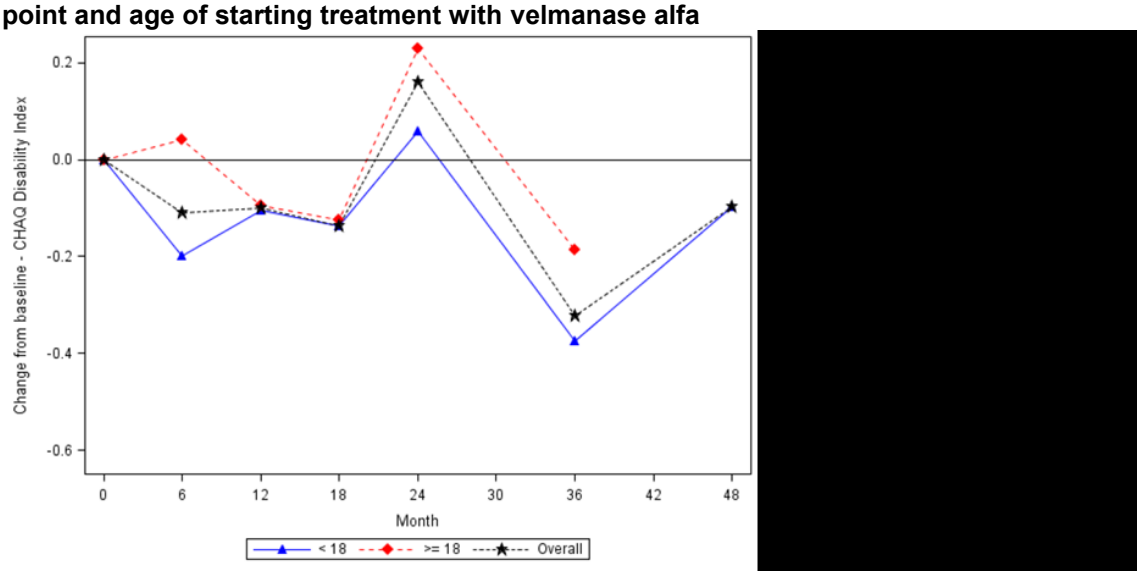
The analysis of the CHAQ disability index and pain (VAS) by time point and age of starting treatment with velmanase alfa is presented in Figure 23 and Figure 24. While both paediatric and adult patients showed a trend towards an improvement, a greater improvement in CHAQ disability index scores was observed in paediatric patients compared with adults. The relative mean (SD) change from baseline to last observation was –6.82% (57.09%) for patients aged <18 years and 2.94% (24.73%) for patients aged ≥18 years; the absolute mean (SD) changes from baseline were –0.24 (0.48) and 0.02

(0.36), respectively. In contrast, a greater improvement in CHAQ pain (VAS) scores was observed in adult patients compared with paediatric patients. The relative mean (SD) change from baseline to last observation was –0.40% (144.3%) for patients aged <18 years and –35.3% (54.27%) for patients aged ≥18 years; the absolute mean (SD) changes from baseline were –0.07 (0.60) and –0.31 (0.70), respectively. This may be explained by the higher level of pain experienced by adults (0.834) compared with paediatric patients (0.450) at baseline, which would allow more room for change.

The analysis of the CHAQ disability index and pain (VAS) by time point and parental study is presented in Appendix 7 (Section 17.7.2.2, Figure 56 and Figure 57). Although CHAQ disability index scores were more improved in paediatric patients compared with adults, patients from rhLAMAN-05 showed greater improvements compared with patients from the Phase I/II trial, who were all <18 years old at enrolment. This result is largely attributed to the relatively large improvements in CHAQ disability index scores observed in the paediatric patients from rhLAMAN-05.

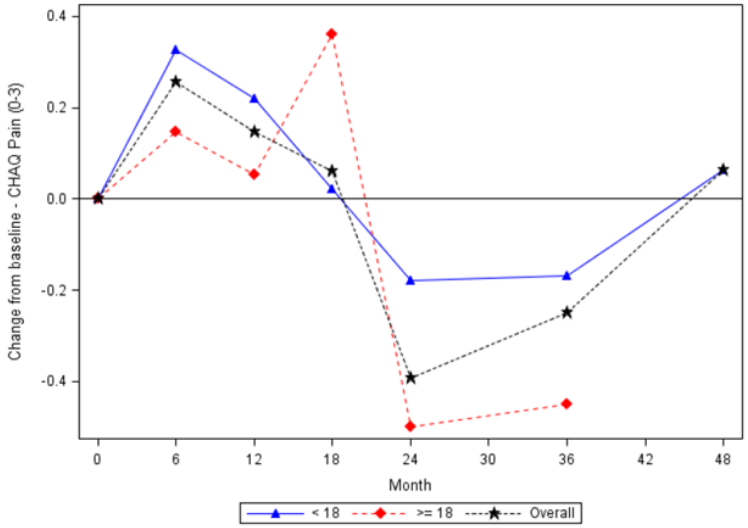
The analysis of CHAQ disability index by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in modest reductions in the number of patients considered to be seriously impaired based on the CHAQ disability index (27.3% at baseline to 18.2% at last observation) (Appendix 7, Section 17.7.2.3). In addition, a small increase in the number of patients considered to have no or some impairment was apparent based on CHAQ pain scores (75.0% at baseline to 84.8% at last observation).

Figure 23: CHAQ disability index (score) – absolute mean change from baseline by time point and age of starting treatment with velmanase alfa



P-value for change from baseline to last observation for overall population: 0.095.
Abbreviations: BL, baseline; CHAQ, childhood health assessment questionnaire; M, month.

Figure 24: CHAQ pain (VAS) – absolute mean change from baseline by time point and age of starting treatment with velmanase alfa



	Overall	<18	≥18
BL	N=32	N=18	N=14
M6	n=23	n=14	n=9
M12	n=30	n=17	n=13
M18	n=9	n=8	n=1
M24	n=9	n=3	n=6
M36	n=7	n=5	n=2
M48	n=9	n=9	n=0

P-value for change from baseline to last observation for overall population: 0.139.
Abbreviations: BL, baseline; CHAQ, childhood health assessment questionnaire; M, month; VAS, visual analogue scale.

CHAQ – assistance required for ambulation

If aids or assistive devices were used by patients, the minimum score for the corresponding domain is 2 (with much difficulty). The CHAQ classifies ambulatory aids as a cane, walker, crutches, or wheelchair use; a category exists for walking that requires assistance from another person (99). Aids or assistive devices also include devices to assist with dressing, eating, or using a pencil.

Overall, ten patients required help from a person, walking aids, or a wheelchair at baseline. Of the ten patients, seven (70%) became device- or third party-independent at last observation: 4/5 (80%) paediatric patients and 3/5 (60%) adults. In particular, two paediatric patients and one adult forced to adopt the wheelchair for long distance mobility/functional capacity at baseline discontinued use at last observation.

Overall, three patients out of the 23 (13%) who did not require help from a person, walking aids, or a wheelchair at baseline, did so at last observation (one adult and two paediatric patients). The two paediatric patients who did not require walking help and/or aids at baseline required assistance from another person to ambulate at last observation. The rationale for ambulatory assistance from another person was not defined, and both paediatric patients improved in overall function as measured by a reduction in the CHAQ disability index. The adult patient did not use a wheelchair at baseline, but required use of a wheelchair at the last observation; the patient had an amputation and required a walker and a wheelchair post-surgery. A second adult patient had osteoarthritis and used a walker at baseline but also required a wheelchair at last observation. Both adult patients had significant musculoskeletal impairments and had previous orthopaedic surgeries.

EQ-5D

The results from the EQ-5D questionnaire showed improvements in QoL in the overall population (Table 26). The analysis of the EQ-5D index and VAS by age group may

suggest that both paediatric and adult patients treated with velmanase alfa have improvements in QoL. While the mean relative change from baseline in EQ-5D index scores was greater in paediatric patients (17.49% [SD: 28.27]) compared with adults (6.75% [SD: 21.82]), EQ-5D VAS scores were more improved in adult patients (20.1% [SD: 34.3] vs –1.9 [SD: 29.9]).

Motor function – BOT-2

In the overall population, treatment with velmanase alfa resulted in a statistically significant (relative change only) and sustained improvement in motor function as measured by BOT-2 (Table 26). In addition, a significant relative mean change from baseline to last observation was observed for three out of the four BOT-2 domains (see Appendix 7, Section 17.7.2.1). In the subgroup analysis by age class, the benefit of velmanase alfa on motor function was predominantly restricted to paediatric patients, with higher scores observed in patients <18 years old for the BOT-2 total point score than in patients >18 years old. The results of the BOT-2 by age class and parental study are presented in Appendix 7, Section 17.7.2.1 and 17.7.2.2.

BOT-2 subtest total point scores can also be converted to age equivalent scores, which indicate the average age at which healthy children typically achieve the raw score, and to scale scores which reflect the patient's performance relative to healthy, same-aged peers. An increase in age equivalent values indicates skill acquisition and the results are presented in Appendix 7 (Section 17.7.2.1). Overall, although the children are not functioning at their chronological age, there was an overall reduction in the dexterity and coordination challenges and fine motor delay relative to healthy peers.

Cognition – Leiter R

In the overall population, a statistically significant improvement in cognitive function was observed after treatment with velmanase alfa, as measured by the Leiter-R VR battery (Table 26). However, the absolute and relative increase from baseline to last observation for the Leiter-R AME battery did not reach statistical significance (Table 26); data for this endpoint was only collected in rhLAMAN-05.

In the subgroup analysis by age class, both paediatric and adult patients improved from baseline; however, there was a trend for a greater improvement in paediatric patients compared with adults for both Leiter-R batteries. The results of the Leiter-R batteries by age class and parental study (Leiter-R VR only) are presented in Appendix 7 Section 17.7.2.1 and 17.7.2.2.

Hearing – PTA

In the overall population, the measures used for PTA demonstrated an overall trend towards (but not statistically significant) a reduction in hearing loss following treatment with velmanase alfa (Table 26).

The analysis of PTA measures by age class revealed no consistent trend. The results for bone conduction in the best ear and air conduction in the left ear were more favourable in paediatric patients compared with adults. In contrast, the results for air conduction in the right ear were more improved in adult patients. The results of the PTA

measures by age class and parental study are presented in Appendix 7, Section 17.7.2.1 and 17.7.2.2.

The analysis of PTA measures by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in modest reductions in the number of patients considered to be seriously impaired based on air conduction in left (72.7% at baseline to 63.6% at last observation) and right ear (66.7% at baseline to 57.6% at last observation) (Appendix 7, Section 17.7.2.3). No change in patient status was seen with regards to bone conduction (best ear).

Additional secondary outcomes

Although less relevant to the decision problem, the results for the change from baseline in CSF oligosaccharides, tau, NFLp and GFAp at last observation are presented in Appendix 7, Section 17.7.2.1 and 17.7.2.2 for completeness.

Post-hoc analysis – results by age class

In order to further evaluate the efficacy of velmanase alfa by age groups more relevant to the decision problem, efficacy data from the rhLAMAN clinical trials were assessed in a post-hoc analysis by the following age classes; this classification is the age of patients at the time of starting treatment (100):

- 6–11 years
- 12–17 years
- ≥18 years

Note that while some of the results for the ≥18 years old subgroup have been reported previously in this submission, the results are repeated here to aid comparison.

Of the 33 patients included in the rhLAMAN-10 integrated data set, nine were 6–11 years old, 10 were 12–17, and 14 were ≥18 years at the time of starting treatment with velmanase alfa. All patients included in this post-hoc analysis had been receiving velmanase alfa for a period of ≥12 months. Patients from the Phase I/II trial had been receiving velmanase alfa for the longest time (48 months), while patients in the active treatment group of rhLAMAN-05 will have received a maximum of 36 months of treatment. However, patients from the placebo group of rhLAMAN-05 were exposed to velmanase alfa for relatively shorter time periods (via rhLAMAN-07, rhLAMAN-09 or the compassionate use programme) prior to inclusion in the rhLAMAN-10 integrated data set.

The change from baseline to last observation in serum oligosaccharides, 3-MSCT, 6-MWT (metres and % of predicted) and FVC (% of predicted) is presented by age class (6–11, 12–17 and ≥18 years) for rhLAMAN-10 in Table 27. The analysis of serum oligosaccharide clearance showed that all age groups benefit from velmanase alfa, with the greatest improvements observed in patients aged 12–17 years old. The analysis of mobility/functional capacity (as measured by the 3-MSCT and the 6-MWT) showed that while all age groups had improvements, the benefit of velmanase alfa is largely restricted to paediatric patients. Overall, scores for the 3-MSCT and 6-MWT (metres) in rhLAMAN-10 improved similarly in both paediatric age groups. The results for the 6-MWT (% of predicted) were also similar to the results for the 6-MWT (metres); however, the

benefit observed in patients aged 6–11 was more similar to adults than patients aged 12–17. The benefit of velmanase alfa on lung function was also largely restricted to paediatric patients; FVC (% of predicted) was most improved in the 12–17 age group. The results are also presented by parental trial (Phase I/II trial and rhLAMAN-05 split into active and placebo-to-active arms) in Appendix 7, Section 17.7.2.5, Table 145.

Table 27: rhLAMAN-10 – outcomes by age class (6–11, 12–17 and ≥18 years)

Change from baseline to last observation	Mean (SD)		
	6–11	12–17	≥18
n	9	10	14
Serum oligosaccharides (µmol/L)			
Absolute	-4.60 (3.78)	-5.86 (3.79)	-3.68 (2.20)
Relative, %	-60.9 (44.8)	-71.6 (27.5)	-57.6 (30.5)
3-MSCT (steps/min)			
Absolute	10.56 (12.59)	10.73 (8.49)	0.60 (7.97)
Relative, %	28.46 (37.05)	18.29 (14.57)	1.08 (17.65)
6-MWT (metres)			
Absolute	23.33 (71.33)	53.25 (64.38)	-0.29 (50.50)
Relative, %	12.67 (37.10)	11.25 (13.74)	0.67 (11.55)
6-MWT (% of predicted)			
Absolute	-2.54 (11.01)	5.83 (8.87)	0.21 (7.51)
Relative, %	1.73 (29.49)	8.64 (13.16)	1.09 (11.86)
FVC (% of predicted)			
n	7	10	12
Absolute	8.64 (19.59)	13.70 (12.98)	3.00 (12.35)
Relative, %	15.51 (28.52)	17.05 (17.77)	2.14 (16.67)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; FVC, forced vital capacity; SD, standard deviation.

Post-hoc analysis – patients switching from placebo to velmanase alfa

A post-hoc analysis was performed to assess the response to treatment in patients who switched from placebo (received during rhLAMAN-05) to velmanase alfa upon entry into the after-trial studies or compassionate use programme (55). The results are presented in Table 28 for the 3-MSCT, 6-MWT and serum IgG, and Table 29 for the CHAQ-DI and CHAQ pain (VAS).

Patients experienced an initial worsening in the 3-MSCT and 6-MWT whilst receiving placebo; however, after switching to treatment with velmanase alfa, an improvement at last observation (12–18 months of active treatment) was observed compared with the baseline value reported in rhLAMAN-05. Similarly, patients showed little change in serum IgG levels whilst receiving placebo, but exhibited an improvement in serum IgG levels after switching to velmanase alfa.

Patients who received placebo in rhLAMAN-05 also benefited from improvements in QoL after switching to velmanase alfa. Patients receiving placebo experienced a worsening in QoL, as shown by increased scores from baseline at Month 12 for the CHAQ disability index and CHAQ pain (VAS); however, when compared with the baseline scores recorded in rhLAMAN-05, a reduction (improvement) in CHAQ disability index and CHAQ pain (VAS) scores was observed at last observation after switching to velmanase alfa.

Table 28: Change in 3-MSCT, 6-MWT and serum IgG after switching from placebo to velmanase alfa

Outcome	Mean relative change from baseline value reported in placebo, double blind phase, % (SD)	
	Placebo double blind phase, month 12 (n=10)	Velmanase alfa only phase, last observation (n=9)
3-MSCT	-3.6 (13.5)	9.0 (25.1)
6-MWT	-0.8 (10.8)	2.2 (13.1)
Serum IgG	1.0 (16.9)	37.3 (16.1)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; SD, standard deviation.

Table 29: Improvement in quality of life after switching from placebo to velmanase alfa

Outcome	Placebo double blind phase		Velmanase alfa only phase
	Baseline (n=9)	Month 12 (n=9)	Last observation (n=9)
CHAQ-DI, mean (SD)	1.56 (0.67)	1.71 (0.50)	1.43 (0.50)
CHAQ pain (VAS), mean (SD)	0.42 (0.59)	0.52 (0.66)	0.36 (0.51)

Abbreviations: CHAQ, childhood health assessment questionnaire; DI, disability index; SD, standard deviation; VAS, visual analogue scale.

Conclusion

- Overall, treatment with velmanase alfa resulted in statistically significant and sustained improvements in serum oligosaccharide levels and the 3-MSCT from baseline. From baseline to last observation:
    - there was a statistically significant absolute (–4.59 µmol/L; 95% CI: –5.74, –3.45; p<0.001) and relative (–62.8%; 95% CI: –74.7, –50.8; p<0.001) decrease in serum oligosaccharides
    - there was a statistically significant absolute (6.38 steps/min; 95% CI: 2.65, 10.12; p=0.001) and relative (13.77%; 95% CI: 4.61, 22.92; p=0.004) increase in the 3-MSCT
- An improvement in mobility/functional capacity and motor function was also shown by an absolute increase in the 6-MWT (22.4 m; 95% CI: 0.0, 44.8; p=0.050) and a relative increase in BOT-2 total scores (13.0%; 95% CI: 1.0, 25.0; p=0.035) from baseline to last observation.

- Treatment with velmanase alfa resulted in statistically significant improvements in all but one (FEV_1 % of predicted) of the PFT secondary endpoints, indicating an overall improvement in lung function. Statistically significant changes from baseline (relative or absolute, or both) in cognitive function (Leiter-R VR battery), hearing (air conduction in left ear), QoL (EQ-5D Index) and serum IgG levels (suggestive of improved immunity) were also observed with velmanase alfa treatment
- Of the ten patients who required a device or third-party assistance for ambulation at baseline, seven became independent of assistance at last observation. In particular, two paediatric patients and one adult who required a wheelchair for long-distance mobility at baseline discontinued use at last observation
- A limited number of patients developed ADAs and there was no clear effect of the presence of ADAs on the primary efficacy endpoints of serum oligosaccharides and 3-MSCT, or on the 6-MWT, CSF oligosaccharides or serum IgG

Velmanase alfa treatment in adults and paediatric patients

- While both adult and paediatric patients receiving velmanase alfa had favourable changes in the primary endpoints, greater changes were observed in patients aged <18 years at the time of starting velmanase alfa:
    - Relative change from baseline to last observation in serum oligosaccharides was -66.6% in the <18 group and -57.6% in the ≥18 group.
    - Relative change from baseline to last observation in the 3-MSCT was 23.11% in the <18 group and 1.08% in the ≥18 group.
- Across the majority of secondary endpoints, greater changes were observed in paediatric patients compared with adults, including the 6-MWT, PFTs, motor function and cognitive impairment. However, patients who initiated velmanase alfa treatment in adulthood still received a benefit. Most notably, adult patients experienced an increase in serum IgG and a reduction in pain with velmanase alfa treatment
- Velmanase alfa may therefore be of particular value in patients aged <18 years at the time of starting treatment

9.6.1.3 Post-hoc, multi-domain responder analysis

Results

For this aggregated multi-domain responder analysis, a patient qualified as a responder to treatment if the response criteria were reached in at least two domains (see Section 9.4.1.4 for methods). Requiring a response in two domains provides treatment effect sensitivity, whereas a single response domain does not. A patient was considered a responder in a domain if they showed a response for at least one efficacy parameter within that domain by achieving the adopted MCID for that outcome.

The results of the aggregated responder analysis are presented in Table 30; the aggregated response for each patient is shown in Appendix 7, Section 17.7.3.3. Based on the data at last observation from rhLAMAN-10, 88% of patients achieved a response to velmanase alfa treatment (100% of paediatric patients and 71% of adult patients); 46% of patients achieved a response in all three domains (53% of paediatric patients and 36% of adult patients). By this model of response, only four patients (all adults) failed to achieve a response to treatment with velmanase alfa, with three patients (9%) and one patient (3%) having response in one domain or no domains, respectively.

When the 12-month results for rhLAMAN-05 only were examined, 87% of patients in the velmanase alfa group achieved a response to treatment, compared with 30% in the placebo group; 13% of patients in the velmanase alfa group achieved a response in all three domains, compared with 0% in the placebo group. Overall, the use of a two-domain responder criterion provides enough sensitivity to observe a treatment effect compared with placebo over 12 months. The higher proportion of three-domain responders at last observation in rhLAMAN-10 compared with rhLAMAN-05 (46% vs 13%) may be indicative of benefit received from long-term treatment with velmanase alfa.

Table 30: Results of multi-domain responder analysis

Responder	rhLAMAN-10 (N=33)			rhLAMAN-05 (N=25)	
	All (N=33)	<18 (n=19)	≥18 (n=14)	VA (n=15)	Placebo (n=10)
Responder (≥2 domains), n (%)	29 (87.9)	19 (100.0)	10 (71.4)	13 (86.6)	3 (30.0)
Three domains, n (%)	15 (45.5)	10 (52.6)	5 (35.7)	2 (13.3)	0
Two domains, n (%)	14 (42.4)	9 (47.4)	5 (35.7)	11 (73.3)	3 (30.0)
One domain, n (%)	3 (9.1)	0	3 (21.4)	2 (13.3)	3 (30.0)
No domains, n (%)	1 (3.0)	0	1 (7.1)	0	4 (40.0)

Source: Table 146 and Table 147 in Appendix 7.
Abbreviations: VA, velmanase alfa.

The response to each domain and parameter is shown in Table 31; the individual responses for each outcome across the three domains are shown in scatter plots in Appendix 7, Section 17.7.3.2. In total, 30 (91%), 24 (73%) and 22 (67%) patients in rhLAMAN-10 met the response criteria for the pharmacodynamics, functional and QoL domains, respectively. In rhLAMAN-05, the proportion of patients achieving the response criteria for the pharmacodynamics and functional domains was higher in the velmanase alfa group (100% and 60%) compared with the placebo group (20% and 30%). The proportion of patients who achieved the response criteria for the QoL domain was the same between the two groups (40%).

Table 31: Domain/parameter response at last observation in rhLAMAN-10 and at Month 12 in rhLAMAN-05

Domain/parameter	Response, n (%)		
	rhLAMAN-10 (N=33)	rhLAMAN-05 (N=25)	
		VA (n=15)	Placebo (n=10)
Pharmacodynamic			
Serum oligosaccharides	30 (90.9)	15 (100.0)	2 (20.0)
Functional			
3-MSCT	16 (48.5)	3 (20.0)	1 (10.0)
6-MWT	16 (48.5)	3 (20.0)	1 (10.0)
FVC (% of predicted)	13 (39.4)	5 (33.3)	2 (20.0)
Overall domain response	24 (72.7)	9 (60.0)	3 (30.0)
Quality of life			
CHAQ disability index	14 (42.2)	3 (20.0)	2 (20.0)
CHAQ pain (VAS)	15 (45.5)	5 (33.3)	4 (40.0)
Overall domain response	22 (66.7)	6 (40.0)	4 (40.0)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; CHAQ, childhood health assessment questionnaire; FVC, forced vital capacity; VA, velmanase alfa; VAS, visual analogue scale.

Conclusion

- The benefit of velmanase alfa was assessed across multiple domains in order to capture the treatment effect against the backdrop of the heterogeneity of the disease
- Overall, the multi-domain responder analyses demonstrate a meaningful treatment effect in both the controlled and uncontrolled data analyses
- In rhLAMAN-05, 87% of patients in the velmanase alfa group achieved a response to treatment, compared with 30% in the placebo group at 12 months
    - In the velmanase alfa group, 73% responded to two domains, while 13% achieved a response to all three domains
    - No patient in the placebo group achieved a response to all three domains and only three (30%) patients responded to two domains
    - Overall, the use of a two-domain responder criteria provides enough sensitivity to observe a treatment effect compared with placebo over 12 months
- Overall, 88% of patients analysed in the rhLAMAN-10 integrated data set achieved a response to velmanase alfa treatment at last observation
    - The analysis in rhLAMAN-10 demonstrated that all paediatric patients (100%) and the majority of adult patients (71%) achieved a response in at least two domains and, therefore, experienced disease improvement (as opposed to disease stabilisation which is not captured in the analysis)
    - At last observation, 46% responded to all three domains, while 42% responded to two domains
    - The high proportion of three domain responders in rhLAMAN-10 (up to 48 months) supports the continued benefit of longer term treatment of AM with velmanase alfa

9.6.2 *Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.*

Analysis of efficacy was carried out on the FAS in both rhLAMAN-05 and rhLAMAN-10, which was defined as all patients who received ≥1 dose of velmanase alfa and whose efficacy was evaluated post-baseline. This can be considered as modified intention-to-treat (mITT) analysis, which is an approach commonly employed in clinical trials; in particular, studies of ERT in other LSDs have used a mITT approach (48, 49).

9.7 *Adverse events*

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 *Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.*

Adverse events were recorded throughout the velmanase alfa clinical development programme; the identification, study details, methodologies and results of the rhLAMAN trials are presented in Section 9.1–9.6. The most comprehensive safety data is provided by the rhLAMAN-10 integrated data set. In addition, rhLAMAN-05 provides comparative 12-month safety data between velmanase alfa and placebo. Safety data were also collected in the Phase I-II study (rhLAMAN-02, 03 and 04); as these data are represented in rhLAMAN-10, the results are presented in Appendix 7, Section 17.7.4.

9.7.2 *Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.*

9.7.2.1 rhLAMAN-05

The AEs reported in rhLAMAN-05 are summarised in Table 32. Only one patient (receiving placebo) did not experience any AEs. The most frequently reported AEs were nasopharyngitis, pyrexia and headache. All treatment-related AEs were mild (27 events) or moderate (12 events) in intensity. Only one patient (who received velmanase alfa) experienced IRRs (11 events which were all mild or moderate in intensity).

Five patients reported a SAE (knee deformity [genua valga both sites], joint swelling [swollen ankle], Sjogren's syndrome, sepsis and renal failure acute); only one (sepsis) was classified as a severe AE, while one SAE (renal failure) was possibly related to treatment. No deaths, events leading to treatment discontinuation, or clinically harmful signals were reported, and the long-term safety profile of velmanase alfa was found to be acceptable.

In addition, no special safety concerns were raised from any of the monitored safety endpoints (haematology, blood chemistry, urinalysis, ADAs, physical examination, vital signs, echocardiogram), including immunogenicity. Of the patients who were ADA positive, four were receiving velmanase alfa and four were receiving placebo; the finding of ADA production among the patients in the placebo group suggests that caution should be taken when interpreting the data.

Table 32: rhLAMAN-05 – adverse events across patient groups

AE	VA (N=15)		Placebo (N=10)	
	n (%)	Events	n (%)	Events
Summary of AEs				
Any AE	15 (100.0)	157	9 (90.0)	113
Treatment-related AE	7 (46.7)	30	5 (50.0)	9
SAE	5 (33.3)	5	0	0
Treatment-related SAE	1 (6.7)	1	0	0
Severe AE	1 (6.7)	1	0	0
Discontinuations due to AE	0	0	0	0
Deaths	0	0	0	0
AEs reported by ≥2 patients				
Infections and infestations	13 (86.7)	48	7 (70.0)	23
Nasopharyngitis	10 (66.7)	30	7 (70.0)	16
Urinary tract infection	1 (6.7)	1	1 (10.0)	3
Ear infection	2 (13.3)	2	1 (10.0)	1
Acute tonsillitis	2 (13.3)	2	0	0
Influenza	2 (13.3)	2	0	0
Gastroenteritis	2 (13.3)	2	0	0
Gastrointestinal disorders	9 (60.0)	18	8 (80.0)	24
Vomiting	3 (20.0)	5	4 (40.0)	6
Diarrhoea	2 (13.3)	2	3 (30.0)	3
Toothache	2 (13.3)	3	0	0
Constipation	1 (6.7)	1	1 (10.0)	1
Dental caries (cavities)	1 (6.7)	1	1 (10.0)	1
Nausea	1 (6.7)	1	1 (10.0)	1
General disorders and administration site conditions	6 (40.0)	20	7 (70.0)	18
Pyrexia	6 (40.0)	11	5 (50.0)	11
Oedema peripheral	1 (6.7)	1	1 (10.0)	4
Fatigue	1 (6.7)	1	1 (10.0)	1
Musculoskeletal and connective tissue disorders	7 (46.7)	11	5 (50.0)	16
Arthralgia	3 (20.0)	4	1 (10.0)	6
Pain in extremity	1 (6.7)	1	1 (10.0)	4
Back pain	2 (13.3)	2	1 (10.0)	1
Nervous system disorders	6 (40.0)	11	5 (50.0)	12
Headache	5 (33.3)	7	3 (30.0)	9
Dizziness	1 (6.7)	1	2 (20.0)	2
Syncope	2 (13.3)	2	0	0

AE	VA (N=15)		Placebo (N=10)	
	n (%)	Events	n (%)	Events
Respiratory, thoracic and mediastinal disorders	4 (26.7)	7	2 (20.0)	4
Epistaxis	1 (6.7)	4	1 (10.0)	3
Immune system disorders	2 (13.3)	5	2 (20.0)	2
Hypersensitivity	2 (13.3)	5	0	0
Ear and labyrinth disorders	0	0	3 (30.0)	3
Ear discomfort	0	0	2 (20.0)	2

Abbreviations: AE, adverse event; VA, velmanase alfa.

9.7.2.2 rhLAMAN-10

Overall, mean (SD) exposure was 890.5 (461.5) days (Table 33). Exposure was greater in patients whose parental study was the Phase I/II trial (mean exposure 1585.2 days), than in those whose parental study was rhLAMAN-05 (mean exposure of 630.0 days). As the Phase I/II trial only enrolled paediatric patients, exposure for patients aged <18 years was higher than for patients aged ≥18 years.

The mean (SD) number of infusions reported was 84.8 (63.1), with a higher number reported in patients whose parental study was the Phase I/II trial, and consequently in patients aged <18 years. The actual number of infusions was higher than that reported, as administrations in the compassionate use programme were not recorded.

Table 33: Extent of exposure to VA

	Overall (N=33)	<18 years (n=19)	≥18 years (n=14)	Phase I/II trial (n=9)	rhLAMAN-05 (n=24)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Number of infusions	84.9 (63.1)	105.6 (71.0)	56.7 (36.4)	143.8 (70.2)	62.8 (44.2)
Exposure (days)	890.5 (461.5)	1085.9 (508.7)	625.4 (185.8)	1585.2 (21.6)	630.0 (191.0)

Abbreviations: SD, standard deviation; VA, velmanase alfa.

The AEs reported in rhLAMAN-10 are summarised in Table 34. Overall, 29 (87.9%) patients experienced any AE, which was similar for patients aged <18 years and those aged ≥18 years. Twelve patients (36.4%) experienced SAEs and only three patients (9.1%) experienced AEs that were severe in intensity. In total, 17 patients (51.5%) experienced an AE related to treatment; however, only two patients (6.1%) had a treatment-related SAE. The number of events reported and proportion of patients reporting treatment-related AEs was higher in patients aged <18 years, who had a longer treatment exposure, than in patients aged ≥18 years. There were no deaths and no AEs led to treatment discontinuation.

The most frequently reported AEs were nasopharyngitis, headache, pyrexia, vomiting and diarrhoea, and cough. Other AEs reported in >10% of patients overall (in descending order of frequency) were arthralgia, wound, pain in extremity, contusion, ear infection,

gastroenteritis, weight increased, excoriation, rash, back pain, hypersensitivity, erythema, abdominal pain upper, post lumbar puncture syndrome, and tooth extraction. All of the events reported in >10% of patients occurred more frequently in patients <18 years (who had a longer treatment exposure) than in patients aged ≥18 years, with the exception of rash and hypersensitivity, which occurred slightly more frequently in adult patients. All AEs were mild or moderate in severity except for pyrexia and tremor (one patient, considered related to treatment), loss of consciousness (one patient, considered related to treatment) and sepsis (one patient, not considered related to treatment). IRRs were reported in 3/33 (9.1%) patients (19 events; 14 of which occurred in a single patient) and were mild or moderate in intensity and resolved spontaneously.

A conservative approach was taken when considering patients as ADA positive. The analysis included patients who were ADA positive at any time, including pre-treatment, and a relatively low threshold of 1.4 U/mL (the lower limit of detection for the assay) was used to determine ADA status. With this definition, 10 patients (30.3%) were ADA positive at some point during the study, and 23 patients (69.7%) were ADA negative at all time points. Two patients had ADA measurements ≥1.4 U/mL before receiving active treatment, but once on active treatment all values were <1.4 U/mL. Therefore, only eight patients had ADA positive values at any time under treatment, of whom six had at least two tests ≥1.4 U/mL during active treatment. Of the eight patients, six had values that fluctuated around the cut-off value of 1.4 U/mL. The remaining two patients had more elevated levels (maximum values of 1012 U/ml and 440 U/ml, respectively), and both experienced IRRs.

Table 34: rhLAMAN-10 – adverse events across patient groups

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Summary of AEs,						
Any AE	29 (87.9)	546	17 (89.5)	423	12 (85.7)	123
Treatment-related AE	17 (51.5)	84	12 (63.2)	69	5 (35.7)	15
SAE	12 (36.4)	14	7 (36.8)	9	5 (35.7)	5
Treatment-related SAE	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Severe AE	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Discontinuations due to AE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
AEs reported by ≥1 patients						
Blood and lymphatic system disorders	2 (6.1)	2	2 (10.5)	2	0	0
Lymphadenopathy	2 (6.1)	2	2 (10.5)	2	0	0
Cardiac disorders	1 (3.0)	1	1 (5.3)	1	0	0
Congenital, familial and genetic disorders	1 (3.0)	1	1 (5.3)	1	0	0
Ear and labyrinth disorders	4 (12.1)	8	3 (15.8)	7	1 (7.1)	1
Eye disorders	8 (24.2)	18	5 (26.3)	10	3 (21.4)	8
Conjunctival hyperaemia	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Eye infection	2 (6.1)	2	2 (10.5)	2	0	0
Eye pruritus	3 (9.1)	5	2 (10.5)	4	1 (7.1)	1

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Gastrointestinal disorders	21 (63.6)	51	13 (68.4)	36	8 (57.1)	15
Abdominal pain	3 (9.1)	3	3 (15.8)	3	0	0
Abdominal pain upper	4 (12.1)	4	4 (21.1)	4	0	0
Diarrhoea	9 (27.3)	11	6 (31.6)	7	3 (21.4)	4
Nausea	3 (9.1)	3	3 (15.8)	3	0	0
Reflux gastritis	2 (6.1)	2	2 (10.5)	2	0	0
Toothache	2 (6.1)	3	2 (14.3)	3	0	0
Vomiting	10 (30.3)	14	8 (42.1)	12	2 (14.3)	2
General disorders and administration site conditions	17 (51.5)	59	11 (57.9)	46	6 (42.9)	13
Chills	2 (6.1)	9	2 (10.5)	9	0	0
Fatigue	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Malaise	2 (6.1)	3	2 (10.5)	3	0	0
Oedema peripheral	3 (9.1)	3	1 (5.3)	1	2 (14.3)	2
Pyrexia	11 (33.3)	26	9 (47.4)	23	2 (14.3)	3
Immune system disorders	4 (12.1)	10	2 (10.5)	5	2 (14.3)	5
Hypersensitivity	4 (12.1)	9	2 (10.5)	4	2 (14.3)	5
Infections and infestations	24 (72.7)	141	15 (78.9)	112	9 (64.3)	29
Acute tonsillitis	2 (6.1)	2	2 (10.5)	2	0	0
Ear infection	6 (18.2)	7	4 (21.1)	5	2 (14.3)	2
Gastroenteritis	6 (18.2)	7	5 (26.3)	6	1 (7.1)	1
Influenza	3 (9.1)	3	2 (10.5)	2	1 (7.1)	1
Laryngitis	2 (6.1)	2	2 (10.5)	2	0	0
Nasopharyngitis	23 (69.7)	89	14 (73.7)	71	9 (64.3)	18
Urinary tract infection	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Otitis media	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Injury, poisoning and procedural complications	15 (45.5)	65	13 (68.4)	63	2 (14.3)	2
Arthropod bite	3 (9.1)	4	3 (15.8)	4	0	0
Contusion	6 (18.2)	10	6 (31.6)	10	0	0
Excoriation	5 (15.2)	18	5 (26.3)	18	0	0
Ligament sprain	2 (6.1)	2	2 (10.5)	2	0	0
Post lumbar puncture syndrome	4 (12.1)	4	3 (15.8)	3	1 (7.1)	1
Wound	7 (21.2)	10	6 (31.6)	9	1 (7.1)	1
Investigations	11 (33.3)	14	10 (52.6)	13	1 (7.1)	1
Weight increased	6 (18.2)	7	6 (31.6)	7	0	0
Metabolism and nutrition disorders	4 (12.1)	4	2 (10.5)	2	2 (14.3)	2
Increased appetite	2 (6.1)	2	2 (10.5)	2	0	0
Musculoskeletal and connective tissue disorders	18 (54.5)	47	11 (57.9)	38	7 (50.0)	9
Arthralgia	7 (21.2)	14	5 (26.3)	10	2 (14.3)	4
Back pain	5 (15.2)	5	3 (15.8)	3	2 (14.3)	2
Myalgia	2 (6.1)	3	2 (10.5)	3	0	0
Pain in extremity	6 (18.2)	14	5 (26.3)	13	1 (7.1)	1

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (6.1)	2	2 (10.5)	2	0	0
Skin papilloma	2 (6.1)	2	2 (10.5)	2	0	0
Nervous system disorders	16 (48.5)	43	10 (52.6)	34	6 (42.9)	9
Dizziness	3 (9.1)	4	3 (15.8)	4	0	0
Headache	13 (39.4)	27	9 (47.4)	22	4 (28.6)	5
Loss of consciousness	2 (6.1)	2	2 (10.5)	2	0	0
Syncope	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Psychiatric disorders	5 (15.2)	10	3 (15.8)	4	2 (14.3)	6
Renal and urinary disorders	4 (12.1)	5	1 (5.3)	1	3 (21.4)	4
Pollakiuria	2 (6.1)	2	0	0	2 (14.3)	2
Respiratory, thoracic and mediastinal disorders	15 (45.5)	28	11 (57.9)	20	4 (28.6)	8
Bronchitis	2 (6.1)	2	2 (10.5)	2	0	0
Cough	9 (27.3)	12	8 (42.1)	11	1 (7.1)	1
Rhinorrhoea	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Skin and subcutaneous tissue disorders	14 (42.4)	23	9 (47.4)	13	5 (35.7)	10
Acne	2 (6.1)	2	0	0	2 (14.3)	2
Erythema	4 (12.1)	5	3 (15.8)	4	1 (7.1)	1
Rash	5 (15.2)	5	2 (10.5)	2	3 (21.4)	3
Scar pain	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Surgical and medical procedures	8 (24.2)	11	8 (42.1)	11	0	0
Catheter removal	2 (6.1)	2	2 (10.5)	2	0	0
Ear tube insertion	2 (6.1)	2	2 (10.5)	2	0	0
Tooth extraction	4 (12.1)	4	4 (21.1)	4	0	0
Vascular disorders	3 (9.1)	3	2 (10.5)	2	1 (7.1)	1

Abbreviations: AE, adverse event; VA, velmanase alfa.

9.7.3 *Provide a brief overview of the safety of the technology in relation to the scope.*

Overall, velmanase alfa was well tolerated throughout the clinical development programme; rhLAMAN-05 demonstrated that the safety profile of velmanase alfa was similar to placebo at Month 12, while rhLAMAN-10 showed that long-term treatment with velmanase alfa was well tolerated. No deaths were recorded and no patient permanently discontinued treatment due to an AE. One patient in rhLAMAN-03 withdrew following a long-term interruption of treatment due to repeated (three events) IRR (mild, treatment-related, anaphylactoid reaction) and the patient's desire not to receive premedication; however, the patient resumed treatment with velmanase alfa (following enrolment in rhLAMAN-05) after a treatment gap of approximately 18 months. The same patient also experienced IRRs (11 events) in rhLAMAN-05, but did not discontinue treatment as a result.

Recurrent infections and immunodeficiency are hallmarks of AM. Throughout the clinical development programme, treatment with velmanase alfa resulted in a statistically significant and sustained improvement in serum IgG levels, which may indicate an overall improvement in immune function and reduce the frequency of infections over time. An increase in serum IgG was seen in all patients with baseline hypogammaglobulinaemia and in some cases, complete reversion to IgG levels within the normal range was observed. The result of increased serum IgG was achieved in both adults and paediatric patients; the result is particularly relevant for adults, who have a shortened life expectancy with infections being one of the main causes for early deaths (17). An increase in serum IgG is expected to result in a reduction in infections, particularly in those with lower baseline levels. Although data on infections were not systematically collected, the proportion of patients experiencing an 'infection or infestation' in rhLAMAN-10 integrated data set (up to 48 months) was 72.7% compared with 86.7% (Month 12) in patients receiving velmanase alfa in rhLAMAN-05, potentially reflecting a reduction in infections over time.

The clinical development programme showed potential for immunogenicity. At any time under treatment, eight patients (24% of rhLAMAN-10 integrated data set) developed IgG-class antibodies to velmanase alfa. However, no clear correlation was found between antibody levels (velmanase alfa IgG antibody level) and reduction in efficacy or occurrence of anaphylaxis or other hypersensitivity reactions.

9.8 *Evidence synthesis and meta-analysis*

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

No evidence synthesis and/or meta-analysis was plausible for this submission.

9.8.1 *Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.*

Not applicable.

9.8.2 *If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.*

Not applicable.

9.9 *Interpretation of clinical evidence*

9.9.1 *Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed*

to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

9.9.1.1 Summary of the clinical benefit of velmanase alfa

The efficacy and safety of velmanase alfa was demonstrated throughout a comprehensive clinical development programme, which included the first placebo-controlled study of AM.

In rhLAMAN-05, treatment with velmanase alfa for 12 months significantly (statistically) improved serum oligosaccharide levels and resulted in numerical advantages for measures of mobility/functional capacity (3-MSCT and 6-MWT) and lung function (FVC % of predicted) compared with placebo. Post-hoc analyses revealed that while both adult and paediatric patients receiving velmanase alfa had favourable changes from baseline across a range of efficacy measures, the difference between velmanase alfa and placebo was greater in the paediatric group (<18 years old) than in adults. Velmanase alfa may therefore be of particular value in patients aged ≥6 to <18 years at the time of starting treatment. In addition, levels of serum immunoglobulin G (IgG) were significantly (statistically) greater in the velmanase alfa group compared with the placebo group at Month 12. This result suggests that velmanase alfa may help to improve immune function in patients with AM. Overall, treatment with velmanase alfa was generally well tolerated; only one patient experienced IRRs (11 events).

The long-term data provided by the rhLAMAN-10 integrated data set showed that treatment with velmanase alfa resulted in statistically significant and sustained improvements in serum oligosaccharide levels, mobility/functional capacity, motor function and lung function from baseline to last observation. Statistically significant changes from baseline in cognitive function, hearing, QoL and serum IgG levels (suggestive of improved immunity) were also observed with velmanase alfa treatment. Of note, of the ten patients who required a device or third-party assistance for ambulation at baseline, seven became independent of assistance at last observation. In particular, two paediatric patients and one adult who required a wheelchair for long-distance mobility at baseline discontinued using the wheelchair at last observation. Subgroup analysis by age in rhLAMAN-10 also suggested that while both adults and paediatric patients benefit from velmanase alfa, the benefits may be more prominent in paediatric patients. Overall, velmanase alfa was well tolerated. No special safety concerns were raised, including immunogenicity, and the long-term safety profile of velmanase alfa was found to be acceptable. In total, IRRs were reported in three patients (19 events; 14 of which occurred in a single patient) and were mild or moderate in intensity and resolved spontaneously.

To further explore the clinical value of velmanase alfa, a post-hoc, multi-domain responder analysis was performed. Key endpoints were grouped into three domains that reflect the pathophysiology and the burden of the disease: a pharmacodynamic domain (serum oligosaccharide), a functional domain (3-MSCT, 6-MWT and FVC [% of predicted]) and a QoL domain (childhood health assessment questionnaire [CHAQ] disability index and CHAQ pain [visual analogue scale, VAS]). For this responder analysis, a patient qualified as a responder to treatment if the response criteria was reached in at least two of the three prior listed domains; a patient was considered a responder in a domain if they showed a response for at least one efficacy parameter

within that domain by achieving the adopted MCID for that outcome. In rhLAMAN-05, 87% of patients in the velmanase alfa group achieved a response to treatment at 12 months, compared with 30% in the placebo group. Therefore, the use of a two-domain responder criterion provides enough sensitivity to observe a treatment effect compared with placebo over 12 months. Overall, 88% of patients analysed in the rhLAMAN-10 integrated data set achieved a response to velmanase alfa treatment at last observation (12–48 months). The analysis in rhLAMAN-10 also demonstrated that all paediatric patients and the majority of adult patients experienced disease improvement (as opposed to disease stabilisation which is not formally captured in the analysis) in at least two domains. The higher proportion of three-domain responders at last observation in rhLAMAN-10 compared with rhLAMAN-05 (46% vs 13%) may also be indicative of benefit received from long-term treatment (up to 48 months) with velmanase alfa.

9.9.1.2 Numbers Needed to Treat/Harm

As a placebo/no treatment group is required to estimate the number needed to treat (NNT)/number needed to harm (NNH), no such calculations were possible for rhLAMAN-10. However, while no appropriate categorical data were available from rhLAMAN-05, it is possible to calculate the NNT using the data from the post-hoc, multi-domain responder analysis. The calculation of NNT considers the NNT in order to achieve a clinical response (clinical response requires response to ≥2 domains). In rhLAMAN-05, 86.6% achieved a response following treatment with velmanase alfa, while 30% of patients in the placebo group achieved a response regardless of treatment; therefore, 56.6% achieved a response due to treatment with velmanase alfa. Therefore, the NNT in order to achieve a clinical response in one person is two (Table 35).

Table 35: NNT to achieve a clinical response

Clinical response at Month 12		ARR	NNT
VA	Placebo		
0.866	0.300	0.566	1/0.566 = 1.77 (2)

Abbreviations: ARR, absolute risk reduction; NNT, number needed to treat; VA, velmanase alfa.

While no discontinuations due to AEs occurred in rhLAMAN-05, IRRs were considered an AE of special interest. Overall, one patient (6.7%) in the velmanase alfa group experienced ≥1 IRR event, compared with none in the placebo group. This would suggest a NNH of 15 in relation to IRRs (Table 36).

Table 36: NNH for IRR

Proportion of patients experiencing ≥1 IRR event with 12 months		ARR	NNH
VA	Placebo		
0.066	0	0.066	1/0.066 = 15.2 (15)

Abbreviations: ARR, absolute risk reduction; IRR, infusion related reaction; NNH, number needed to harm; VA, velmanase alfa.

9.9.2 *Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.*

9.9.2.1 Strengths of the evidence base

The evidence base for velmanase alfa is derived from the clinical development programme that includes a Phase III, 12-month, placebo-controlled trial (rhLAMAN-05) and up to 48 months of follow-up data from rhLAMAN-10. The programme also represents the first attempt at assessing a pharmacological, disease-modifying intervention in the treatment of AM. The data from rhLAMAN-10 demonstrated significant and sustained improvements from baseline to last observation (12–48 months) across a range of clinical outcomes following treatment with velmanase alfa. Results from rhLAMAN-05 and rhLAMAN-10 were also presented by age class (both pre-specified and post-hoc), allowing the efficacy of velmanase alfa to be compared between cohorts receiving treatment initiation as adults and as paediatrics.

Overall, the clinical development programme includes a population that broadly reflects the clinical landscape in the UK; that is, a heterogeneous population with regards to symptomology and age. The outcomes assessed throughout the clinical development programme also reflect the wide range of symptoms present in AM and covered mobility, lung function, motor function, QoL, cognitive impairment and hearing impairment. The outcomes were also consistent with clinical trials of other LSDs, which share similar clinical features to AM (43). For example, the 3-MSCT and 6-MWT have been widely adopted to assess endurance in other LSDs (66, 67) and results have been used as clinical endpoints to support the approval of ERT products for mucopolysaccharidosis type 1 (MPS I), MPS II, MPS VI, and MPS IVA (68). The use of biomarkers (oligosaccharides and serum IgG) also provided evidence of the effect that velmanase alfa has at the cellular level.

The evidence base for velmanase alfa is further strengthened by the addition of data from a post-hoc, multi-domain responder analysis (Section 9.6.1.3). The responder analysis was designed to capture the pathophysiology and the burden of the disease and a robust approach to defining MCIDs for the included outcomes (de novo for AM) was taken (see Appendix 7, Section 17.7.3.1). This approach was shown to mitigate the limitations in sample size (typical of a rare disease) and the potential loss of statistical power, as a clear treatment effect was apparent with velmanase alfa (clinical response, 87%), compared with placebo (clinical response, 30%).

9.9.2.2 Limitations of the evidence base

While rhLAMAN-05 achieved the co-primary endpoint for change in serum oligosaccharides, no statistically significant difference was observed between velmanase alfa and placebo for the co-primary endpoint, 3-MSCT. In addition, no statistically significant differences were observed for the prioritised secondary endpoints, 6-MWT and FVC (% of predicted). While numerical improvements were observed for these outcomes in the velmanase alfa group compared with the placebo group, the ability to detect a significant treatment effect may have been limited by sample size and patient heterogeneity. These tests are also subject to limitations as patients may fail to complete the tests or score poorly due to lack of motivation and/or understanding.

In rhLAMAN-05, no formal sample size calculation was performed. The total of 25 patients represented a compromise between availability of patients who can fulfil the admission criteria and the minimum amount of data that can support an assessment of efficacy and safety of the treatment regimen. Low patient numbers are typical in clinical trials of rare diseases and confound the ability to observe a statistically significant result, with results more prone to being impacted by the presence of outliers (101). Ultimately, demonstrating statistical significance in a small sample size requires a large treatment effect (101). In rhLAMAN-05, the ability to observe a large treatment effect in functional outcomes (mobility and lung function) may have been limited, as patients were generally at the more mobile end of the AM functional impairment axis at baseline; as patients were required to have the ability to physically and mentally cooperate in the tests (with respect to the 3-MSCT and 6-MWT), this suggests that no patients were wheelchair bound or severely disabled. This limitation is known as a 'ceiling effect' and suggests that improvement is more difficult to observe in patients who have baseline values approaching the normal range. Ceiling effects are common across functional outcomes (69) and have been previously observed for the 6-MWT (102, 103). To overcome this limitation, one study of ERT for the treatment of MPS IVA (Morquio A syndrome) restricted the patient population to those who had a baseline 6-MWT distance of 30 to 325 metres in order to 'identify patients most likely to show improvement' (49). Consequently, the study successfully demonstrated a significant improvement in 6-MWT compared with placebo following ERT (49). In contrast, the mean 6-MWT distance of patients in rhLAMAN-05 was 460–466 metres; therefore, the rhLAMAN-05 population may have had less potential for improvement.

The results for the 3-MSCT and 6-MWT may have also been confounded by the lack of patient selection at baseline according to mobility and motor performance. This led to a potential unbalance in the severity of patients in favour of placebo, with a higher proportion of more compromised patients randomised to the velmanase alfa group; however, as previously mentioned, all patients were reasonably mobile and recorded as being able to walk (with or without aids/assistance) at baseline. Ultimately, the treatment effect may have been eroded by a combination of the ceiling effect, limiting the ability to observe improvement in the velmanase alfa group, and higher-functioning patients in the placebo group who may have possessed a greater ability to perform well in these tests.

Composite endpoints may address the limitations in detecting a significant treatment effect in a single outcome by accounting for the heterogeneity of LSDs (101). The post-hoc, multi-domain responder analysis presented in this submission was able to demonstrate a clear treatment effect between velmanase alfa and placebo. [redacted], it is subject to some limitations. First, no statistical analysis was possible for this analysis. Furthermore, patients were considered to respond to an outcome when they achieved the required MCID. Prior to this analysis, the MCIDs for the clinical endpoints used in the trials of velmanase alfa had not previously been defined for patients with AM, which is typical of an orphan condition. A robust approach to defining MCIDs for the included outcomes (de novo for AM) was taken (see Appendix 7, Section 17.7.3.1); however, uncertainty remains in the scientific and clinical community regarding MCID thresholds in AM and the level of response required to define a "responder" given the heterogeneity of the disease and severity across the different measurement

parameters. [redacted]

Finally, as discussed in Section 9.4, the rhLAMAN clinical development programme employed the use of CHAQ in both adults and paediatric patients to assess QoL. While this questionnaire is likely to be appropriate for this population, its use in adults is unprecedented; therefore, the results should be interpreted with caution.

9.9.3 *Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.*

The evidence base is relevant to the scope in both terms of study population and the specified outcome measures.

The results from rhLAMAN-05 and rhLAMAN-10 are the most relevant to the decision problem; rhLAMAN-05 provides data on the relative 12-month efficacy of velmanase alfa compared with placebo (placebo serves as proxy for BSC), while rhLAMAN-10 provides up to 48 months of follow-up data. In view of the multiple organ systems adversely affected in AM, and in response to a request by the EMA, a post-hoc, multi-domain responder analysis combining multiple endpoints into single domains representing clinical effects was also conducted for rhLAMAN-05 and rhLAMAN-10. Together, these studies/analyses provide evidence of the effect of velmanase alfa on mobility and motor function, hearing and language, cognition, lung function and QoL

In addition to the scope, data on the change from baseline in serum oligosaccharides are presented. Serum oligosaccharides are an important biomarker that demonstrate the effect that velmanase alfa has at the cellular level and is a surrogate marker of potential clinical complications. It was also a primary endpoint in the rhLAMAN clinical trial programme and a component of the post-hoc, multi-domain responder analysis.

While infections were not formally captured in the clinical trial programme, data on serum IgG were presented. Immunoglobulins play a major role in adaptive immunity (64). In particular, serum IgG levels comprise 70–80% of the total serum immunoglobulin content and low levels of serum IgG are associated with an increased risk of infections (64). Serum IgG levels were measured to assess the level of immunodeficiency, with an increase in levels representing an improvement. The biomarker of serum IgG is well accepted as a surrogate for humoral deficiency, and for patients with hypogammaglobulinaemia, and the standard therapy is replacement with immunoglobulins (65). [redacted]

9.9.4 *Identify any factors that may influence the external validity of study results to patients in routine clinical practice.*

Overall, the clinical development programme includes a population that broadly reflects the clinical landscape in the UK; that is, a heterogeneous population with regards to symptomology and age. It should be noted that the clinical trial programme included 2 UK patients; one of which is an adult patient who remains on treatment through an aftercare/compassionate programme.

[redacted]

Generally, low oligosaccharide levels corresponded to a longer walking distance (6-MWT) and more steps climbed (3-MSCT) in the natural history study of AM (12), suggesting that the level of oligosaccharides may be clinically relevant. Throughout the clinical development programme, serum oligosaccharides were preferred to urine oligosaccharides as a biomarker of velmanase alfa efficacy. Urine oligosaccharides are more widely measured than serum oligosaccharides in clinical practice in the UK (18) as the procedure is not invasive; however, the measurement of serum oligosaccharides was found to be more reliable in the clinical trial setting. The level of serum oligosaccharides provides important evidence of the effect that velmanase alfa has at the cellular level.

All the patients included in the clinical development programme are within the licensed indication of velmanase alfa. However, as part of the trial eligibility criteria, patients with a history of allogeneic HSCT were excluded from the trial population. While the licensed indication for velmanase alfa does not prohibit access to patients with a history of allogeneic HSCT, the effect of treatment in these patients is unknown. In clinical practice, allogeneic HSCT in patients with AM appears to be a rare procedure – [redacted] Furthermore, allogeneic HSCT is traditionally reserved for paediatric patients (≤5 years) with extensive disease (Section 8.3.3) (18). This suggests that the results from the velmanase alfa clinical development programme are likely to be applicable to the majority of AM patients in the UK.

9.9.5 *Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.*

Velmanase alfa is suitable within its licensed indication as an ERT for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

Initiation of velmanase alfa is subject to the start and stop criteria defined in Section 10.1.16.

10 Measurement and valuation of health effects

Patient experience

10.1.1 *Please outline the aspects of the condition that most affect patients' quality of life.*

The aspects of the condition that affect the patient's QoL are discussed in Section 7.1.

10.1.2 *Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.*

As discussed in Section 7.1., the QoL of patients is expected to deteriorate with time. Patients may also experience a sudden reduction in QoL following major clinical event (17).

HRQL data derived from clinical trials

10.1.3 *If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.*

- ***Method of elicitation.***
- ***Method of valuation.***
- ***Point when measurements were made.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***

Data on the HRQoL of patients were collected as part of the rhLAMAN clinical development programme. The CHAQ (all trials) and EQ-5D questionnaires (rhLAMAN-05 and rhLAMAN-10 only) were both used as methods of elicitation (Section 9.4) for details, and Table 37. The data were not sufficient to support the economic model as, due to the trial eligibility criteria, no patients were wheelchair-dependent or severely immobile at baseline. However, it was possible to estimate the health state utilities for 'walking unassisted' and 'walking with assistance', using ambulatory information from the CHAQ questionnaire and the EQ-5D scores at baseline in rhLAMAN-10. At baseline (before treatment), the mean EQ-5D score for patients with AM who could walk (without aids/assistance) was 0.652. This analysis showed that moving from 'walking unassisted' to 'walking with assistance' was associated with a disutility of 0.075 for patients with AM. Furthermore, treatment with velmanase was associated with a utility improvement of 0.05 and 0.058 in the 'walking unassisted' and 'walking with assistance' health states, respectively.

Table 37: EQ-5D scores in rhLAMAN-10 – patients treated with VA for 12–48 months

Time point	Walking unassisted		Walking with assistance†	
	n‡	Mean EQ-5D score (SD)	n‡	Mean EQ-5D score (SD)
Baseline	15	0.652 (0.149)	9	0.577 (0.200)
Last observation				
Actual score	25	0.702 (0.171)	6	0.635 (0.085)
Change from baseline		0.05		0.058

Abbreviations: EQ-5D, EuroQol five-dimension questionnaire; SD, standard deviation.
†This includes patients who required help from another person, crutches and/or walking frames; the small number of patients (n=3) that used a wheelchair were excluded from the analysis as it was unclear how frequently the patient used the wheelchair. ‡The number of patients represents those patients who had an EQ-5D score at the associated time point.

Mapping

10.1.4 ***If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.***

- ***Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.***
- ***Details of the methodology used.***
- ***Details of validation of the mapping technique***.

No mapping exercises were performed.

HRQL studies

10.1.5 ***Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.***

A systematic review was performed to identify studies reporting the QoL of patients with AM and their caregivers. The review also aimed to identify studies reporting relevant health state utility values (HSUVs).

The full search strategies used in the searches are shown in Appendix 4, Section 17.4. Medline, Medline in-process, Embase and the Cochrane Library (Cochrane Reviews, DARE, CENTRAL, HTA Database and NHS EED were searched on January 25th 2017 and again on 31st October 2017. In addition to these databases, hand-searching (reference lists of included publications, conference proceedings, previous HTA submissions [NICE, SMC, CADTH, INESSS and PBAC] and other sources) was used as a supplementary measure to identify further relevant studies that were not captured in the electronic database search.

Records identified in the searches underwent primary screening of titles and abstracts, assessed against defined eligibility criteria (Table 38).

Table 38. Eligibility criteria for inclusion in the QoL review

Criteria	Include
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age)
Treatments	No restriction
Outcomes	HSUV/QoL SR • Utilities values directly elicited using TTO/SG techniques • Utility values derived using generic preference-based instruments for relevant health states (e.g. EQ-5D, SF-6D, HUI3) • Mapping studies allowing generic or disease-specific measures to be mapped to preference-based utilities • Generic or disease-specific measures reporting the QoL associated with AM
Setting/study design	HSUV/QoL SR, no limitation and to include: • HSUV elicitation studies • Interventional studies • Observational studies e.g. cohort studies
Language of publication	No restriction. On completion of citation screening on the basis of title and abstract, a list of foreign-language publication was forwarded to Chiesi. A decision was then taken on whether the studies were conducted in a country of interest.
Date of publication	No restriction
Countries/global reach	No restrictions

Abbreviations: AM, alpha-mannosidosis; EQ-5D, EuroQol five dimensions questionnaire; HUI3, health utilities index Mark 3; HSUV, health-state utility value; QoL, quality of life; SG, standard gamble; SF-6D, short form 6D; SR, systematic review; TTO, time-trade-off.

10.1.6 *Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.*

- ***Population in which health effects were measured.***
- ***Information on recruitment.***
- ***Interventions and comparators.***
- ***Sample size.***
- ***Response rates.***
- ***Description of health states.***
- ***Adverse events.***
- ***Appropriateness of health states given condition and treatment pathway.***
- ***Method of elicitation.***
- ***Method of valuation.***
- ***Mapping.***

- ***Uncertainty around values.***
- ***Consistency with reference case.***
- ***Results with confidence intervals.***

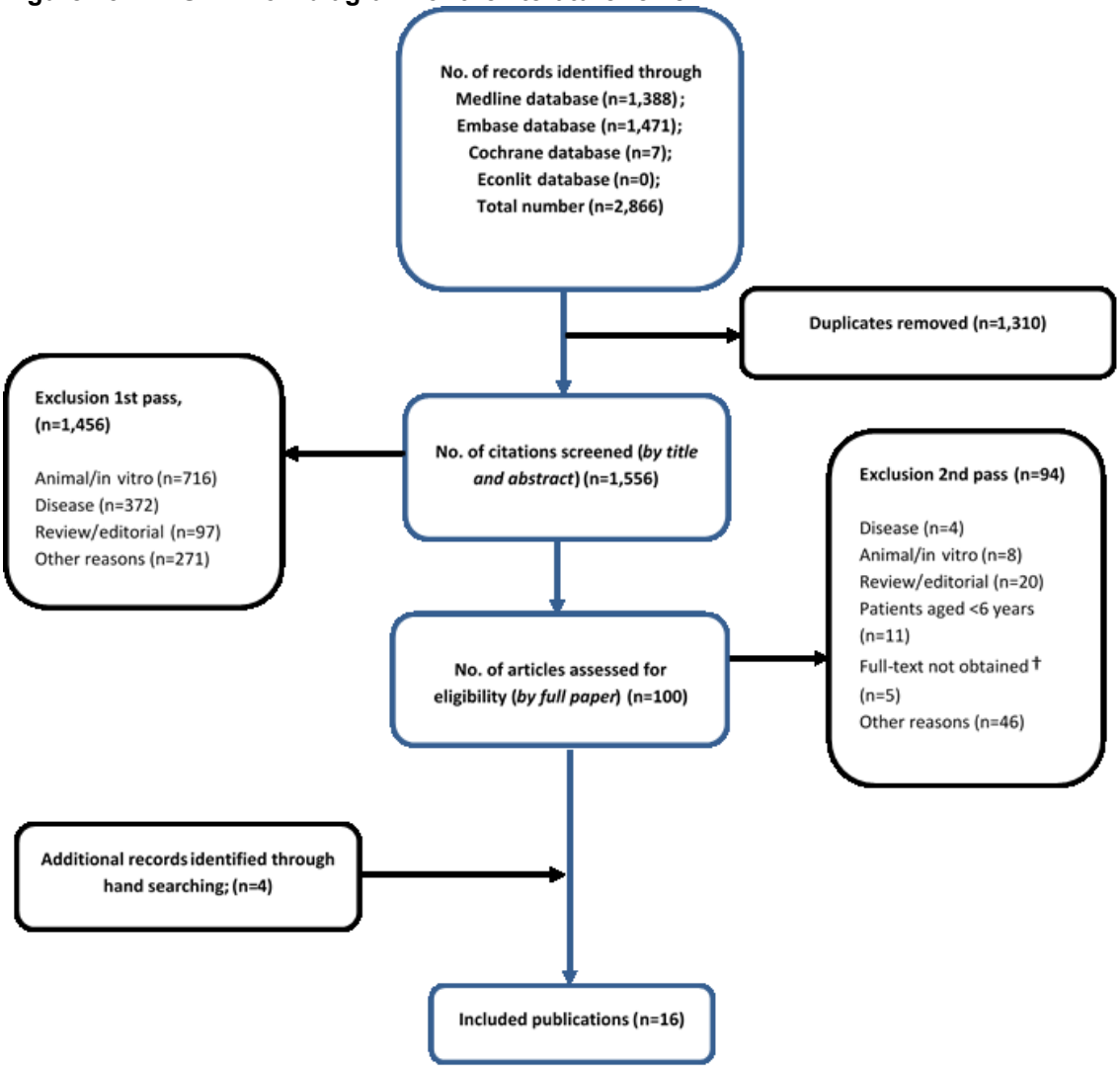
10.1.6.1 Study selection

The electronic database searches identified a total of 2,866 citations. After removing duplicate papers, 1,556 titles and abstracts were screened. At this stage, a total of 1,462 articles were excluded, and 100 were deemed to be potentially relevant. Upon review of the full texts, a further 94 articles were excluded. Hand searching yielded an additional four relevant publications for inclusion. This resulted in a total of 10 publications that met the eligibility criteria of the review.

In the update, 92 papers were identified through the electronic database searches. Following the removal of 27 duplicate papers, 65 citations were screened on the basis of title and abstract. At this stage, all the studies were excluded based on titles and abstracts. Hand searching yielded six relevant publications for inclusion. Thus, a total of six publications were identified in the update that met the eligibility criteria of the review.

The overall flow of studies across the original review and the update is reported in the PRISMA flow diagram in Figure 25. A separate PRISMA for the updated review is also shown in Appendix 4, Section 17.4.7.

Figure 25: PRISMA flow diagram for the literature review



†It was not possible to source these publications from their internal sources or the British Library. Study authors were also contacted to obtain a copy of the full publication wherever contact details were available, but no response was received.
Studies excluded using "Other" exclusion code at 1st pass screening: Genetic/biomarker or diagnostic studies, (n=192); Studies reporting disease characteristics only, (n=71); 'Non-relevant' country (Japan), (n=5); Conference abstract superseded by full paper (n=3).
Studies excluded using "Other" exclusion code at 2nd pass screening: Epidemiology/clinical studies, (n=29); Genetic/biomarker or diagnostic studies, (n=10); Study reporting only disease characteristics, (n=4); Treatment for comorbidities, (n=2); Treatment before surgical procedure, (n=1).

10.1.6.2 Results

The current review included a total of seven unique studies associated with 16 publications (10, 12, 16, 32, 38, 55-63, 104, 105). The baseline characteristics and key findings of these studies are presented in Appendix 5, Table 128. One cross-sectional study (Borgwardt et al, 2015) reported general QoL data based on the baseline EQ-5D and CHAQ data of patients from rhLAMAN-02 and rhLAMAN-05. Ten abstracts based on rhLAMAN-10 also reported effect of treatment (velmanase alfa) on QoL, as measured by the CHAQ questionnaire; these results are reported in Section 9.6.1.2. Overall, no published HSUVs were identified in the included studies.

10.1.7 ***Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.***

No HSUVs were identified in the systematic literature review.

Adverse events

10.1.8 ***Please describe how adverse events have an impact on HRQL.***

The specific impact that AEs have on HRQoL was not assessed in the clinical trial programme; however, velmanase alfa was well-tolerated when compared with placebo (Section 9.7.2.1). In total, three patients experienced an IRR and all events were mild or moderate in intensity and resolved spontaneously; no patients discontinued velmanase alfa as a result of an IRR. In the cost-effectiveness analysis, IRRs are assumed not to incur a disutility. This assumption is supported by a recent publication by White et al. (2017), which shows that IRRs in patients with LSDs receiving ERT requires minimal intervention (106).

Quality-of-life data used in cost-effectiveness analysis

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

10.1.9.1 Base case

The primary utility values used in the base case cost-effectiveness analysis are presented in Table 39.

Table 39: Summary of quality-of-life values for cost-effectiveness analysis

	Utility value	CI	Reference in submission	Justification
Health state utility				
Walking unassisted	[redacted]	-	KOL (unpublished) AM patient audit (17)	These values are specific AM patient utility (EQ-5D-5L) values (n=7) proxy completed by clinician, and provide coverage across the four ambulatory health states used to model disease progression. [redacted] Short end stage assumed equivalent to severe immobility.
Walking with assistance	[redacted]			
Wheelchair-dependent	[redacted]			
Severe immobility / short end stage	[redacted]			
VA on-treatment utility increment				
Utility increment while on VA	0.1	-	Assumption, UK KOL interviews (17)	See below table and Section 12.1.4
Disutilities				
Severe infection	0.18	-	Drabinski et al, 2001 (107)	A published source of EQ-5D values during 6-month follow-up/recovery from sepsis
Major surgery	0.25	-	Elosulfase alfa [ID744] HST, company submission, Table D14, p178 (108)	Accepted value by NICE for a related MPS condition (MPS IVA)
Caregiver disutilities				
Walking unassisted	-0.01	-	UK KOL interviews (17) EDSS caregiver disutility (109)	Gani is a published source of caregiver disutility stratified by level of severity in patients with multiple sclerosis using the EDSS instrument. WU, WWA, WC and SI were assumed by clinical expert opinion to have an EDSS level of 2.5, 4.5, 6.5 and 8.5, respectively.
Walking with assistance	-0.02	-		
Wheelchair-dependent	-0.05	-		
Severe immobility / Short end stage	-0.14	-		

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol five-dimension questionnaire; KOL, key opinion leader; MPS, mucopolysaccharidosis; VA, velmanase alfa; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

Treatment with velmanase alfa has been shown to provide a utility benefit in rhLAMAN-10 (Section 10.1.3). However, it is likely that the utility gain observed in this

trial is underestimated due to the difficulty in assessing QoL (see Section 7.1 for further discussion). Furthermore, it is possible that some of the QoL benefits as a result of velmanase alfa treatment will only materialise after longer-term treatment, beyond that of the latest time point in the clinical trial (up to 48 months in rhLAMAN-10). This includes potential benefits of velmanase alfa treatment that were not possible to incorporate into the cost-utility analysis, due to the heterogeneity and complexity of the condition and the pragmatic model design (Section 12.1.4). These additional benefits include the impact of treatment on minor infections, minor surgeries, psychiatric complications, ventilator dependency, and intra-ambulatory health state improvement/progression (i.e. reducing the number of ambulatory aids required). For these reasons, an on-treatment utility increment of 0.1 is included in the base case analysis, and was validated by UK KOL experts (17). It was assumed that this on-treatment utility increment stopped if a patient discontinued treatment, although this assumption is tested within the scenario analysis (Section 12.5.16).

A severe infection results in a disutility of 0.18 for 6 months (Quality adjusted life year [QALY] decrement of 0.09). This is from a publication of the HRQoL of patients recovering from severe sepsis (107). The use of sepsis as a proxy for all 'severe infections' is aligned with expert UK KOL opinion, with severe infections defined as an infection requiring hospital admission (e.g. sepsis, pneumonia, bone infection etc.) (17). If a patient experiences a severe infection, they transition to a 'tunnel' state for one cycle (a year), where they incur the disutility of the severe infection (0.18 over 6 months). It is assumed that a patient cannot have a major surgery while in a 'tunnel' state. At the end of the cycle, the patient can then either return to the primary health state (i.e. recover) or progress immediately to the short end stage because they have not recovered from the severe infection.

Major surgery results in a disutility of 0.25 for 3 months. This is from the BioMarin elosulfase alfa NICE HST submission for major surgical procedures (108). The data from this submission is from a Delphi survey of clinicians for patients with MPS IVA. During the major surgical event, the patient remains in their current health state; however, patients are at the risk of transitioning to the 'severe immobility' health state due to a complication, or to the dead state due to surgical mortality.

In the absence of direct trial data on caregiver disutility, a targeted literature search was conducted to identify caregiver disutility in similar proxy conditions (Appendix 6, Section 17.6.1). Three papers were identified, of which two were deemed as appropriate and included in the model.

Carer disutility is captured in the model using the Extended Disability Status Scale (EDSS). Whilst the EDSS questionnaire is designed to capture the disease states associated with multiple sclerosis, there are some parallels with the functional impairment status of patients with AM and patients with multiple sclerosis. Furthermore, carer disutility (in the form of EQ-5D utility decrement) compared with controls by multiple sclerosis severity level (according to the EDSS) are publicly available and are shown in Table 40. Gani et al, (2008) (109) uses the EDSS, and Acaster et al, (2013) (110) employed the similar Patient Determined Disease Steps (PDDS) instrument (Table 41). The most appropriate EDSS and PDDS level for each primary health state were validated by the UK KOLs (17).

The data from Gani et al, (2008), shows that carer disutility increases linearly as the disease becomes more severe. In contrast, Acaster et al, (2013), demonstrated that carers of the most severe patients (wheelchair bound or bedridden) incurred a lower disutility than those caring for patients who could still walk with support. The linear increase in disutility as disease severity increases was considered more clinically appropriate and is used in the base case economic model analysis. In the model, the utility decrement for short end stage is assumed to be equivalent to severe immobility. While this decrement is applied for a full year, a patient is assumed to be in the short end stage state for four weeks. This assumption is to account for the bereavement process of carers and their family, and is tested as a part of the scenario analyses reported in Section 12.5.16.

Table 40: EQ-5D utility decrement associated with caregivers compared to controls by EDSS level (Gani et al, 2008)

EDSS level	EDSS level description	EQ-5D carer utility decrement	Health states
0	Mild disease	0.00	-
1		0.00	-
1.5–2.0		0.00	-
2.5–3.0		-0.01	Walking unassisted
3.5–4.0	Moderate disease	-0.01	-
4.5–5.0		-0.02	Walking with assistance
5.5–6.0		-0.03	-
6.5–7.0	Severe disease	-0.05	Wheelchair
7.5–8.0		-0.11	-
8.5–9.5		-0.14	Severe immobility; short end stage

Source: Gani et al, 2008 (109) and UK KOL interviews (17)
Abbreviations: EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol five-dimension questionnaire.

Table 41: EQ-5D utility decrement associated with caregivers compared to controls by PDDS level (Acaster et al, 2013)

PDDS level	PDDS level description	EQ-5D carer utility decrement	Health states
0–1	Normal – mild disability	0.00	-
2–3	Moderate disability – gait disability	-0.05	Walking unassisted
4	Early cane	-0.14	Walking with assistance
5	Late cane	-0.16	-
6	Bilateral support	-0.17	-
7	Wheelchair/scooter	-0.03	Wheelchair
8	Bedridden	-0.09	Severe immobility; short end stage

Source: Acaster et al, 2013 (110) and UK KOL interviews (17)
Abbreviations: EQ-5D, EuroQol five-dimension questionnaire; PDSS, Patient Determined Disease Steps.

10.1.9.2 Scenario analysis – health state utility values

As the UK AM audit data are unpublished (17), we have assessed alternative health state utility values in scenario analyses reported in Section 12.5.16.

Patients in each health state will experience both functional disutility (relating to ambulatory status) and other clinical features leading to disutility. In terms of other clinical features, UK KOL opinion was that pain, cognition and hearing would be the major drivers of 'wider disease' disutility not related to ambulatory status. By identifying both functional and 'wider disease' disutilities, multi-morbid utilities can be generated to represent proxy AM health state utility values. For the purpose of the scenario analyses in the economic model, age- and gender-specific UK general population utility values were generated using the regression model from the Ara et al (2010) study (111).

Functional disutility

As the data identified in the SR and obtained during the rhLAMAN clinical development programme were not sufficient for the analysis, a targeted literature search was performed to identify appropriate proxy data for (Appendix 6, Section 17.6.1 and 17.6.2):

- QoL due to functional impairment
- QoL due to hearing impairment, cognitive impairment, and pain

Two studies (Hendriksz et al, (2014) (112) and Kanters et al, (2015) (113)) were identified as studies that provided appropriate proxy disutility scores for each of the primary health states. Both were studies of LSDs (MPS IVA and Pompe disease, respectively) and included EQ-5D utility values stratified by ambulatory status. The values from these studies were then matched to the corresponding primary health states for the economic model. The disutilities are presented in Table 42.

Similar to AM, Pompe disease and MPS IVA are both progressive LSDs that affect the ambulatory status of patients (112, 113). The functional impact of MPS IVA was considered to more closely relate to the functional impairment of AM.

Table 42: Disutility incurred due to functional impairment

Primary health state	Hendriksz 2014 – MPS IVA	Kanters 2015 – Pompe disease
Walking unassisted	-0.07	-0.11
Walking with assistance	-0.33	-0.20
Wheelchair	-0.86	-0.30
Severe immobility	-0.86	-0.30

Source: Hendriksz et al, (2014) (112) and Kanters et al, (2015) (113)

Wider disease disutility

To capture the multi-morbid nature of AM, each primary health state includes three key clinical features of AM in addition to functional impairment – hearing impairment,

cognitive impairment, and pain. These were identified as the clinical features that were most likely to affect patient QoL by the UK KOLs (17).

To model the disutility due to these clinical features, EQ-5D utility values were extracted from Currie et al, (2006) for pain (114), Jonsson et al, (2006) for cognitive impairment (115), and HUI-3 values were retrieved from Colquitt et al, (2011) (116) (Table 43). These data were selected as they reported three levels of clinical severity (mild, moderate and severe).

Table 43: Disutility incurred for 'wider disease' clinical features of alpha-mannosidosis

Clinical complication	Mild	Moderate	Severe	Source
Hearing	-0.03	-0.24	-0.42	Colquitt 2011 (116)
Cognition	-0.14	-0.27	-0.39	Jonsson 2006 (115)
Pain	-0.25	-0.36	-0.63	Currie 2006 (114)

Based on the distribution of clinical features per primary health state (i.e. the proportion of mild, moderate and severe in each health state [Table 49]), weighted 'wider disease' disutility scores were calculated (Table 44).

Table 44: Weighted 'wider disease' disutility scores per primary health state

Symptom	Hearing impairment	Cognitive impairment	Pain
Walking unassisted	-0.15	-0.21	-0.34
Walking with assistance	-0.16	-0.22	-0.41
Wheelchair	-0.21	-0.25	-0.45
Severe immobility	-0.25	-0.29	-0.46

Multi-morbid disutility

Using the functional and 'wider disease' disutility scores, it is possible to calculate an age-specific multi-morbid utility score for each of the primary health state. Three approaches are possible (where baseline utility is the general population age and gender adjusted utility score):

- Additive: Baseline utility + functional disutility + 'wider disease' disutility = multi-morbid utility
- Multiplicative: (baseline utility + functional disutility) x (baseline utility + hearing disutility) x (baseline utility + cognition disutility) x (baseline utility + hearing disutility) = multi-morbid utility
- Minimum: Only the largest disutility score is subtracted from the baseline utility

An example of each approach, based on a patient aged 17 and using the functional disutility data from Hendriksz et al, (2014) (112) is shown in Table 45.

Overall, using the 'minimum' method would appear to be the most appropriate/conservative approach, as this method produces utilities that are more aligned to those published in the literature (from proxy diseases) as well as the utilities derived from the EQ-5D data from the rhLAMAN trials. The 'walking unassisted' and 'walking with assistance' utility values are similar to those observed in rhLAMAN-10 (Section 10.1.3). The difference between 'walking unassisted' and 'walking with assistance' (~0.07) was also similar to that observed in the clinical trial data (0.075). The 'wheelchair' and 'severe immobility' health states were also associated with further disutility. It is assumed that the utility values for the short term end state is equivalent to the severe immobility health state.

Table 45: Multi-morbid utility calculations

Source	Method	Primary health states			
		Walking unassisted	**Walking with assistance**	**Wheelchair**	**Severe immobility**
Multi-morbid utility method (Hendriksz 2014 functional disutility)	Additive	0.151	-0.196	-0.842	-0.927
	Multiplicative	0.245	0.146	0.013	0.011
	Minimum	0.579	0.511	0.064	0.064
EQ-5D rhLAMAN-10 scores (baseline, overall population)		0.652	0.577	N/A	N/A
UK AM audit (17)		[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AM, alpha-mannosidosis; EQ-5D, EuroQol five-dimension questionnaire; N/A, not applicable.

10.1.10 ***If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:***

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

Please see Section 12.2.5 where details are provided about how clinical experts assessed the applicability of the utility values used in the economic model.

Chiesi are working with the UK MPS Society to conduct a patient/carer survey to gain qualitative and quantitative data on the QoL of patients/carers with AM in the UK. This survey is currently ongoing and additional evidence is likely to be available in the next 12 months.

10.1.11 ***Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?***

In the absence of any robust published HRQoL data in patients with AM, it was assumed that patients HRQoL within a health state stayed stable in the base case. It is noted that this is a simplifying assumption. Also it should be noted that adjusting HRQoL due to time spent in a health state is not possible due to the Markovian assumption implicit in the model structure. Instead, only age-adjusted (time in model-adjusted) utility is possible in the model and this is included when undertaking multi-morbid utility calculations in a scenario analysis.

10.1.12 ***Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?***

No health effects were excluded.

10.1.13 ***If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?***

Not applicable.

10.1.14 ***Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.***

HRQoL changes over time as patients progress through the model health states. HRQoL will also change if a patient experiences a severe infection and if they withdraw from velmanase alfa treatment (patients lose the on-treatment utility increment).

10.1.15 ***Have the values been amended? If so, please describe how and why they have been altered and the methodology.***

All amendments to utility values have been described in Section 10.1.9.

Treatment continuation rules

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

- ***The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).***

- ***The robustness and plausibility of the endpoint on which the rule is based.***
- ***Whether the 'response' criteria defined in the rule can be reasonably achieved.***
- ***The appropriateness and robustness of the time at which response is measured.***
- ***Whether the rule can be incorporated into routine clinical practice.***
- ***Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.***
- ***Issues with respect to withdrawal of treatment from non-responders and other equity considerations.***

In order to provide guidance on the appropriate management of patients treated with velmanase alfa, Chiesi have developed a start-stop criteria. It should be noted that Chiesi are currently in discussion with UK KOLs on the suitability and/or generalisability of these criteria to UK clinical practice; therefore, the details provide on the treatment continuation rules may be subject to further change.

10.1.16.1 Eligibility

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

Patients will not be eligible to receive treatment with velmanase alfa if any of the following apply:

- the patient does not have a confirmed diagnosis of alpha-mannosidosis; or
- the patient has experienced a severe allergic reaction to velmanase alfa or to any of the excipients (disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol and glycine); or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient is unwilling or unable to comply with the associated monitoring criteria, i.e. that all patients are required to attend their appointed clinics two times per year for assessment

10.1.16.2 Start criteria

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

- Patient eligibility criteria must be met as defined in Section 10.1.16.1

- A full set of baseline biochemical, functional and QoL assessments have been obtained

10.1.16.3 Stop criteria

Patients will cease treatment with velmanase alfa if any of the following apply:

- the patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 18-month period); or
- the patient fails to meet two of the three criteria as defined in multi-domain responder analysis at their Year 1 assessment (Section 9.4.1.4 and 9.6.1.3)
- the patient is unable to tolerate infusions due to infusion related severe AEs that cannot be resolved; or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g. due to repeated recurrent chest infection or progressive and sustained lack of mobility; or
- the patient misses more than four infusions of velmanase alfa in any 12-month period, excluding medical reasons for missing dosages.

Patients whose treatment with velmanase alfa is discontinued due to stop criteria will continue to be monitored for disease progression and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

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

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

Summary of existing economic studies

- A systematic literature review (SR) was undertaken to identify previous cost-effectiveness analyses relevant to the decision problem. The same SR was used to identify cost and resource use associated with alpha-mannosidosis (AM)
- No studies met the pre-defined eligibility criteria for inclusion in the economic evaluation/cost and resource SR

Summary of the *de novo* cost-effectiveness analysis

Design

- A *de novo* economic model and cost-utility analysis was developed to estimate the impact of treatment with velmanase alfa in terms of costs and effects (quality adjusted life years [QALYs]) on patients with AM
- The analysis compares best supportive care (BSC) without velmanase alfa (the "best support care" strategy) against velmanase alfa plus BSC (the "velmanase alfa" strategy). The base case analysis is conducted from an NHS/ Personal Social Services (PSS) perspective and estimates costs and QALYs over a lifetime time horizon
- The model is a cohort Markov state-transition design, with four primary health states representing different levels of ambulatory status (walking unassisted, walking with assistance, wheelchair dependent, and severe immobility)
- The model can present three different cohorts based on age at treatment initiation with velmanase alfa: a paediatric cohort (6–11 years), an adolescent cohort (12–17 years) and an adult cohort (≥18 years). These cohorts correspond to a post-hoc analysis of the rhLAMAN clinical programme by three age groups (Section 9.6.1.2). The starting state distribution for the model is based on the ambulatory status of the rhLAMAN-10 baseline population, which is used as a proxy of the prevalent population in England and Wales
- The chronic and progressive nature of AM is modelled via the gradual progression (deterioration) of ambulatory status and functional capacity. Patients move through the health states in sequence unless they die due to background mortality, a severe infection, or major surgery; they may also move directly to the severe immobility health state due to a surgical complication
- The primary benefit of velmanase alfa is to delay the rate of disease progression, but the modelled benefit of velmanase alfa also includes the ability for disease improvement (the ability for a patient's ambulatory status to

improve, and revert to a less severe health state), a reduction in the rates, recovery disutility and mortality from severe infections, and a reduction in the recovery disutility, complications and mortality from major surgery. Velmanase alfa is also modelled to have a benefit by reducing the necessity and complexity of ventilation required by patients in the more severe health states. Estimates of long term progression and the treatment effect of velmanase alfa have been derived from a UK Expert Elicitation Panel (UK-EEP) and validated by UK key opinion leader (KOL) interviews

Base case results

- In the base case analysis (presented in Section 12.5), the incremental cost-effectiveness ratio (ICER) for velmanase alfa vs BSC was [redacted] in the paediatric cohort, [redacted] in the adolescent cohort and [redacted] in the adult cohort. The budget impact analysis estimates that the treated cohort will comprise 40% paediatric patients, 20% adolescent patients, and 40% adult patients. Using these proportions, the weighted cohort ICER is [redacted]
- After discounting costs at 1.5%, BSC was associated with a lifetime total cost of £894,169, £899,375, and £914,049 in the paediatric, adolescent, and adult cohorts, respectively. Velmanase alfa was associated with a lifetime incremental cost of [redacted], and [redacted] in the paediatric, adolescent and adult cohorts, respectively
- After discounting QALYs at 1.5%, BSC was associated with lifetime total QALYs of 5.65, 5.26, and 4.41 in the paediatric, adolescent, and adult cohorts, respectively. Velmanase alfa was associated with a lifetime incremental QALYs (vs BSC) of 2.25, 2.38, and 2.39 in the paediatric, adolescent and adult cohorts, respectively
- The disaggregated results (Table 85) show that treatment with velmanase alfa will lead to PSS cost savings

Results of the sensitivity analyses

- The one-way sensitivity analysis shows that the parameters in the model affecting the ICER are the discount rate used for QALYs and the cost of velmanase alfa.
- The ICER was also sensitive to the rate of backwards transitions (disease improvement to patients' ambulatory health state) on velmanase alfa. Assuming that 70% of patients treated with velmanase alfa experience a reverse transition from 'walking with assistance' to 'walking unassisted' in Year 1, the ICERs vs BSC are:
    - [redacted] for paediatrics
    - [redacted] for adolescents
    - [redacted] for adults
- The probabilistic sensitivity analysis (PSA) demonstrated combined parameter uncertainty in the model, with mean probabilistic results that were very similar to the deterministic analysis, and broad 95% confidence intervals (CIs) around

the ICERs (paediatric ICER [95% CI]: [redacted] adolescent ICER [95% CI]: [redacted], adult ICER [95% CI]: [redacted])

- The results of the multi-way scenario analysis demonstrated that there are more optimistic analyses to explore. For example, assuming the upper limit of the treatment effect of velmanase alfa from the UK-EEP lowers the ICER to [redacted], and [redacted] for paediatrics, adolescents, and adults, respectively. Assuming that velmanase alfa slows disease progression by 50% lowers the ICERs further to [redacted], and [redacted], for paediatrics, adolescents, and adults, respectively. An optimistic scenario where velmanase alfa halts disease progression lowers the ICERs further to [redacted], and [redacted], for paediatrics, adolescents, and adults, respectively. It is noted that such levels of optimism with respect to delayed disease progression (i.e. 50% reduction to halting disease progression) have been considered as part of other enzyme replacement therapy (ERT) NICE HST appraisals

Summary of cost to the NHS and Personal Social Services

- The UK MPS Society Patient Registry has identified [redacted] with AM over the age of 6 years in England and Wales (4)
- Specifically, there are [redacted] paediatric patients (aged 6–11), [redacted] adolescent patients (aged 12–17) and [redacted] adults (aged ≥18) (4)
- The budget impact model estimates that after accounting for market share estimates, incident patients, discontinuation and mortality, [redacted] patients will be treated with velmanase alfa in Year 1, rising to [redacted] in Year 5
- These patient numbers account for a budget impact associated with velmanase alfa treatment and administration of £1.3m in Year 1, rising to £1.9m in Year 5, and a total cumulative budget impact over 5 years of £7.8m

11 Existing economic studies

11.1 *Identification of studies*

11.1.1 *Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.*

A systematic literature review was undertaken to identify previous cost-effectiveness analyses relevant to the decision problem. The same SR was used to identify cost and resources use associated with AM.

Original systematic review

An overview of the strategies employed in the original systematic review are outlined below. Full details of the search strategy are provided in Appendix 3.

Databases searched

The following electronic databases were searched via the OVID platform on 25th January 2017:

- MEDLINE® In-Process & Other Non-Indexed Citations
- MEDLINE, 1946 to present
- Embase, 1980 to present
- The Cochrane Library, incorporating:
    - the Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - the Database of Abstracts of Reviews of Effects (DARE)
    - the Cochrane Central Register of Controlled Trials (CENTRAL)
    - the Health Technology Assessment (HTA) Database
    - the National Health Service Economic Evaluation Database (NHS EED)
- OVID EconLit, 1961 to present (for economic review only)

In addition to these databases:

- Hand-searching was used as a supplementary measure to identify further relevant studies that were not captured in the electronic database search
- Reference lists of included studies were scanned to identify potential relevant publications for inclusion
- To identify any recent studies for which there were currently no full publications, the conference proceedings were examined for relevant abstracts (and posters/slide decks, if available) from the last three years.
- Submission documents from HTA agencies (NICE, SMC, CADTH, INESSS and PBAC) were reviewed for relevant data. Additional databases, as recommended by NICE, were also hand-searched

Update to original systematic review

An update of the search was conducted on 31st October 2017 to identify relevant papers published post-January 2017. The search strategies used for the cost-effectiveness/cost and resource SR for the updated review are detailed in Appendix 3.

11.1.2 ***Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.***

Table 46: Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age).
Interventions	Not restricted (see Section 17.1.6 for details on treatments to include).

Outcomes	**Economic evaluation SR**
	• Main outcomes:
	  o ICERs: cost per QALY, cost per DALY, cost per event avoided
	• Additional outcomes:
	  o Range of ICERs as per sensitivity analyses
	  o Assumptions underpinning model structures
	  o Key cost drivers
	  o Sources of clinical, cost and quality of life inputs
	  o Discounting of costs and health outcomes
	  o Model summary and structure
	Cost of illness/resource use SR
	• Direct costs
	• Direct medical and pharmacy healthcare costs per patient per year (interventions, concomitant medications, treatment of AEs/co-morbidities)
	• Method of valuation
	• Indirect costs
	  o Productivity loss costs
	  o Presenteeism: at work productivity level (also from patients' viewpoint)
	  o Short- and long-term sick leave (absenteeism)
	  o Withdrawal from labour force
	  o Method of valuation (Human capital or friction cost approach or contingent valuation)
	  o Costs of special schooling for patients
	  o Costs of adapting home settings to account for progressive disability
	• Patient and family/caregiver costs
	  o Travel, co-payments
	  o Annual loss of income
	  o Formal and informal care
	• Caregiver burden

Study design	**Economic evaluation SR** • Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses **Cost of illness/resource use SR** • For studies to be eligible: o Epidemiological approach should be specified for the design

	○ Perspective of the study should be clear ○ Objectives of the study must include an assessment of costs of illness or an assessment of interventions in management of AM ○ Studies reporting predictors of costs were considered for inclusion
Language restrictions	Unrestricted
Search dates	Unrestricted
Exclusion criteria	
Population	Patients aged <6 years with AM (all patients were included at first pass regardless of age).
Interventions	Unrestricted
Outcomes	Restricted to those stated in the eligibility criteria.
Study design	Restricted to those stated in the eligibility criteria.
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: AE, adverse events; AM, alpha- mannosidosis; CSF, cerebrospinal fluid; DALY, Disability-adjusted life year; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SR, systematic review.

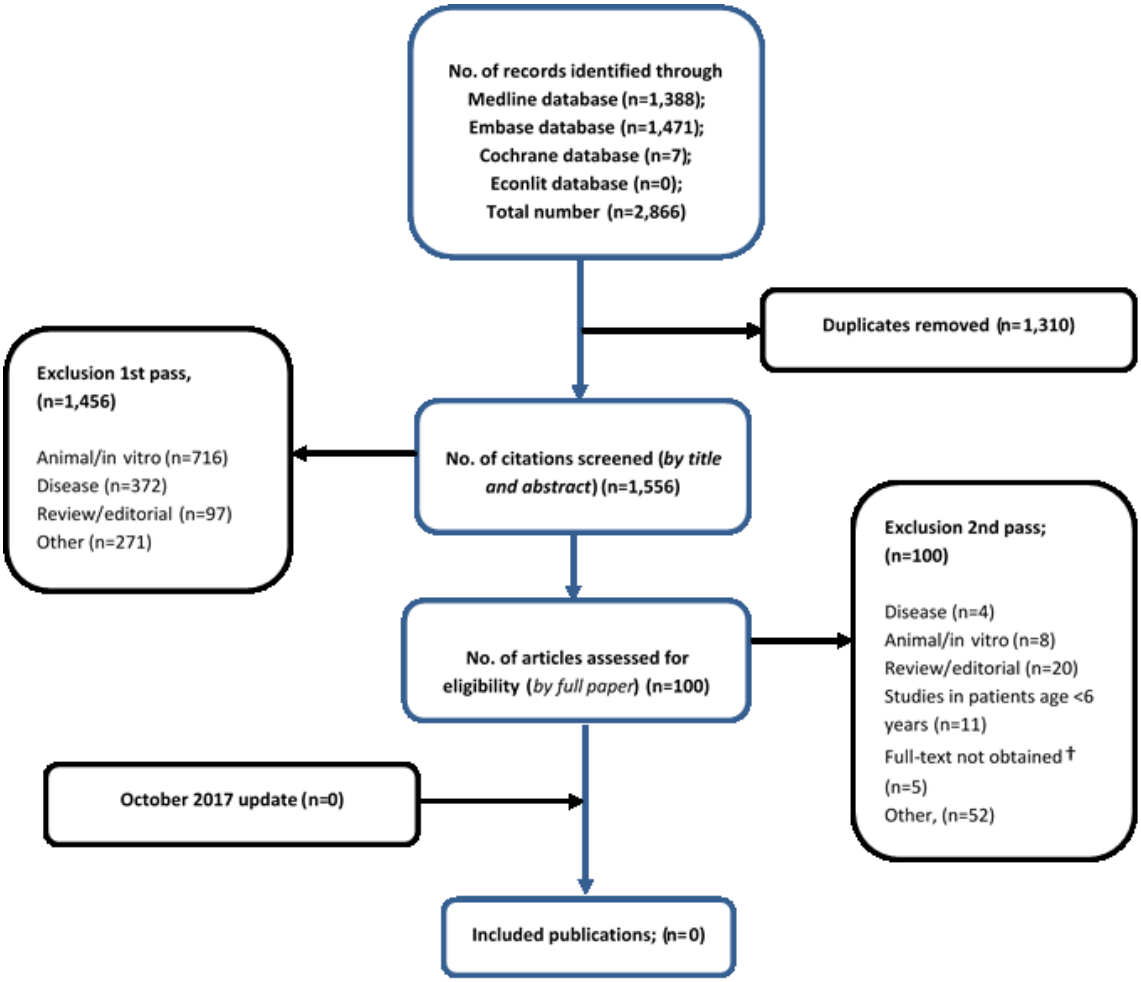
11.1.3 *Report the numbers of published studies included and excluded at each stage in an appropriate format.*

The electronic database searches identified a total of 2,866 citations. After removing duplicate papers, 1,556 titles and abstracts were screened. At this stage, a total of 1,456 articles were excluded and 100 were deemed to be potentially relevant. After reviewing full-texts, no eligible studies reporting on cost/resource use or economic evaluation were identified.

In the update, 92 papers were identified through the electronic database searches. Following the removal of 27 duplicate papers, 65 citations were screened on the basis of title and abstract. At this stage, all the studies were excluded based on titles and abstracts. Hence, no eligible studies reporting on cost/resource use or economic evaluation were identified in the update.

The overall flow of studies across the original review and the update is reported in the PRISMA flow diagram in Figure 26. A separate PRISMA for the updated review is also shown in Appendix 3, Section 17.3.7.

Figure 26: PRISMA flow diagram for the economic/cost resource systematic literature review



†It was not able to source these papers from their internal sources, Chiesi, or the BL. Study authors were also contacted, wherever contact details were available, but no response was received
Studies excluded using "Other" exclusion code at 1st pass screening: Genetic/biomarker or diagnostic studies, (n=192); Study reporting only disease characteristics, (n=71); 'Non-relevant' country (Japan), (n=5); Conference abstract superseded by full paper (n=3).
Studies excluded using "Other" exclusion code at 2nd pass screening: Epidemiology/QoL studies, (n=35); Genetic/biomarker or diagnostic studies, (n=10); Study reporting only disease characteristics, (n=4); Treatment for comorbidities, (n=2); Treatment before surgical procedure, (n=1).

11.2 *Description of identified studies*

11.2.1 *Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.*

No studies met the pre-defined eligibility criteria for inclusion in the economic evaluation/cost and resource SR.

11.2.2 *Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.*

No studies met the pre-defined eligibility criteria for inclusion in the economic evaluation/cost and resource SR.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 *Description of the de novo cost-effectiveness analysis*

Patients

12.1.1 *What patient group(s) is (are) included in the cost-effectiveness analysis?*

Within the license indication, velmanase alfa is positioned in patients with AM alongside BSC for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible. An economic case for velmanase alfa is only presented in a patient cohort aged 6 years or above. This approach is taken as:

- Trial data are limited to those aged 6 years and older, and,
- In the UK, allogeneic HSCT is typically reserved for those with severe disease aged 5 years or younger. Modelling a patient cohort aged 6 years and above excludes patients with early/infant onset, severe disease

To account for the potential heterogeneity in a patient's treatment response to velmanase alfa based on their age at treatment initiation, the model assesses three age cohorts:

- Paediatric cohort: 6–11 years
- Adolescent cohort: 12–17 years
- Adult cohort: ≥18 years

Technology and comparator

12.1.2 *Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.*

The cost-utility model compares velmanase alfa + best supportive care (BSC) with BSC alone (aligned to the definitions provided by UK KOLs; see Section 8.2.4)

Although included in the decision problem, allogeneic HSCT is not a comparator assessed in the model presented. This decision is because the model considers patients aged ≥6 years and expert clinical KOL feedback provided to Chiesi indicates that allogeneic HSCT is unlikely to be clinically indicated for patients aged 6 years and older. Allogeneic HSCT is typically reserved for AM patients with extensive disease presenting in early infancy (aged ≤5 years); a form of disease that is often lethal soon thereafter if untreated (18). Additionally, the ideal age for transplant is considered to

be <2 years old and only in exceptional circumstances would allogeneic HSCT be considered in patients >5 years old (18). Furthermore, the suitability of allogeneic HSCT also depends on the availability of a matched sibling or matched umbilical cord donor, and the absence of comorbidities/recurrent infections (17, 18).

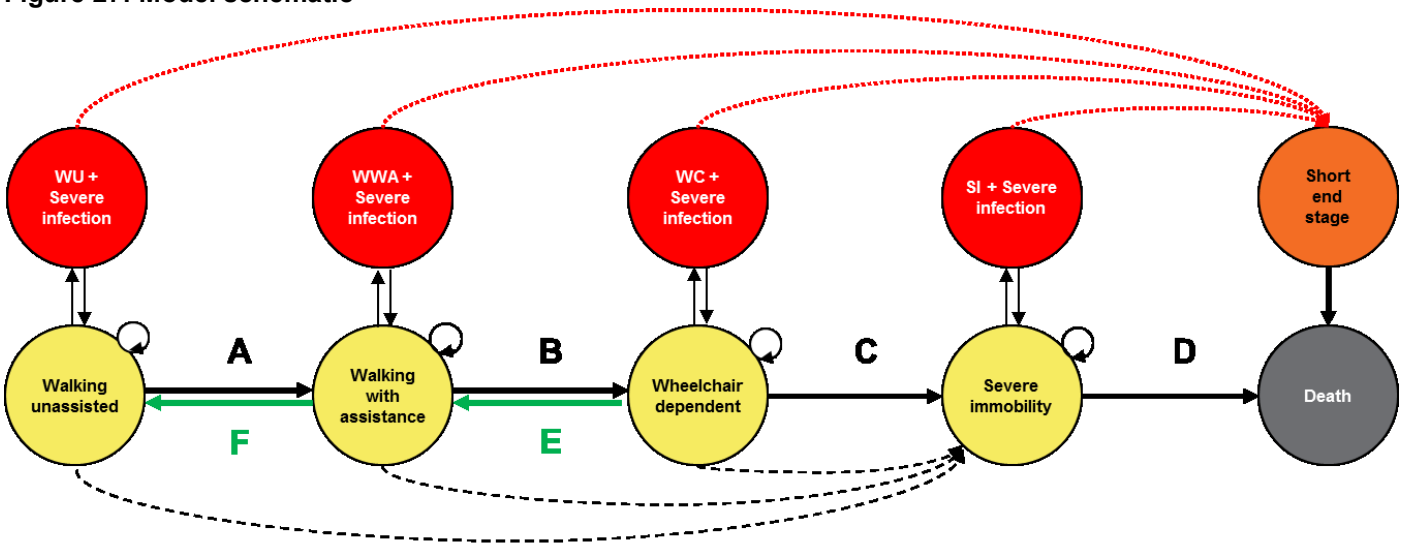
As velmanase alfa is positioned in patients with AM alongside BSC for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible, there is a discordance in the patient populations clinically indicated to receive velmanase alfa and allogeneic HSCT.

Model structure

12.1.3 *Provide a diagram of the model structure you have chosen.*

The cost-utility model is specifically a cohort Markov state-transition model. The structure of the model is shown in Figure 27.

Figure 27: Model schematic



Each health state accounts for the key drivers of disutility and costs due to the functional impairment, hearing impairment, cognitive impairment and pain experienced by patients with alpha mannosidosis

- Tunnel state: accounts for the cost, disutility and mortality risk associated with a severe infection
- Primary health state: patients start in the model in one of the four primary health states
- Short end stage: patients can only transition to short end stage from a severe infection tunnel state
- Death: patients can transition to death due to background mortality or surgery-related mortality from any health state
- Green arrow designates a disease improvement transition due to treatment with velmanase alfa
- Dashed arrow designates a transition to severe immobility as a result of a post-surgical complication
- Dashed arrow designates a transition to short end stage as a result of a severe infection that leads to death

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

The model structure captures the progression of AM using four primary health states based on ambulatory status – walking unassisted, walking with assistance, wheelchair dependent, and severe immobility, shown as yellow circles in the model schematic. Functional impairment is a key clinical feature of AM, due to loss of motor function, skeletal deformities, skeletal/joint destruction, reduced endurance and decreased lung function. A brief description of the functional status of patients, by primary health states are described in Table 47.

Table 47: Functional status across the primary ambulatory health states

State	Clinical features
Walking unassisted	• Patient is able to walk and go upstairs unassisted • Patient may have radiological skeletal abnormalities, but these may not present as clinical symptoms • Ataxia may be present but it does not greatly impact the patients' mobility
Walking with assistance	• The patient requires any form of assistance to walk (e.g. help from another person, footwear to support stability, a walking cane, wheelchair for long distances, hand rails etc.) • Patient may have radiological skeletal abnormalities presenting as clinical symptoms • Ataxia may be present and it may impact a patients' mobility
Wheelchair dependent	• Endurance is reduced; the patient is wheelchair-bound, but can still operate walking aids/use assistance to traverse short distances • Patient has some joint destruction that impacts mobility, however the patient can still transfer themselves without carer support (e.g. the patient can transfer from the wheelchair into bed independently) • Patient presents with some joint weakness and loss of joint flexibility
Severe immobility	• Patient requires a wheelchair/mobility device continuously and cannot transfer independently (i.e. requires hoists and other assistive equipment) • Joint destruction is present in weight-bearing joints (cervical spine, hips and/or knees), which severely restricts movement • Patient presents with poor muscle function and manual dexterity; for example, dressing unaided is impossible

Source: Data on file: UK key opinion leader interviews (17).

In addition to functional impairment being a key driver of AM disease progression, three clinical features were identified by UK KOLs as being prevalent in AM and key determinants of patients' overall health and QoL: hearing impairment (which impacts patients' ability to integrate socially and learn), cognitive impairment and pain (17). The definitions of each clinical feature by level of severity were validated by clinical experts via UK KOL interviews and are shown in Table 48.

Table 48: Definition of clinical features by level of severity

Clinical feature	Mild	Moderate	Severe
Hearing impairment	Some high frequency auditory loss – conductive and/or sensorineuronal hearing loss	Patient is able to follow speech but only with hearing aids	Complete deafness, or unable to follow conversation even with aids
Cognitive impairment	IQ of >70, level of cognition does not impact a patient's motivation and understand of the clinical benefits of completing physical exercise; patient can still form social/learning interactions with peers/caregiver	IQ 50–70, level of cognition starts to impact a patient's motivation and understand to exercise/undergo physiotherapy; patients' ability to interact with peers/caregiver is affected	IQ<50, patient does not understand the importance of exercise and disuse atrophy occurs; patients' ability to interact with peers/caregiver is significantly affected
Pain	Pain is present, but episodes are infrequent (less than three episodes per month, managed with analgesics)	Patient requires analgesics in response to frequent pain episodes (up to two episodes per week, managed with analgesics); pain impacts on patients' utility	Patient requires the chronic use of pain medications (experiences over three pain episodes per week); pain significantly impacts on patients' utility

Source: Data on file: UK key opinion leader interviews (17).

Table 49 shows the distribution (derived from clinical expert opinion via UK KOL interviews (17)) of the patient cohort experiencing mild, moderate or severe forms of these three clinical features stratified by the four primary health states. These clinical features are accounted for in the estimation of health state utilities (scenario analysis only) and health state resource use, however, they do not affect the probability of the model cohort transitioning between health states.

Table 49: Distribution of clinical features per primary health state

Walking unassisted	**Mild**	**Moderate**	**Severe**	**Total**
Hearing impairment	52%	35%	13%	100%
Cognitive impairment	55%	35%	10%	100%
Pain	55%	30%	15%	100%
Walking with assistance	**Mild**	**Moderate**	**Severe**	**Total**
Hearing impairment	50%	33%	17%	100%
Cognitive impairment	50%	40%	10%	100%
Pain	30%	40%	30%	100%
Wheelchair dependent	**Mild**	**Moderate**	**Severe**	**Total**
Hearing impairment	37%	37%	27%	100%
Cognitive impairment	35%	45%	20%	100%
Pain	15%	45%	40%	100%
Severe immobility	**Mild**	**Moderate**	**Severe**	**Total**
Hearing impairment	30%	30%	40%	100%
Cognitive impairment	15%	55%	30%	100%
Pain	13%	45%	43%	100%

Source: Data on file: UK key opinion leader interviews (17).

The model assumes that patients can only progress one level in functional impairment (shown by the black arrows labelled 'A' to 'D' in the model schematic) in any 12-month cycle, for example, from 'walking unassisted' to 'walking with assistance'. The exception to this assumption is that some patients may progress two or more levels along the functional impairment axis to the 'severe immobility' state (as shown by the black dashed arrows in the model schematic) because of surgical intervention (for example, post-operative complications arising from a ventriculoperitoneal shunt, cervical decompression therapy or a replacement joint failing); patients can become severely immobile as a result of such surgery-related adverse complications.

Disease improvements to the ambulatory status of patients based on treatment intervention are captured by backward transitions along the functional impairment axis (shown by the green arrows labelled 'E' and 'F' in the model schematic). Whilst improvements to patients' ambulation are clinically plausible with BSC (for example, a successful hip replacement allowing a patient to move out of a 'wheelchair dependent' state to 'walking with assistance'), the model excludes backward transitions for the patient cohort on BSC alone. This is a simplifying assumption, as the probability of backward transitions because of BSC are assumed to be equivalent in both the intervention (velmanase alfa + BSC) and comparator (BSC) arms, and are therefore not formally modelled. Instead, the model allows backward transitions for patients treated with velmanase alfa + BSC only; this is to account for the ability of velmanase alfa (over and above BSC) to achieve disease improvements in the ambulatory status of patients.

Expert clinical opinion derived from UK KOL interviews agreed that disease improvement (backward transitions) as a result of treatment with velmanase alfa (over and above BSC) were clinically plausible (17) and improvement in the ambulatory status of patients was also observed in the velmanase alfa clinical trial programme (Section 7.2.1 and 9.6.1.2). The model assumes that:

- Backward transitions are only possible for patients receiving velmanase alfa + BSC, to reflect the treatment effect of velmanase alfa over and above BSC alone:
    - Patients can only transition backwards (improve) one level in functional impairment, e.g. 'walking with assistance' to 'walking unassisted', per year (per cycle)
    - Patients are more likely to transition backwards in the first two years (i.e. first two cycles) after treatment initiation; i.e. the probability of disease improvement from Year 3 onwards is assumed to be lower than during the first two years of treatment with velmanase alfa

The primary health states are also associated with a 'tunnel state' (shown by the red circles in the model schematic). Each tunnel state is a replica of the corresponding, underlying primary health state – patients can move into a tunnel state for one cycle only (a year), during which patients incur the costs, mortality risk and recovery disutility associated with a severe infection (defined as an infection requiring hospital admission, e.g. sepsis, pneumonia, bone infection, etc.).

Patients can transition to 'death' due to background mortality from any health state (noting that not every patient will enter every health state before death); background mortality is informed by UK (England) Office for National Statistics life tables, 2014–2016 (released September 2017). Patients can also transition to 'death' from any of the primary health states due to major surgery mortality (the model assumes major surgery will not be conducted if a patient is in a severe infection tunnel state). The model also includes an additional 'short end stage' state, which captures the severe/terminal health status of patients prior to death following a severe infection. The 'short end stage' is defined as a severe infection leading to the requirement of intensive care support, followed by end of life care before death (average time spent in short end stage is assumed to be 4 weeks) (17). Therefore, patients can only transition to the 'short end stage' states from a severe infection tunnel state.

12.1.4 *Justify the chosen structure in line with the clinical pathway of care.*

Expert clinical opinion was sought via UK KOL interviews to identify the main drivers of morbidity, mortality and QoL associated with AM (17) and to ensure that the natural progression of AM is modelled accurately. Aligned to the expert advice provided, the model structure accounts for the following:

- Functional impairment (capturing changes to patients' mobility, musculoskeletal system, endurance and lung function)
- Cognitive impairment
- Hearing impairment
- Pain

- Severe infections
- Minor and major surgeries
- Ventilation dependency
- Caregiver disutility

Expert clinical opinion was also sought via UK KOL interviews to confirm the key resource utilisation costs associated with BSC, to ensure the model accurately captured the current UK clinical pathway of care (17). Aligned to the expert advice provided, the model structure accounts for the following key determinants of costs associated with BSC:

- Healthcare visits to the multidisciplinary team (MDT) responsible for the care of AM patients, to provide a '*needs-based approach as symptoms arise'*
- Costs to treat severe infections
- Costs associated with minor and major surgeries
- Personal/social services costs
- Ventilation costs
- End of life costs

The model is also in line with the NHS Standard Contract for LSD services (40) with respect for the administration of an ERT; i.e. administration is assumed to be first completed in an LSD specialist centre before transfer of administration to an alternative setting (homecare or local hospital).

Notably, AM presents as a highly heterogeneous condition in which the clinical features observed for an individual (and the associated morbidity, mortality-risk and impact on QoL) may be strikingly different to the experiences of another patient. AM is a multi-morbid, progressive, life-limiting condition that impacts on many systems at any one time – e.g. aberrations to the musculoskeletal, central nervous, respiratory and immunological systems, leading to different cumulative effects on patients' overall health and utility. Furthermore, the impact of AM on the caregiver's and/or family's QoL is also likely to be significant and heterogeneous between patients, depending on the socioeconomic status and structure of the caregiver/family unit (e.g. sole caregiver; multiple caregivers; presence or absence siblings).

A cohort model, by design, cannot fully account for this heterogeneity and complexity, but was it was chosen due to the paucity of data that would be required to populate a 'patient-level' model. Thus, a pragmatic approach to modelling had to be taken, in which only the key elements of how a 'typical' AM patient cohort progresses are accounted for. As a result of this pragmatic approach to modelling, it should be noted that numerous aspects of AM are incompletely captured in the model structure including:

- The true heterogeneity and complexity of the condition, including all potential combinations of clinical features observed in AM

- Costs and disutility associated with minor infections (infections treated in primary care)
- Costs and disutility associated with psychiatric problems, such as acute psychosis, sleep disorder and anxiety
- Disutility associated with minor surgeries (tonsillectomy/adenoidectomy, grommet surgery, inguinal hernia repair, carpal tunnel release surgery, feeding tube insertion)
- Mortality risk associated with other key causes of death in AM patients including cardiorespiratory failure (due to causes other than severe infection), cardiac arrhythmia and cardiac failure
- Disutility associated with ventilator-dependency (nocturnal and/or 24-hour)
- 'Intra-ambulatory health state' improvements/progression; for example, the model does not formally account for the cost or utility changes that a patient may experience when moving from requiring one aid for walking (e.g. footwear for stability) to requiring multiple aids/assistance for walking
- Utility benefit associated with homecare

12.1.5 *Provide a list of all assumptions in the model and a justification for each assumption.*

A full list of assumptions, justification and sources are provided in Table 50.

Table 50: Model assumptions

Parameter		Assumption	Source(s)
1	**Disease progression**	VA has a long-term treatment effect to delay disease progression in multi-domain responders, compared with BSC:	UK Expert Elicitation Panel (117) (Section 12.2.5) rhLAMAN-10, multi-domain responder analysis (23) (Section 9.6.1.3)
	Paediatric cohort	Over the lifetime of a patient starting VA as a paediatric (aged 6–11 years), VA treatment is assumed to delay disease progression by, on average, 3.48 years compared with BSC. This equates to a 10% delay in disease progression compared with BSC.	
	Adolescent cohort	Over the lifetime of a patient starting VA as an adolescent (aged 12–17 years), VA treatment is assumed to delay disease progression by, on average, 4.00 years compared with BSC. This equates to a 12% delay in disease progression compared with BSC.	
	Adult cohort	Over the lifetime of a patient starting VA as an adult (aged ≥18 years), VA treatment is assumed to delay disease progression by, on average, 2.68 years compared with BSC. This equates to an 8% delay in disease progression compared with BSC.	
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 two years of treatment, but may occur in exceptional cases after three or more years of treatment. VA-treated patients can only improve by one level of functional impairment per year (cycle), for example from WWA to WU:	UK KOL interviews (17) (Section 12.2.5) rhLAMAN-10, CHAQ analysis (Section 9.6.1.2)
	Years 1 and 2	Following the first two 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 three or more 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	

Parameter		Assumption	Source(s)
3	**Ventilation dependency**	Treatment with VA will reduce patients' requirements for ventilation compared with BSC alone, in terms of a delay to ventilation, and more simple ventilation requirements once on ventilation, due to an accrued improvement in lung function. The model assumes VA-treated patients spend half the time in ventilation compared with BSC alone.	UK KOL interviews (17) (Section 12.2.5)
4	**Severe infections**	VA-treated patients have a better capacity to respond to/manage severe infections (e.g. better diaphragmatic function, remain more upright, remain more mobile) compared with BSC-treated patients	UK KOL interviews (17) (Section 12.2.5) rhLAMAN-05, serum IgG analysis (Section 9.6.1.1)
	Rate	VA-treated patients have a 50% reduced rate of severe infections compared with BSC-treated patients	
	Recovery disutility	VA-treated patients have a 50% shorter recovery period after a severe infection compared with BSC-treated patients	
	Mortality	VA-treated patients have a 50% reduced risk of infection-related mortality compared with BSC-treated patients	
5	**Major surgery**	VA-treated patients have a better capacity to respond to/manage major surgery† (e.g. lower risk to anesthesia due to improved upper airways and lung function, better ability to regain mobility and manage infections post-surgery) compared with BSC-treated patients	UK KOL interviews (17) (Section 12.2.5)
	Rate	The rate of major surgeries is assumed to be equivalent in VA-treated patients and BSC-treated patients	
	Recovery disutility	VA-treated patients have a 50% shorter recovery period after a major surgery compared with BSC-treated patients	
	Mortality	VA-treated patients have a 50% reduced risk of major surgery-related mortality compared with BSC-treated patients	
	Complications	VA-treated patients have a 50% reduced risk of post-operative complications leading to a transition to SI compared with BSC-treated patients	

Parameter		Assumption	Source(s)
6	**Discontinuation**	Patients can discontinue VA treatment via three routes:	UK KOL interviews (17) (Section 12.2.5) rhLAMAN-05, multi-domain responder analysis (23) (Section 9.6.1.3)
	Non-response	Discontinuation due to a 'non-response' based on the post hoc, multi-domain response in the first year of treatment (13.3%)	
	Health state	Discontinuation due to patients entering the SI or short end stage health states	
	Annual risk	Discontinuation due to an annual risk of withdrawal (10%) due to reasons including IRRs, non-compliance, patient preferences and/or occurrence of other life-limiting conditions (e.g. cancer). This annual risk of discontinuation also accounts for partial/short-term treatment discontinuation (e.g. due to travel, educational studies, ill-health or changes to family/caregiver circumstances preventing treatment) that may occur	
7	**VA on-treatment utility**	Improved clinical outcomes for VA-treated patients versus BSC-treated patients translates into greater HRQoL. A VA on-treatment utility gain of 0.1 is assumed.	UK KOL interviews (17) (Section 12.2.5) rhLAMAN-10, CHAQ analysis (Section 9.6.1.2)
8	**Caregiver disutility**	Caregivers in each health state would suffer from a significant disutility because of caring for patients with multiple and extensive clinical needs (behavioral, mobility-related, selfcare, activities of daily living etc.)	UK KOL interviews (17) (Section 12.2.5) EDSS caregiver disutility (109)
9	**Treatment monitoring**	Any treatment monitoring for VA-treated patients is included as part of routine BSC appointments with metabolic specialists/paediatricians	UK KOL interviews (17) (Section 12.2.5)
10	**Treatment setting**	VA administration is assumed to first be completed in an LSD specialist centre (three IV [once weekly] infusions) before administration occurs via homecare (98% of patients) or a local hospital setting (2% of patients). This ratio of homecare to local hospital setting was deemed appropriate to also capture the minority of patients that may revert to hospital briefly for the management of IRRs, before returning to homecare once the IRRs are resolved.	UK KOL interviews (17) (Section 12.2.5)

Abbreviations: BSC, best supportive care; CHAQ, Childhood Health Assessment Questionnaire; EDSS, Expanded Disability Status Scale; HRQoL, Health-related Quality of Life; IgG, Immunoglobulin G; IRR, infusion-related reaction; KOL, key opinion leader; MCID, minimal clinically important differences; SI, severe immobility; UK, United Kingdom; VA, velmanase alfa; WC, wheelchair dependent; WWA, walking with assistance; WU, walking unassisted. †Major surgery is defined as those requiring hospital admission (ventriculoperitoneal shunts, cervical spine decompression, joint replacement).

In addition to the key model assumptions outlined above, due to a paucity of AM-specific data for several parameters, the model assumes that data from other LSDs and other clinical populations can be used as 'proxy' due to similarities in the clinical features/symptoms experienced by patients and/or caregivers to those seen in AM. Data from the following are used in the model:

- MPS IVA (Morquio A) (112)
    - Provides estimates of the hours of care-giving stratified by patients' ambulatory status
    - Provide estimates of patients' disutility due to functional impairment stratified by ambulatory status (scenario analysis only)
    - Provides an estimate patients' disutility and recovery period duration after a major surgery (108)
- Multiple sclerosis (MS) (109)
    - Provides estimates of carers' disutility stratified by patients' ambulatory/functional status
- General population sepsis survivors (107)
    - Provides an estimate of patients' disutility and recovery period after a severe infection

12.1.6 *Define what the model's health states are intended to capture.*

Details of the model health states are described previously in Section 12.1.3. To summarise, each health state is intended to capture:

- Patients' disutility as the disease progresses along the functional/ambulation impairment axis
- Carers' disutility as the disease progresses along the functional/ambulation impairment axis
- Clinical events that are key drivers in cost, morbidity and mortality of AM patients:
    - Severe infections
    - Major surgery
    - Minor surgery

12.1.7 *Describe any key features of the model not previously reported. A suggested format is presented below in table D4.*

The cost-utility model is a lifetime state-transition Markov cohort model with an annual time cycle and a discount rate for costs and utilities of 1.5%. The key features of the model not previously reported are summarised in Table 51.

Table 51: Key features of the model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime (100 years)	AM is a progressive, lifelong, life-limiting disease and patients will continue to need management and/or treatment for the whole of their lives.	NICE guide to the methods of technology appraisal 2013 (118)
Discount for utilities and costs	1.5%	NICE recommends that a discount rate of 1.5% can be used for costs and QALYs in treatments where patients would otherwise not survive, patients suffer from severely impaired life conditions or when the condition is sustained for over 30 years. As AM is a progressive, life-long, life-limiting condition, treatment with velmanase alfa may delay long-term disease progression, as well as reduce the risk of key drivers of mortality. Therefore, the base case adopts 1.5%	NICE guide to the methods of technology appraisal 2013 (118)
Perspective (NHS/PSS)	NHS and PSS in England with 2016 price year	NICE reference case	NICE guide to the methods of technology appraisal 2013 (118)
Cycle length	Annual	This is considered a reasonable timeframe over which clinical events and/or disease progression and/or disease improvement may occur	UK KOL interviews (17)

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

12.2 *Clinical parameters and variables*

12.2.1 *Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.*

12.2.1.1 Patient characteristics

The data supporting the baseline age, gender and starting health state distribution of patients in the model were taken from the rhLAMAN clinical development programme (either rhLAMAN-05 or rhLAMAN-10). The baseline age of paediatric, adolescent and adults was assumed to be the lowest age of the sub population (6, 12 and 18, respectively); the model also provides the option of using the average age per paediatric, adolescent and adult age brackets (derived from rhLAMAN-10). The proportion of male patients was 61% across each sub population (from the rhLAMAN-10 study).

As patients with AM are similar in weight to their age-matched peers, weight was taken from the UK WHO growth charts Table 52 (119). Patient weight data were taken from

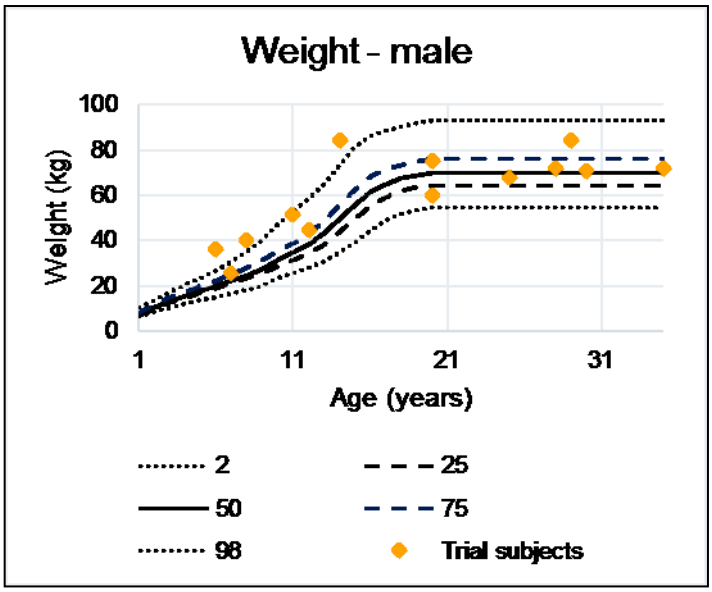
rhLAMAN-05 and placed onto the UK WHO growth chart (see Figure 28 and Figure 29). As the majority of patients fell within the 95% CI, it was considered appropriate to use the UK growth curves as a weight distribution for modelling purposes. The model includes the ability to modify the weight of the cohort, either by a percentage adjustment, or by inserting an alternative growth chart (e.g. for a different country).

Table 52: UK WHO growth chart

	Age (years)												
	6	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**≥18**
Female (kg)	22.4	25.2	28.8	32.2	35.9	40.2	45.1	49.9	53.3	55.5	56.7	57.3	58.0
Male (kg)	22.4	24.9	27.6	31.5	34.7	38.5	43.4	49.7	55.9	61.2	64.8	67.4	68.0

Source: RCPCH growth charts (119)
Abbreviations: WHO, World Health Organization.

Figure 28: Male patient weight data from rhLAMAN-05 placed on the UK WHO growth chart



Key: The numbers 2, 25, 50, 75 and 98 refer to percentiles.

Figure 29: Female patient weight data from rhLAMAN-05 placed on the UK WHO growth chart

Key: The numbers 2, 25, 50, 75 and 98 refer to percentiles.

12.2.1.2 Clinical data

Clinical data in the model were derived from the Phase III rhLAMAN clinical trial (RCT and integrated analysis), UK KOL interviews and a UK Expert Elicitation Panel (UK-EEP) (Section 12.2.5). While ambulatory status was captured as part of the CHAQ questionnaire in the rhLAMAN clinical trials, the data were not solely sufficient to support the economic analysis as, due to the eligibility criteria, no patients were wheelchair-dependent or severely immobile at baseline. In addition, the rate of severe infections and surgeries were not captured throughout the clinical trial programme, and no patient died; therefore, these clinically important aspects (UK KOLs stated that severe infections and major surgery are key drivers of mortality in AM patients) could not be derived from the clinical trial programme. The information provided by the UK KOLs from the UK-EEP and structured interviews was used to develop transition probabilities between the health states. Key clinical events (major surgeries and severe infections) affect both the transition of patients between health states (primary and tunnel) and patient utility.

Clinical trial data

Starting state distribution

The distribution of paediatric, adolescent and adult patients across the four primary health states at baseline was based on rhLAMAN-10 data and is shown in Table 53.

Table 53: Starting health state distribution at baseline (from rhLAMAN-10)

	Walking unassisted, % (n/N)	Walking with assistance, % (n/N)	Wheelchair dependent, % (n/N)†	Severe immobility, % (n/N)
Paediatrics	77.8 (7/9)	22.2 (2/9)	0 (0/9)	0 (0/9)
Adolescents	72.7 (8/11)	27.3 (3/11)	0 (0/11)	0 (0/11)
Adults	61.5 (8/13)	38.5 (5/13)	0 (0/13)	0 (0/13)

Source: rhLAMAN-10.
†Although three patients used a wheelchair in rhLAMAN-10 (according to CHAQ), they were not strictly wheelchair bound (as per the eligibility criteria of the study).

Response at Year 1

Aspects of the treatment continuation rules are applied in the model (Section 10.1.16). For the purposes of the model, all patients are assumed to be eligible. As part of the treatment continuation rules, patients are assessed at Year 1 for response in at least two of the three domains of the multi-domain responder analysis. For the model, the results of the post-hoc, multi-domain responder analysis from rhLAMAN-05 (Section 9.6.1.3) were used to estimate the number of patients who do not achieve a response (13.3%) after one year of treatment with velmanase alfa + BSC; in the model, non-responders at Year 1 discontinue treatment with velmanase alfa and transfer to BSC only.

UK Expert elicitation panel

An elicitation panel (117) with expert clinicians was convened to obtain estimates for unknown quantities of interest (QoI), which are key to the cost-utility assessment of velmanase alfa:

- QoI 1: Disease progression under BSC alone (formally elicited)
- QoI 2: Disease progression under velmanase alfa + BSC (formally elicited)
- QoI 3: Disease improvement under velmanase alfa + BSC (formally elicited)
- QoI 4: Data on severe infections and major surgery by ambulatory status (captured via the experts completing a pre-meeting questionnaire, before the pooled responses were presented and discussed qualitatively during the elicitation panel)

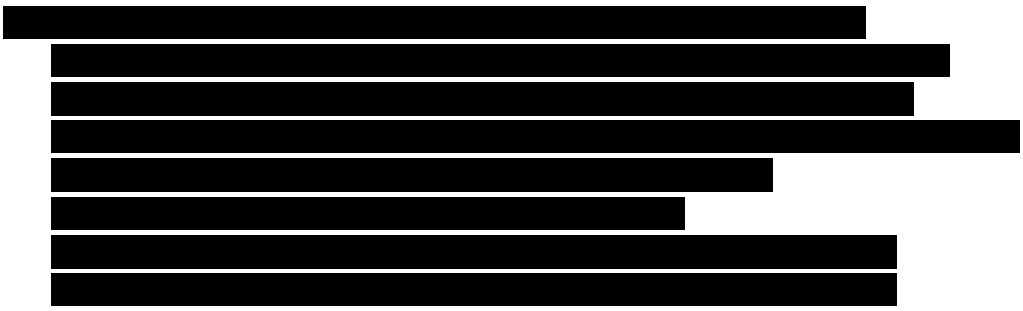
Details of the methods used in the UK-EEP are described in Section 12.2.5.1.

QoI 1 and 2

The elicited values for QoI 1–2 are presented in Table 54 and Table 55.

The rate of disease progression for patients with AM under BSC alone was initially elicited for three age groups, i.e. for patients initiating specialist care/diagnosis either as a paediatric (6–11 years); adolescent (12–17 years) or an adult (≥18 years). Whilst the experts were able to describe three different ‘phenotypes’ of patients that had different rates of disease progression based on their age at initiation of specialist care/diagnosis, several observations were made:

- Experts would expect that the majority of patients with AM to present to specialist care (i.e. be formally diagnosed) as paediatric patients



- Experts were able to describe an 'attenuated' adult phenotype that may present to specialist care in the 3rd to 5th decade of life. However, the experts believed this phenotype falls outside a 'classical' AM phenotype and is predominantly a phenotype driven by neurological aberration. Experts also stated this 'attenuated' form is rare and that ERT will have no treatment benefit on patients' ambulatory status within this phenotype. The experts also commented that they had little experience in treating this type of patient
- Mis- and/or underdiagnoses is common for ultra-rare diseases; therefore, it is plausible that two patients may present with similar symptoms at the same age, but the age of specialist care intervention and formal diagnosis may vary due to several factors, such as geographical location, family history and/or socioeconomic factors

To reflect the above observations, it was confirmed via UK KOL interviews (Section 12.2.5.2) that it is clinically appropriate to use one rate of disease progression for those receiving BSC. This rate of disease progression is based on the elicited values for patients starting BSC/diagnosed as paediatrics, and is shown in Table 54. This approach to modelling assumes that:

- Patients who start specialist care/diagnosed as adolescents or adults are likely to have been mis/underdiagnosed, rather than having a different phenotype or rate of disease progression compared with patients diagnosed as paediatrics (aged 6 years and above)
- The 'attenuated' adult phenotype patient population (which predominantly only exhibit neurological aberrations) is excluded from the model cohort

To account for the potential heterogeneity in a patient's response to velmanase alfa based on their age at treatment initiation, the treatment effect was elicited for patients starting velmanase alfa as a paediatric (6–11 years) and adolescent (12–17 years) (Table 55). The values elicited were the additional years that a patient on velmanase alfa would expect to remain in each health state compared with BSC alone. Only the effect of velmanase alfa in the 'attenuated' adult phenotype was discussed at the panel. During the panel, the experts stated that ERT would not delay disease progression in this 'attenuated' phenotype that presents to specialist care later in life.

Overall, adults were shown to benefit from velmanase alfa in the clinical trial programme (Section 7.2.1 and 9.6). Therefore, to determine the treatment effect of velmanase alfa in patients initiating treatment as adults (who have the 'classical' form

of the disease, i.e. likely to have been diagnosed as a paediatric/adolescent), the relative treatment effect of velmanase alfa in adults (≥18 years) vs paediatrics/adolescents (6–17 years) was taken from the post-hoc, multi-domain responder analysis from rhLAMAN-10 (Section 9.6.1.3) and applied to the elicited treatment effect provided for paediatrics and adolescents. In the post-hoc, multi-domain responder analysis, 100% paediatrics/adolescents (6–17 years) demonstrated a response to velmanase alfa at last observation, compared with 71.4% of adult patients. Therefore, the treatment effect of velmanase alfa in adults was assumed to be 71.4% of the elicited values for paediatrics and adolescents.

Table 54: Disease progression under BSC (QoI 1) – years in health state

Age group	WU			WWA			WC			SI		
	Median	CI		Median	CI		Median	CI		Median	CI	
		2.5%	97.5%		2.5%	97.5%		2.5%	97.5%		2.5%	97.5%
All age groups	11.44	1.70	23.23	10.20	2.60	17.69	9.97	2.54	17.42	3.02	1.06	7.43

Abbreviations: BSC, best supportive care; CI, confidence interval; SI, severe immobility; WC, wheelchair dependent; WU, walking unassisted; WWA, walking with assistance.

Table 55: Disease progression under velmanase alfa + BSC (QoI 2) – additional years in health state vs BSC

Age group	WU			WWA			WC			SI		
	Median	CI		Median	CI		Median	CI		Median	CI	
		2.5%	97.5%		2.5%	97.5%		2.5%	97.5%		2.5%	97.5%
Paediatrics	+1.54	-0.31	+3.64	+1.35	+0.23	+2.59	+0.58	+0.09	+1.68	0.00	0.00	0.00
Adolescents	+2.06	+0.23	+2.59	+1.35	+0.23	+2.59	+0.58	+0.09	+1.68	0.00	0.00	0.00
Adults (elicited)†	+0.00	+0.00	+0.00	+0.00	+0.00	+0.00	+0.00	+0.00	+0.00	0.00	0.00	0.00
Adults (trial-based)‡	+1.30	+0.01	+2.81	+0.96	+0.16	+1.85	+0.42	+0.07	+1.20	0.00	0.00	0.00

Abbreviations: BSC, best supportive care; CI, confidence interval; SI, severe immobility; WC, wheelchair dependent; WU, walking unassisted; WWA, walking with assistance.
†During the panel, the experts stated that VA would not delay disease progression if initiated in patients with an 'attenuated' adult phenotype that presents to specialist care later in life, i.e. for VA, the treatment effect of zero
‡VA treatment effect in adults with a 'classical' form of AM is calculated using a relative risk of response in adults (71.4%) vs paediatrics/adolescents (100%) based on the rhLAMAN10 post-hoc, multi-domain responder analysis. The treatment effect in adults was calculated to be 71.4% of the combined elicited values for paediatrics and adolescents.

QoI 3

Disease improvement under velmanase alfa + BSC (QoI 3) was discussed at the UK-EEP. The experts were presented with data from rhLAMAN-10, which demonstrated that of the 10 patients who were using ambulatory aids at baseline, seven (70%) became independent of assistance at last observation. As rhLAMAN-10 was not placebo controlled, the experts stated it was unclear whether the improvement was solely due to the impact of velmanase alfa and that it is unlikely that velmanase alfa achieved this level (70%) of disease reversibility over and above BSC.

The plausibility of reverse transitions was further explored in the UK KOL interviews (Section 12.2.5.2). Taking into consideration the results from rhLAMAN-10 and the comments from the experts in the UK-EEP, conservative values for reverse transitions were tested. For both the 'walking with assistance' and 'wheelchair dependent' health states, the annual probability of a reverse transition (to the previous health state) was 20% in Year 1 and Year 2. From Year 3 onwards the annual probability of experiencing and reverse transition in these health states was 2.5%. The UK KOLs agreed that these probabilities were clinically plausible and valid (17). In addition, the UK KOLs agreed that (in exceptional cases) more than 2 years of treatment may be required before an improvement in ambulatory health state is observed in patients that (17):

- have severely impaired respiratory function at baseline, as this aberration takes the longest time to change
- are recovering from major surgery, which prevents the patient from reversing
- are wheelchair-dependent, as an improvement to multiple aberrations (e.g. lung function, muscle strength, joint strength) would be required to allow the patient to transition to only using walking aids/assistive means again

QoI 4

The rates of severe infection, risk of death from a severe infection and the probability of a major surgery by health state were captured via the experts completing a pre-meeting questionnaire. The pooled responses were then presented and discussed qualitatively during the UK-EEP. Note that the possibility that velmanase alfa may reduce the risk of these outcomes was interrogated in the UK KOL interviews (17).

The experts first provided the rates of severe infections by health state as years until one severe infection event. These values were subsequently converted to an annual probability (Table 56).

Table 56: Rates of severe infections by health state

	WU	WWA	WC	SI
Years until one severe infection event				
Mean	4.60	4.20	1.47	1.00
Minimum	2.00	2.00	1.00	0.66
Maximum	7.00	6.00	2.00	1.33
Calculated annual probability				
Mean	19.54%	21.19%	49.45%	63.29%
Minimum	39.35%	39.35%	63.21%	78.02%
Maximum	13.31%	15.35%	39.35%	52.85%

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

The annual probability of death from a severe infection by health state is shown in Table 57.

Table 57: Annual probability for death from a severe infection by ambulatory status

	WU	WWA	WC	SI
Mean	4.50%	6.25%	12.50%	23.13%
Minimum	0.50%	2.50%	5.00%	10.00%
Maximum	10.00%	15.00%	30.00%	40.00%

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

Initially, the risk of major surgery was provided as an annual probability per health state by the experts. Upon presenting the mean of the group (per health state) to the experts, they agreed that the annually probability in the severe immobility health state was too high (5%). The experts agreed to reduce the annual risk of surgery in the severe immobility health state to 1.5% (Table 58).

Table 58: Annual risk of major surgery by ambulatory status

	WU	WWA	WC	SI
Mean	8.1%	13.8%	10.0%	1.5%
Minimum	5.0%	8.0%	8.0%	1.5%
Maximum	13.0%	20.0%	13.0%	1.5%

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

Together, the data obtained for QoI 1–QoI 4 were used to calculate the transition probabilities in the model. The transition probabilities for the first cycle of the model are shown in Table 59. Note that green cells indicate a reverse transition (disease improvement) and orange cells indicate a tunnel state.

Table 59: Transition probabilities – first model cycle only (base case)

From	To	Annual transition probability (%)					
		Paediatric cohort		Adolescent cohort		Adult cohort	
		BSC	VA	BSC	VA	BSC	VA
Walking unassisted	Walking with assistance	8.4	7.4	8.4	7.1	8.4	7.5
	Severe immobility	0.8	0.4	0.8	0.4	0.8	0.4
	Severe infection	19.5	9.8	19.5	9.8	19.5	9.8
	Death	0.0	0.0	0.0	0.2	0.0	0.2
Walking unassisted + severe infection	Short end stage	4.5	2.3	4.5	2.3	4.5	2.3
Walking with assistance	Walking unassisted	0.0	19.9	0.0	19.9	0.0	19.9
	Wheelchair dependent	9.3	8.3	9.3	8.3	9.3	8.6
	Severe immobility	1.4	0.7	1.4	0.7	1.4	0.7
	Severe infection	21.2	10.6	21.2	10.6	21.2	10.6
	Death	0.7	0.3	0.7	0.3	0.7	0.3
Walking with assistance + severe infection	Short end stage	6.3	3.1	6.3	3.1	6.3	3.1
Wheelchair dependent	Walking with assistance	0.0	19.9	0.0	19.9	0.0	19.9
	Severe immobility	11.5	10.0	11.5	10.0	11.5	10.2
	Severe infection	49.4	24.7	49.4	24.7	49.4	24.7
	Death	1.0	0.5	1.0	0.5	1.0	0.5
Wheelchair dependent + severe infection	Short end stage	12.5	6.3	12.5	6.3	12.5	6.3

From	To	Annual transition probability (%)					
		Paediatric cohort		Adolescent cohort		Adult cohort	
		BSC	VA	BSC	VA	BSC	VA
Severe immobility	Severe infection	63.3	31.6	63.3	31.6	63.3	31.6
	Death	28.4	28.3	28.4	28.3	28.4	28.3
Severe immobility + severe infection	Short end stage	23.1	11.6	23.1	11.6	23.1	11.6
Short end stage	Death	100.0	100.0	100.0	100.0	100.0	100.0

Key: Green cells = disease improvement transition; Orange cells = tunnel state.
Note: to see these values in the model matrices, treatment discontinuation on VA must be deactivated.
Abbreviations: BSC, best-supportive care; VA, velmanase alfa.

UK KOL interviews

Interviews with UK KOLs (17) were performed to:

- Support the early scoping/design stages of developing the model
- To generate and validate key assumptions of the model
- To generate and validate key model parameters for which published data in AM patients do not exist

Details of the methods used in the UK KOLs are described in Section 12.2.5.2.

The clinical variables that were either provided or validated by the UK KOLs are described in Section 12.1.5 and 12.2.6.

12.2.2 *Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?*

The model assumes that patients will continue to accrue the costs and outcomes assigned to each health state that they experience, and that progression through the model is primarily determined by natural disease progression. Due to the relatively short follow-up period of the rhLAMAN study programme (considering AM is a chronic, life-long condition), the extrapolations assumed beyond the trial duration are based on UK expert opinion (derived from UK KOL interviews and the UK-EEP) and other ERTs in related MPS disorders.

12.2.3 *Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?*

As described in Section 9.4.1.4 and 9.6.1.3, a post-hoc, multi-domain responder analysis was completed as part of the assessment of rhLAMAN-05 and rhLAMAN-10 trial data. A patient qualified as a ‘responder’ to treatment if the response criteria were reached in at least two domains. One of these domains – the pharmacodynamic domain: serum oligosaccharide response – is a surrogate marker for disease progression and is likely to be considered as an ‘intermediate’ outcome measure. [redacted]

Prior to this analysis, the MCIDs for the clinical endpoints used in the trials of velmanase alfa had not previously been defined for patients with AM, which is typical of an ultra-orphan condition. A robust approach to defining MCIDs for the included outcomes (de novo for AM) was taken (see Appendix 7, Section 17.7.3.1); however, uncertainty remains in the scientific and clinical community regarding MCID thresholds in AM and the level of response required to define a “responder” given the heterogeneity of the disease and severity across the different measurement

parameters. As described in Section 12.2.5, to address this uncertainty, a UK-EEP was convened to elicit how the clinical trial data for velmanase alfa translates into long-term clinical outcomes for velmanase alfa, with respect to delayed disease progression along the functional/ambulatory impairment axis.

12.2.4 *Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.*

The model also used clinical data from rhLAMAN-10 to determine the annual probability of IRRs (9.1%); however, in the base case analysis, IRRs are assumed not to incur a disutility or treatment cost. This assumption is supported by a recent publication by White et al. (2017), which shows that IRRs in patients with LSDs receiving ERT requires minimal intervention (106).

12.2.5 *Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.*

Given the paucity of published long-term effectiveness data identified by the clinical-effectiveness SR, the need to use expert clinical opinion to support parameterisation of the cost-utility model was deemed appropriate. Chiesi consulted with expert clinicians for purposes of evidence synthesis and evidence validation via three formal methods:

1. UK Expert Elicitation Panel (UK-EEP): following published SHeffield ELicitation Framework (SHELF) methodology
2. UK KOL interviews: via structured teleconference/WebEx interviews
3. Clinical trial KOL interviews: structured teleconference interviews with specialist clinicians/trial investigators of the velmanase alfa trial programme

12.2.5.1 UK Expert Elicitation Panel

Full details of the objectives and methodology of the UK-EEP are provided as a Chiesi Ltd data on file reference (117).

Objectives

An elicitation panel with expert clinicians was convened to obtain estimates for unknown quantities of interest, which are key to the cost-utility assessment of velmanase alfa. Deterministic sensitivity analyses from an early draft version of the cost-utility model indicated that the results were most sensitive to input parameters concerning the rate of long-term disease progression under BSC alone, and under velmanase alfa. Therefore, these parameters were prioritised for assessment via expert elicitation. In addition to seeking data for long-term disease progression, the UK-EEP was also convened to synthesise and validate parameters concerning important clinical events relevant to the morbidity and mortality of patients with AM, namely severe infections and major surgical interventions.

Criteria for selecting experts

An expert was defined as a healthcare professional with specialist clinical experience of managing patient(s) with AM. In the UK, the coordination of care for a patient with AM is typically completed by consultant metabolic specialists/consultant paediatricians based in one of the UK LSD specialist centres. Therefore, it was expected that the experts would work at one of the UK LSD specialist centres.

For the purposes of answering elicitation panel questions for all three age groups for which velmanase alfa may be initiated (paediatric, adolescent and adult), the expert should also ideally have direct clinical experience of treating AM in paediatric, adolescent and adult patients. However, it should be noted that metabolic specialists in the UK typically have either a paediatric or adult speciality. Finally, as velmanase alfa is not currently licensed for use in the UK, it was not a formal requirement for the experts to have practical experience of using velmanase alfa for the treatment of AM; however, experience of using ERT in any other LSD was required. Hence, to be included as part of the UK-EEP, experts must have:

- Direct specialist clinical experience in treating AM with BSC in the UK:
    - Including current management of one or more patients with AM in the UK
- Direct specialist clinical experience in treating AM and/or other LSDs with ERT in the UK

Experts

The final number of experts recruited for the UK-EEP represents the greatest number that could attend a meeting on the same date in the context of the limited number of healthcare professionals with specialist clinical experience of AM.

The healthcare professionals known to Chiesi to have specialist clinical experience of AM in the UK were contacted and were asked for their availability to attend a one-day meeting. Of the ten experts contacted, the greatest number of experts that could attend a meeting on the same date was five, representing four LSD specialist centres in the UK. The clinical experience of the five experts are described in Table 60.

Table 60: Clinical experience of the UK Expert Elicitation Panel

Patient group	Direct specialist clinical experience (Yes/No)				
	Ex1	Ex2	Ex3	Ex4	Ex5
Paediatric (6–11 years) patients with AM	Yes	No	No	Yes	Yes
Adolescent (12–17 years) patients with AM	Yes	Yes	Yes	Yes	Yes
Adult (≥18 years) patients with AM	No	Yes	Yes	Yes	No
Treatment of AM using BSC	Yes	Yes	Yes	Yes	Yes
Treatment of AM using ERT	Yes	No	No	No	No
Treatment of LSD using ERT	Yes	Yes	Yes	Yes	Yes

Abbreviations: AM, alpha-mannosidosis; BSC, best supportive care; Ex, expert; LSDs, lysosomal storage disorders; ERT, enzyme replacement therapy; VA, velmanase alfa.

The experts involved were:

[redacted]

Remuneration and conflict of interest

All experts had to declare any conflicts of interest prior to participation. Only one expert declared a conflict of interest in relation to previous honoraria received for attendance at lectures and advisory boards from the pharmaceutical industry. Each expert received honoraria (funded by Chiesi) to cover the time required to prepare for the elicitation exercise (pre-reading of the evidence dossier) and attendance at a one-day elicitation panel.

Methods

The UK-EEP followed SHELF methodology, which is a published and recognised methodology for elicitation (120). Formal elicitation requires using a group of experts in order to capture their combined knowledge. SHELF elicits a single distribution from the group but begins by eliciting judgements from each expert independently. This step is followed by the experts discussing their differences, to share their expertise, opinions and interpretations of the evidence. Then group judgements are elicited and the result of the elicitation is a “consensus” or combined distribution fitted to these judgements.

Preparation, piloting and training

An evidence dossier was collated, describing the concepts of expert elicitation, a statement of what would be asked of the experts and a detailed summary of direct/indirect evidence of relevance to the unknown quantities of interest (QoI). Experts were asked to read the dossier carefully and return a consent form confirming their participation, declaring that they had read the information in full. The experts were also asked to provide feedback on the dossier. The feedback received (such as additional studies to include in the direct/indirect evidence) from the experts was then incorporated into the final dossier used to support the elicitation panel.

Internal piloting of the elicitation process was conducted among the research team (facilitator, analyst, recorder and project manager) at a pre-meeting session to finalise the protocol.

Experts were provided with training materials as a part of the evidence dossier. A training exercise was also conducted in order to familiarise the experts with the process of elicitation. The training exercise was devised to simulate an elicitation using the 'Roulette method.

Questions

The unknown QoI on which the elicitation exercise was based spanned four topics:

1. QoI 1: Disease progression under BSC alone
2. QoI 2: Disease progression under velmanase alfa + BSC
3. QoI 3: Disease improvement under velmanase alfa + BSC
4. QoI 4: Rates of severe infection/surgery by ambulatory status
    a. Answers to QoI 4 were captured via the experts completing a pre-meeting questionnaire, before the pooled responses were presented and discussed qualitatively during the elicitation panel

Examples questions related to disease progression include:

- For paediatrics aged 6–11 years (at the time of treatment initiation/under specialist care) under BSC alone, how many years does a typical AM patient spend in a 'walking unassisted' health state before progressing to a 'walking with assistance' health state (Transition A in model schematic)?
- For paediatrics aged 6–11 years (at the time of treatment initiation/under specialist care) under velmanase alfa + BSC, how many years does a typical AM patient spend in a 'walking unassisted' health state before progressing to a 'walking with assistance' health state (Transition A in model schematic)?

Example of questions related to severe infection/surgery include:

- Please estimate the rate of severe infections a patient with AM under BSC is likely to experience over an appropriate time horizon, based on their ambulatory status (e.g. 6 infections per year)?

- Please estimate the risk of mortality (e.g. 20% risk of death) an AM patient experiences when they incur a severe infection, based on their ambulatory status?
- Please estimate the annual risk (%) of an AM patient requiring a major surgery (e.g. joint replacement [knee and hip], ventriculoperitoneal shunt, spinal surgery [cervical decompression, cervical fusion), based on their ambulatory status?

Questions were asked to elicit estimates of the time spent in the four primary health states (labelled A–D in the model schematic; Figure 27) under BSC, and under velmanase alfa + BSC for all three age groups. The list of questions presented at the elicitation panel related to QoI 1–4 are provided as a data on file reference (117).

Data collection and administration of the panel

The elicitation was organised as a face-to-face workshop, held in London on 11th October 2017. The elicitation facilitation group comprised four members (facilitator, analyst, recorder and project manager) of organisations that were external to Chiesi ([redacted]). A medical representative from Chiesi was present in an observational capacity only, but was required to leave the elicitation exercise when experts were responding to unknown QoIs related to the treatment effect of velmanase alfa.

Each unknown quantity of interest for which 'full elicitation' was completed, the SHELF roulette method was adopted. Experts were first asked to quantify their individual lower and upper bounds. The group extremes were then identified and the resulting interval divided into 10–12 equally sized bins. The experts then allocated 20 counters ('probs') across the bins according to the strength of their belief for each value. The total number of probs in each bin was then calculated and entered into the MATCH software tool (a web implementation of SHELF) (120, 121). A best-fit distribution based on these aggregated probs was then generated and used as a basis for discussion. Modifications were made to the distribution until the experts were satisfied that the final distribution was a plausible representation of their uncertainty. For the unknown QoI related to the treatment effect of velmanase alfa, the experts first completed 'full elicitation' for the first transition (transition A in the model schematic), with the same relative effects suggested as a starting point for the remaining transitions. If experts agreed the same relative treatment effect could be applied to the next transition, calculations were completed. If there was not agreement, then full elicitation of the remaining transition(s) was conducted.

Data aggregation

Data were first aggregated via opinion pooling (simply summing up the total number of probs in each bin and fitting a parametric distribution), then adapted using behavioural means. Quantiles of the resulting distribution were discussed and the distribution was modified to ensure they adequately represented the experts' beliefs.

The uncertainty in the experts' beliefs was captured within the elicitation exercise, thus providing median, confidence intervals and associated distributions on which to parameterise the model's deterministic and probabilistic sensitivity analysis.

For data gathered in response QoI 4 (severe infections/surgery rates) the average (mean) and range (minimum and maximum) of the pooled responses from the expert's responses to a pre-meeting questionnaire were presented and discussed qualitatively during the elicitation panel. Pooled data were discussed and adapted using behavioural means, before a group consensus was obtained. The average (mean) and range of responses provided is explored in the model's deterministic and probabilistic sensitivity analysis.

12.2.5.2 UK KOL interviews

Objectives

Three stages of UK KOL teleconference/Webex interview (17) were conducted to:

- Support the early scoping/design stages of developing the model
- To generate and validate key assumptions of the model
- To generate and validate key model parameters for which published data in AM patients do not exist

Criteria for selecting experts

The same criteria for selecting experts was used, as described in the UK-EEP (Section 12.2.5.1).

Experts

The healthcare professionals known to Chiesi to have specialist clinical experience of AM in the UK were contacted and were asked for their availability to complete a series of interview. Of the six KOLs contacted, five KOLs were able to take part in one or more teleconference/Webex interview; one KOL declined on grounds of a conflict of interest. Not all five KOLs participated in all three stages of interview. The clinical experience of the five KOLs and attendance at interview stage are described in Table 61.

Table 61: Clinical experience of the UK KOL interview participants

Patient group	Direct specialist clinical experience (Yes/No)				
	KOL1	KOL2	KOL3	KOL4	KOL5
Paediatric (6–11 years) patients with AM	Yes	No	Yes	No	No
Adolescent (12–17 years) patients with AM	Yes	No	Yes	No	Yes
Adult (≥18 years) patients with AM	Yes	Yes	Yes	Yes	Yes
Treatment of AM using BSC	Yes	Yes	Yes	Yes	Yes
Treatment of AM using ERT	No	No	No	Yes	No
Treatment of LSD using ERT	Yes	Yes	Yes	Yes	Yes
Completion of each interview stage (Yes/No)					
Stage 1	Yes	Yes	Yes	No	No
Stage 2	Yes	Yes	Yes	No	No
Stage 3	Yes	No	Yes	Yes	Yes

Abbreviations: AM, alpha-mannosidosis; BSC, best supportive care; KOL, key opinion leader; LSDs, lysosomal storage disorders; ERT, enzyme replacement therapy; VA, velmanase alfa.

[redacted]

Remuneration and conflict of interest

All KOLs had to declare any conflicts of interest prior to participation. Only one KOL declared a conflict of interest in relation to previous honoraria received for attendance at lectures and advisory boards from the pharmaceutical industry. Each KOL received honoraria (funded by Chiesi) to cover the time required to prepare for the interviews (pre-reading of the interview brief and questions) and time to attend at each interview (each interview lasted between 2–2.5 hours in duration).

Methods

Before each interview pre-reading materials (the list of interview questions and context information [for example, a description of the model structure]) was circulated to each KOL. KOLs were asked to read the pre-reading materials and come prepared to the interview with their answers. During the interview, questions and related context information was displayed to KOLs via teleconference/WebEx link. After completion of the interview, a copy of the minutes/written responses recorded were sent back to each KOL. Each KOL had to confirm in writing that the minutes/summary was an accurate reflection of the discussions and of their responses provided during the interview. Any discrepancies highlighted by the KOLs were incorporated into the final interview minutes/written responses.

In stage 1 and 2 interviews, questions were asked by two researchers of an organisation external to Chiesi ([redacted]). In stage 3 interviews, questions were asked by one researcher of an organisation external to Chiesi ([redacted]) and one medical representative of Chiesi.

Questions

A total of 18, 29 and 36 questions were asked at the stage 1, stage 2 and stage 3 interviews, respectively. Full details of all questions asked are provided in a data on file reference (17).

The main objective and keys questions for each interview stage were as follows:

Stage 1

- Objective: To support the early scoping/design stages of developing the model.
- Key question topics included:
    - Clinical features and complications of AM
    - Natural disease progression
    - Drivers of mortality and morbidity in AM
    - Definition of BSC

Stage 2

- Objective: To generate and validate key assumptions and model parameters
- Key question topics included:
    - Clinical features and complications of AM
    - Structural model assumptions
    - Surgical procedures and associated outcomes
    - Severe infections and associated outcomes
    - Natural disease progression
    - Resource utilisation
    - Patient and carer disutility

Stage 3

- Objective: To validate assumptions and parameters used in the final model
- Key question topics included:
    - Pathway of care
    - Impact of AM on patients and carers:
        - Qualitative testimonials
        - Feedback on quantitative utility estimates
    - Validation of key model assumptions
        - Surgery rates; severe infection rates; utilities; velmanase alfa treatment effect; discontinuation rates

Data aggregation

For key model assumptions, each statement or claim had to be confirmed as being clinically plausible/valid by the majority of KOLs at each interview stage to be included as a model parameter or structural element. For questions where numerical answers were provided by the experts (for example, number of hospital visits expected per year), simple pooling and descriptive statistics were applied to source average (mean) and ranges for each data input to parameterise the model.

12.2.5.3 Clinical trial KOL interviews

Objectives

[redacted]

Criteria for selecting experts

[redacted]

Experts

[redacted]

Table 62: Background information of clinicians

Country	Background information
Denmark	• Medical specialist/ head of department • Presented velmanase alfa clinical trial data at a congress
Belgium	• Head of Paediatric Neurology • Has only been involved with velmanase alfa when used as compassionate use
France	• Head of Centre of Inherited Metabolic Diseases • Involved in preparatory discussions with Zymenex and in phase 1 studies in Denmark
The Netherlands	• Was a velmanase alfa study investigator and was involved in the follow-up study
Spain	• Co-ordinator of the Unit of Inborn Errors of a tertiary hospital and a professor of Paediatrics at a University • Researcher-collaborator in the velmanase alfa trials from phase II
Germany	• Consultant, has been working in the area of inborn disorders of metabolic deficiency for about 25 years • Was involved in the clinical trial and the natural history trial
UK	• Consultant in paediatric inherited metabolic disease • Clinical lead for lysosomal storage disorders

Remuneration and conflict of interest

[redacted]

Methods

[redacted]

Data aggregation

[redacted]

12.2.6 ***Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.***

Details on the variables used in the analysis and the values selected are shown in Table 63. Please note that costs and resource use variables are provided in Section 12.3.6.

Table 63: Summary of variables applied in the cost-effectiveness model

Variable	Value	Range or 95% CI (distribution)	Source	Section
Setting				
Discount rate, costs and QALYs	1.5%	0.0, 3.5%	NICE guide to the methods of technology appraisal (118)	12.1.7
Age when transition to adult NHS service	17	n/a	UK KOL interviews (17)	12.2.5
Clinical				
Starting state distribution				
Paediatric cohort: WU; WWA; WC; SI, %	78%; 22%; 0%; 0%	n/a	rhLAMAN-10, baseline characteristics (23)	12.2.1
Adolescent cohort: WU; WWA; WC; SI, %	73%; 27%; 0%; 0%	n/a		
Adult cohort: WU; WWA; WC; SI, %	62%; 38%; 0%; 0%	n/a		
Disease progression				
BSC, years in state				
WU to WWA	11.44	1.70, 23.23	UK Expert Elicitation Panel (117)	12.2.5
WWA to WC	10.20	2.60, 17.69		
WC to SI	9.97	2.54, 17.42		
SI to death	3.02	1.06, 7.43		
VA – Paediatric cohort, additional years in state vs BSC				
WU to WWA	1.54	-0.31, 3.64	UK Expert Elicitation Panel (117)	12.2.5
WWA to WC	1.35	0.23, 2.59		
WC to SI	0.58	0.09, 1.68		

Variable	Value	Range or 95% CI (distribution)	Source	Section
SI to death	0.00	0.00, 0.00		
VA – Adolescent cohort, additional years in state vs BSC				
WU to WWA	2.06	0.23, 2.59	UK Expert Elicitation Panel (117)	12.2.5
WWA to WC	1.35	0.23, 2.59		
WC to SI	0.58	0.09, 1.68		
SI to death	0.00	0.00, 0.00		
VA – Adult cohort, additional years in state vs BSC				
WU to WWA	1.30	0.01, 2.81	UK Expert Elicitation Panel (117) rhLAMAN-10 responder analysis (23)	9.6.1.3 and 12.2.5
WWA to WC	0.96	0.16, 1.85		
WC to SI	0.42	0.07, 1.20		
SI to death	0.00	0.00, 0.00		
Disease improvement on VA				
Year 1 – WC to WWA	20.0%	0.0%, 70.0%	UK KOL interviews (17) Upper range from rhLAMAN-10, CHAQ analysis (1)	9.6.1.2, 9.6.1.3 and 12.2.5
Year 2 – WC to WWA	20.0%	0.0%, 70.0%		
Year 1 – WWA to WU	20.0%	0.0%, 70.0%		
Year 2 – WWA to WU	20.0%	0.0%, 70.0%		
Year 3+ – WC to WWA	2.5%	0.0%, 5.0%	UK KOL interviews (17)	12.2.5
Year 3+ – WWA to WU	2.5%	0.0%, 5.0%		
Discontinuation from VA				
Time-period assessed (years)	1	N/A	rhLAMAN-05 responder analysis (23)	9.6.1.3

Variable	Value	Range or 95% CI (distribution)	Source	Section
Probability of a 'non-response' from post hoc, multi-domain responder analysis	13.33%	N/A	rhLAMAN-05 responder analysis (23)	9.6.1.3
Annual risk of withdrawal	10%	N/A	UK KOL interviews (17)	12.2.5
Minor surgery				
Probability in WU state	100%	N/A	UK KOL interviews (17)	12.2.5
Probability in WWA state	50%	N/A		
Probability in WC state	50%	N/A		
Probability in SI state	0%	N/A		
Adverse events				
IRR rate	9.1%	N/A	rhLAMAN-10 (1)	9.7.2.2
Population				
Proportion male	60.6%	N/A	rhLAMAN-10 (1)	9.4.3.3
Severe infection				
Annual probability – WU	19.54%	13.31%, 39.35%	UK Expert Elicitation Panel (117)	12.2.5
Annual probability – WWA	21.19%	15.35%, 39.35%		
Annual probability – WC	49.45%	39.35%, 63.21%		
Annual probability – SI	63.29%	52.85%, 78.02%		
Infection-related mortality – WU	4.50%	0.50%, 10.00%		
Infection-related mortality – WWA	6.25%	2.50%, 15.00%		
Infection-related mortality – WC	12.50%	5.00%, 30.00%		
Infection-related mortality – SI	23.13%	10.00%, 40.00%		

Variable	Value	Range or 95% CI (distribution)	Source	Section
Reduction in rates of severe infections when on VA	50%	N/A	UK KOL interviews (17)	12.2.5
Reduction to infection-related mortality risk when on VA	50%	N/A		
Time in short end-stage state, weeks	4	N/A		
ICU LoS paediatrics, days	6.25	N/A	Paul et al, 2012 (122)	N/A
ICU LoS adult, days	7.80	N/A	Levy et al, 2012 (123)	
General care LoS paediatrics, days	2.98	N/A	Paul et al, 2012 (122)	
General care LoS adult, days	15.00	N/A	Levy et al, 2012 (123)	
Major surgery				
Annual probability – WU	8.10%	5.0%, 13.0%	UK Expert Elicitation Panel (117)	12.2.5
Annual probability – WWA	13.80%	8.0%, 20.0%		
Annual probability – WC	10.00%	8.0%, 13.0%		
Annual probability – SI	1.50%	1.5%, 1.5%		
Surgery-related mortality risk – WU	5.00%	N/A	UK KOL interviews (17)	12.2.5
Surgery-related mortality risk – WWA	5.00%	N/A		
Surgery-related mortality risk – WC	10.00%	N/A		
Surgery-related mortality risk – SI	10.00%	N/A		
Surgery-related complication risk – WU	10.00%	N/A		
Surgery-related complication risk – WWA	10.00%	N/A		
Surgery-related complication risk – WC	20.00%	N/A		

Variable	Value	Range or 95% CI (distribution)	Source	Section
Surgery-related complication risk – SI	20.00%	N/A		
Reduction in risk of surgery-related mortality when on VA	50%	N/A		
Reduction in risk of surgery-related complications when on VA	50%	N/A		
Utility				
Severe infection – number of weeks of disutility	26	N/A	Drabinski et al, 2001 (107)	10.1.9
Severe infection disutility	0.18	N/A	Drabinski et al, 2001 (107)	
Reduction in severe infection disutility period on VA (reflecting a shorter recovery period when treated with VA)	50.00%	N/A	UK KOL interviews (17)	12.2.5
Major surgery – number of weeks of disutility	26	N/A	Elosulfase alfa [ID744] HST, company submission, Table D14, p178 (108)	10.1.9
Major surgery disutility	0.25	N/A	Elosulfase alfa [ID744] HST, company submission, Table D14, p178 (108)	
Reduction in major surgery disutility period on VA (reflecting a shorter recovery period when treated with VA)	50.00%	N/A	UK KOL interviews (17)	12.2.5
VA on-treatment increment	0.1	N/A	Assumption, UK KOL interviews (17)	12.2.5
Health state patient disutility – WU	[redacted]	N/A	KOL (unpublished) AM patient audit (17)	10.1.9
Health state disutility – WWA	[redacted]	N/A	KOL (unpublished) AM patient audit (17)	
Health state disutility – WC	[redacted]	N/A	KOL (unpublished) AM patient audit (17)	
Health state disutility – SI	[redacted]	N/A	KOL (unpublished) AM patient audit (17)	

Variable	Value	Range or 95% CI (distribution)	Source	Section
Health state caregiver disutility – WU	0.01	N/A	UK KOL interviews (17) EDSS caregiver disutility (109)	12.2.5
Health state caregiver disutility – WWA	0.02	N/A		
Health state caregiver disutility – WC	0.05	N/A		
Health state caregiver disutility – SI and short end stage	0.14	N/A		

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

12.3 *Resource identification, measurement and valuation*

NHS costs

12.3.1 *Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.*

The cost-utility model uses UK KOL expert opinion to inform the clinical management, pathway and resources used to care for patients with AM. A full list of NHS reference costs used within the model are provide in Table 67. The clinical management information provided by KOLs is in line with the adult and children lysosomal storage and metabolic disorders NHS service specifications (40).

Resource identification, measurement and valuation studies

12.3.2 *Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.*

As described in Section 11.1, a systematic literature review was undertaken to identify cost and resources use associated with AM. After reviewing full-texts, no eligible studies reporting on cost/resource use were identified. As a result, resource identification and measurement is informed by expert clinical opinion sourced via UK KOL interviews (Section 12.3.3).

12.3.3 *Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.*

As described in Section 12.2.5.2, structured interviews were conducted with UK KOLs to determine key resource utilisation parameters, such as number of visits to the MDT and the likely administration costs associated with velmanase alfa.

Technology and comparators' costs

12.3.4 *Provide the list price for the technology.*

The list price for velmanase alfa is £886.61 (excluding VAT) per 10 mg vial. When reconstituted, 1 mL of the solution contains 2 mg of velmanase alfa (10 mg/5 ml)

12.3.5 *If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.*

The list price is used in the cost-effectiveness model. A confidential discounted price offered through a patient access scheme is offered in a PAS template appendix.

12.3.6 *Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.*

Please consider all significant costs associated with treatment that may be of interest to commissioners.

The costs associated with velmanase alfa are shown in Table 64. The cost of monitoring is assumed to be covered by BSC.

Table 64: Costs per treatment/patient associated with the technology in the cost-effectiveness model

Items	Value	Source
Price of the technology per treatment	£886.61 (excluding VAT) per 10 mg vial. The recommended dose is 1 mg/kg.	Chiesi Limited
Administration cost in hospital, per infusion (once weekly)	£213	NHS National prices and national tariff 2015-16. Vascular access except for renal replacement therapy without CC. Outpatient procedure tariff (124)
Number of (once weekly) infusions at LSD centre before transfer to home infusion or local hospital setting	3	UK KOL Interviews (17)
Proportion of patients receiving home infusion	98%	
Proportion of patients receiving local hospital infusion	2%	

Abbreviations: KOL, key opinion leader; LSD, lysosomal storage disorder; NHS, National Health Service.

The comparator considered in the model is BSC alone. The cost of BSC considers healthcare consultations with the MDT responsible for managing AM patients, severe infections, minor surgery and major surgery and a summary of the total cost of BSC is presented in Table 65 by health state. Note that the 'short end stage' cost is calculated as 4 weeks in an intensive care unit.

Table 65: A summary of the total cost of BSC by health state

Patient type	WU	WWA	WC	SI	WU + SInf	WWA + SInf	WC + SInf	SI + SInf	SES
Paediatric	£4,386	£4,080	£3,731	£2,156	£13,031	£12,948	£13,020	£13,244	£46,782
Adult	£4,361	£4,069	£3,720	£2,145	£16,038	£15,968	£16,040	£16,264	£36,603

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

The type and frequency of consultations as part of BSC is shown in Table 66. A full breakdown of the unit costs of healthcare resources and surgeries is shown in Table 67. The cost associated with minor and major surgeries is calculated as a weighted average assuming equal split between procedure types.

Table 66: Type and frequency of consultations as part of BSC

Resource	Paediatric visits (annual)				Adult visits (annual)			
	WU	WWA	WC	SI	WU	WWA	WC	SI
Metabolic medicine	2	2	2	3	2	2	2	3
ENT specialist	2	1	1	1	2	1	1	1
Orthopaedic	1	1	1	0	1	1	1	0
Ophthalmologist	1	1	1	0	1	1	1	0
GP	6	4	6	8	6	4	6	8
Physiotherapy	1	3	3	3	1	3	3	3

Source: Data on file: UK key opinion leader interviews (17).
Abbreviations: ENT, ear, nose and throat; GP, general practitioner; SI, severe immobility; WC, wheelchair dependent; WWA, walking with assistance; WU, walking unassisted

Table 67: Unit costs of healthcare resources and surgeries

Resource	Cost	Source
Metabolic medicine		
Paediatric – first visit	£634.32	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Metabolic medicine – paed – first visit – cost (124)
Adult – first visit	£634.32	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Metabolic medicine - adult - first visit – cost (124)
Paediatric – follow-up	£397.89	NHS reference costs 2015-16 Consultant led non-admitted F2F attendance, Metabolic medicine - paed - follow-up – cost (124)
Adult – follow-up	£397.89	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Metabolic medicine - adult - follow-up – cost (124)
ENT specialist		
Paediatric – first visit	£122.78	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, ENT specialist – paed – first visit – cost (124)
Adult – first visit	£111.78	NHS reference costs 2015-16 Consultant led non-admitted F2F attendance, ENT specialist – adult – first visit – cost (124)
Paediatric – follow-up	£102.65	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, ENT specialist – paed – follow-up – cost (124)
Adult – follow-up	£89.14	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, ENT specialist – adult – follow-up – cost (124)
Orthopaedic		
Paediatric – first visit	£135.74	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Orthopaedic – paed – first visit – cost (124)
Adult – first visit	£135.74	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Orthopaedic – adult – first visit – cost (124)

Resource	Cost	Source
Paediatric – follow-up	£120.63	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Orthopaedic – paed – follow-up – cost (124)
Adult – follow–up	£109.51	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Orthopaedic – adult – follow-up – cost (124)
Ophthalmologist		
Paediatric – first visit	£110.48	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Ophthalmologist – paed – first visit – cost (124)
Adult – first visit	£110.48	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Ophthalmologist – adult – first visit – cost (124)
Paediatric – follow-up	£86.92	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Ophthalmologist – paed – follow-up – cost (124)
Adult – follow-up	£86.92	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Ophthalmologist – adult – follow-up – cost (124)
Physiotherapy		
Physio – paediatric – first visit	£56.60	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Physio – paed – first visit – cost (124)
Physio – adult – first visit	£56.60	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Physio – adult – first visit – cost (124)
Physio – paediatric – follow-up	£45.86	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Physio – paed – follow-up – cost (124)
Physio – adult – follow-up	£45.86	NHS reference costs 2015–16 Consultant led non-admitted F2F attendance, Physio – adult – follow-up – cost (124)
GP		
GP unit cost	£36.00	PSSRU (125)
Major surgery		
Ventriculoperitoneal shunt	£4,948.66	NHS reference costs 2015–16 AA54A – Intermediate Intracranial Procedures, 19 years and over, with CC Score 4+ (124)
Cervical fusion, complex	£12,685.33	NHS reference costs 2015–16 HC61A – Complex Extradural Spinal Procedures with CC Score 4+ (124)
Cervical fusion, very complex	£14,201.00	NHS reference costs 2015–16 HC60A – Very Complex Extradural Spinal Procedures with CC Score 4+ (124)
Hip replacement	£13,389.69	NHS reference costs 2015–16 HN12A – Very Major Hip Procedures for Non-Trauma with CC Score 10+ (124)
Knee replacement	£10,259.05	NHS reference costs 2015–16 HN22A – Very Major Knee Procedures for Non-Trauma with CC Score 10+ (124)
Minor surgery		

Resource	Cost	Source
Tonsillectomy	£1,556.16	NHS reference costs 2015–16 CA60B Tonsillectomy, 18 years and under – Elective Inpatient (124)
Carpal tunnel surgery	£1,792.76	NHS reference costs 2015–16 NH45A Minor Hand Procedures for Non-Trauma, 19 years and over – Elective Inpatient (124)
Grommets	£1,783.14	NHS reference costs 2015–16 CA54B – Minor Ear Procedures, 18 years and under – Elective Inpatient (124)
Severe infection		
ICU unit (paediatrics)	£1,670.80	National Schedule of Reference Costs – Year 2015–16_weighted average of following HRG codes from Non-elective excess bed days (NEL-XS) sheet: WJ05A;WJ05B; WJ06A; WJ06B; WJ06C; WJ06D; WJ06E;WJ06F; WJ06G; WJ06H; WJ06J (124)
ICU unit (adults)	£1,307.26	National Schedule of Reference Costs – Year 2015–16_Weighted average for adult critical care (CC) costs (124)
General care unit (paediatrics)	£272.60	National Schedule of Reference Costs – Year 2015–16_weighted average of following HRG codes from Total HRG's sheet: XB01Z; XB02Z; XB03Z; XB04Z; XB05Z; XB06Z; XB07Z; XB08Z; XB09Z (124)
General care unit (adults)	£272.60	National Schedule of Reference Costs – Year 2015–16_weighted average of following HRG codes from Total HRG's sheet: XB01Z; XB02Z; XB03Z; XB04Z; XB05Z; XB06Z; XB07Z; XB08Z; XB09Z (124)

Abbreviations: ENT, ear, nose and throat; GP, general practitioner; ICU, intensive care unit; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

When the patient cohort incurs a major surgical event in the model, a 'weighted' cost is applied for that event assuming equal split (20% each) between the five listed major surgical interventions. When the patient cohort incurs a minor surgical event in the model, a 'weighted' cost is applied for that event assuming equal split (33% each) between the three listed minor surgical interventions. Unit costs for major surgeries use the NHS reference costs with the highest complication and comorbidity (CC) score, to reflect that AM patients present with complex symptoms and/or risk profiles (e.g. high risk of anaesthesia complications).

Health-state costs

12.3.7 ***If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.***

The cost per health state is described previously in Table 65.

Adverse-event costs

12.3.8 ***Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all***

adverse events and complication costs, both during and after longer-term use of the technology.

While IRRs are included as an AE within the model, they are assumed in the base case to be associated with no cost. This assumption is supported by a recent publication by White et al. (2017), which shows that IRRs in patients with LSDs receiving ERT requires minimal intervention (106).

Miscellaneous costs

12.3.9 ***Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.***

12.3.9.1 Personal social service caregiver costs

A study by Hendriksz et al, 2014 (112) was used to provide estimates of the hours of care-giving by ambulatory status in patients with MPS IVA. This was used as a proxy for homecare requirements in the AM population, with assumptions required to estimate the proportion of care provided professionally. This provides an estimate of the health state-wise total annual PSS cost, as shown in Table 68.

Table 68: Personal social service caregiver costs by health state

	WU	WWA	WC	SI	Source
Proportion of care delivered by professionals	10%	20%	50%	80%	Assumption
Hours of care-giving / day	1.3	3.9	13.8	13.8	Hendriksz 2014 (112)
Professional carer cost / hour	£24.00				PSSRU Unit Cost 2016 – Homecare worker per weekday hour (125)
Cost / day	£3	£19	£166	£265	Calculation
Cost / year	£1,139	£6,833	£60,444	£96,710	Calculation

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

Ventilation costs

The UK KOLs indicated that patients with AM typically require ventilatory support as disease severity worsens (17). Furthermore, the experts suggested that velmanase alfa may help to reduce the need for ventilatory support, due to the positive effects of treatment on lung function. [redacted] A summary of ventilation costs is provided in Table 69 and the use of ventilation by health state is presented for BSC and velmanase alfa in Table 70.

Table 69: Ventilation costs

Ventilation type/setting	Annual cost	Source
24-hour care ventilation – institutional	£301,888	Noyes 2006 (126)
24-hour care ventilation – home	£239,855	Noyes 2006 (126)
Overnight ventilation – institutional	£80,279	Noyes 2006 (126)
Overnight ventilation – home	£80,279	Noyes 2006 (126)
Proportion of patients at home	50%	UK KOL interview (17)
Proportion of patients in institution	50%	UK KOL interview (17)

Abbreviations: KOL, key opinion leader.

Table 70: Ventilation resource use and total cost by health state for BSC vs velmanase alfa

Treatment	Walking unassisted	Walking with assistance	Wheelchair dependent	Severe immobility	Source
No ventilation					
BSC	100%	100%	80%	0%	UK KOL interviews (17)
VA	100%	100%	90%	50%	
Overnight ventilation only					
BSC	0%	0%	20%	50%	UK KOL interview (17)
VA	0%	0%	10%	25%	
24-hour care ventilation					
BSC	0%	0%	0%	50%	UK KOL interview (17)
VA	0%	0%	0%	25%	
Average total ventilation cost					
BSC	£0	£0	£19,090	£208,751	Calculation
VA	£0	£0	£9,545	£104,375	

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

The total personal social service costs, combining the costs of caregiving and ventilation, are shown in Table 71 by health state.

Table 71: Total personal social service cost (caregiver and ventilation costs) by health state

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

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

12.3.9.2 Personal carer expenditure and productivity loss

A targeted search (Appendix 6, Section 17.6.3 and 17.6.4) was conducted to identify papers that reported the social costs and/or personal costs and/or productivity losses for those patients (and carers of patients) with rare, chronic diseases. No studies in a relevant proxy condition were identified. A study by Woolley et al, 2004 (127) was identified that estimated that for families caring for a severely disabled child, personal annual expenditure was £5,000 (inflated to £6,393). It was assumed that this cost applies in the 'wheelchair dependent' and 'severe immobility' health states, and that 50% of the cost applies in the 'walking unassisted' and 'walking with assistance' health states. For the short end stage state, a publication provided a three-month end-stage caregiver estimates of £370, which has been scaled and converted into a 4-week cost for short end stage (£123) (128).

Caregiver productivity loss has been estimated using the human capital method (Table 72). The estimates of caregiver time from Hendriksz 2014 (112) are assumed to equate to the reduction in employment required by a caregiver to provide homecare. This is multiplied by the UK average hourly earnings (£13.41). Due to the 'wheelchair dependent' and 'severe immobility' health states requiring an estimated 13.8 hours of care per day, it is assumed that no employment is possible at all when caring for a person in these health states.

Table 72: Carer productivity loss by health state

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

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

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

There are no additional cost savings identified at this time; however, as the clinical community's understanding of the treatment and disease will continue to increase, other cost savings may become apparent (see Section 14 for further discussion).

12.4 *Approach to sensitivity analysis*

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 *Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-effectiveness analysis.*

Structural assumptions were explored in extensive scenario analyses reported in Section 12.5.12. These examined the effect of alternative assumptions and scenarios relating to disease progression, utility values, velmanase alfa treatment effect, model starting health state distribution, and rates of major surgeries. A comprehensive set of scenario analyses are conducted across a range of model assumptions, and are summarised in Section 12.5.16.

12.4.2 *Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what*

was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic and probabilistic sensitivity analyses were undertaken. The variables used, together with the range of the variation (upper and lower values) and the method used, are summarised in Section 12.4.3.

12.4.3 *Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.*

The variables used in the one-way scenario-based deterministic sensitivity analysis are shown in Table 73. The distributions used in the probabilistic sensitivity analysis are shown in Table 74.

Table 73: Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Value	Lower bound	Upper bound	Method for upper and lower bounds
Setting				
Discount rate - costs and QALYs	1.5%	0.0%	3.5%	NICE guide to the methods of technology appraisal 2013 (118)
Clinical				
Progression (years)				
BSC - WU to WWA (years in state)	11.44	1.70	23.23	UK Expert Elicitation Panel (117), 95% CI rhLAMAN-10, multi-domain responder analysis
BSC - WWA to WC (years in state)	10.20	2.60	17.69	
BSC - WC to SI (years in state)	9.97	2.54	17.42	
BSC - SI to death (years in state)	3.02	1.06	7.43	
VA - Paediatric sub-population - WU to WWA (additional years in state compared to BSC)	1.54	0.00	3.64	
VA - Paediatric sub-population - WWA to WC (additional years in state compared to BSC)	1.35	0.23	2.59	
VA - Paediatric sub-population - WC to SI (additional years in state compared to BSC)	0.58	0.09	1.68	
VA - Paediatric sub-population - SI to death (additional years in state compared to BSC)	0.00	0.00	0.00	
VA - Adolescent sub-population - WU to WWA (additional years in state compared to BSC)	2.06	0.23	2.59	
VA - Adolescent sub-population - WWA to WC (additional years in state compared to BSC)	1.35	0.23	2.59	
VA - Adolescent sub-population - WC to SI ((additional years in state compared to BSC)	0.58	0.09	1.68	
VA - Adolescent sub-population - SI to death (additional years in state compared to BSC)	0.00	0.00	0.00	

Variable	Value	Lower bound	Upper bound	Method for upper and lower bounds
VA - Adult sub-population - WU to WWA (additional years in state compared to BSC)	1.30	0.01	2.81	
VA - Adult sub-population - WWA to WC (additional years in state compared to BSC)	0.96	0.16	1.85	
VA - Adult sub-population - WC to SI (additional years in state compared to BSC)	0.97	0.07	1.20	
VA - Adult sub-population - SI to death (additional years in state compared to BSC)	0.00	0.00	0.00	
Disease improvement on VA				
Year 1 - WC to WWA	20.0%	0.0%	70.0%	Plausible range (upper value from rhLAMAN-10 CHAQ change) (Section 9.6.1.2)
Year 2 - WC to WWA	20.0%	0.0%	70.0%	Plausible range (upper value from rhLAMAN-10 CHAQ change) (Section 9.6.1.2)
Year 1 - WWA to WU	20.0%	0.0%	70.0%	Plausible range (upper value from rhLAMAN-10 CHAQ change) (Section 9.6.1.2)
Year 2 - WWA to WU	20.0%	0.0%	70.0%	Plausible range (upper value from rhLAMAN-10 CHAQ change) (Section 9.6.1.2)
Year 3+ - WC to WWA	2.5%	0.0%	10.0%	Plausible range
Year 3+ - WWA to WU	2.5%	0.0%	10.0%	Plausible range
Adverse events				
VA IRR rate	0%	0%	0%	N/A
VA IRR treatment cost	£0	£0	£273	Upper bound assumes general care 1-night stay
All other clinical variables	Varied by +/- 25%			
Serious infections				
Serious infection probability - WU	20%	13%	39%	UK Expert Elicitation Panel (117), max/min values
Serious infection probability - WWA	21%	15%	39%	

Variable	Value	Lower bound	Upper bound	Method for upper and lower bounds
Serious infection probability - WC	49%	39%	63%	
Serious infection probability - SI	63%	53%	78%	
Serious infection-related mortality – WU	5%	1%	10%	
Serious infection-related – WWA	6%	3%	15%	
Serious infection-related mortality – WC	13%	5%	30%	
Serious infection-related mortality – SI	23%	10%	40%	
Short end stage - time in state (weeks)	4	3	5	+/- 25%
Major surgery				
Surgery probability – WU	8.1%	5.0%	13.0%	UK Expert Elicitation Panel (117), max/min values
Surgery probability – WWA	13.8%	8.0%	20.0%	
Surgery probability – WC	10.0%	8.0%	13.0%	
Surgery probability – SI	1.5%	1.5%	1.5%	
All other surgery variables	Varied by +/- 25%			
Costs	Varied by +/- 25%			
Resource use	Varied by +/- 25%			
Utilities				
All utility variables	Varied by +/- 25%			

Abbreviations: BSC, best supportive care; CHAQ, childhood health assessment questionnaire; CI, confidence interval; IRR, infusion-related reaction; KOL, key opinion leader; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-years; SI, severe immobility; VA, velmanase alfa; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

Table 74: Variable values used in probabilistic sensitivity analysis

Variable (group)	Distribution	Method
Clinical parameters		
Progression		
BSC - WU to WWA (years in state)	Normal	UK Expert Elicitation Panel (117), 95% CI
BSC - WWA to WC (years in state)	Normal	
BSC - WC to SI (years in state)	Beta	
BSC or VA - SI to death (years in state)	Gamma	
VA - Paediatric cohort - WU to WWA (additional years versus BSC in state)	Beta	
VA - Paediatric cohort - WWA to WC (additional years versus BSC in state)	Normal	
VA - Paediatric cohort - WC to SI (additional years versus BSC in state)	Gamma	
VA - Adolescent cohort - WU to WWA (additional years versus BSC in state)	Normal	
VA - Adolescent cohort - WWA to WC (additional years versus BSC in state)	Normal	
VA - Adolescent cohort - WC to SI (additional years versus BSC in state)	Gamma	
VA - Adult cohort - WU to WWA (additional years versus BSC in state)	Normal	
VA - Adult cohort - WWA to WC (additional years versus BSC in state)	Normal	
VA - Adult cohort - WC to SI (additional years versus BSC in state)	Normal	
Other clinical parameters		
Severe infection length of stay parameters	Gamma	Using +/- 25% range to estimate 95% CI and standard error
All other clinical probability parameters	Beta	Using +/- 25% range to estimate 95% CI and standard error
Severe infection		
Severe infection probabilities	Beta	Using +/- 25% range to estimate 95% CI and standard error
Severe infection - time in short term end stage	Gamma	Using +/- 25% range to estimate 95% CI and standard error
Major surgery		
All surgery probabilities	Beta	Using +/- 25% range to estimate 95% CI and standard error
Costs		
All costs	Gamma	Using +/- 25% range to estimate 95% CI and standard error
Resource use		
Proportion of caregiving by professional (by health state)	Beta	Using +/- 25% range to estimate 95% CI and standard error
All other resource use costs	Gamma	Using +/- 25% range to estimate 95% CI and standard error

Variable (group)	Distribution	Method
Utility		
Disutility/increment values	Gamma	Using +/- 25% range to estimate 95% CI and standard error
Reduction in disutility periods on VA	Beta	Using +/- 25% range to estimate 95% CI and standard error

Abbreviations: BSC, best supportive care; CI, confidence interval; IRR, infusion-related reaction; KOL, key opinion leader; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-years; SI, severe immobility; VA, velmanase alfa; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

12.4.4 *If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.*

Model setting parameters (cohort size, time horizon), the treatment cost, and population parameters (distribution at baseline, age at model entry) were not included in the PSA. These were assumed to be constant.

12.5 *Results of economic analysis*

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 *When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.*

The base case results are presented for the paediatric (Table 75), adolescent (Table 76) and adult (Table 77) cohorts. The results for the weighted average are shown in Table 78 and assumes that the treated cohort will comprise 40% paediatric patients, 20% adolescent patients, and 40% adult patients. The ICER for velmanase

alfa vs BSC was [redacted] in the paediatric cohort, [redacted] in the adolescent cohort and [redacted] in the adult cohort. The ICER in the weighted cohort was [redacted].

Table 75: Base case results – paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£894,169	18.89	5.65	-	-	-	-
Velmanase alfa	[redacted]	21.69	7.90	[redacted]	2.80	2.25	[redacted]

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

Table 76: Base case results – adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£899,375	18.54	5.26	-	-	-	-
Velmanase alfa	[redacted]	21.41	7.64	[redacted]	2.87	2.38	[redacted]

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

Table 77: Base case results – adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£914,049	17.85	4.41	-	-	-	-
Velmanase alfa	[redacted]	20.71	6.80	[redacted]	2.86	2.39	[redacted]

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

Table 78: Base case results – weighted average

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£903,139	18.41	5.08	-	-	-	-
Velmanase alfa	[redacted]	21.24	7.41	[redacted]	2.84	2.33	[redacted]

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

12.5.2 ***For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.***

Not applicable. The model assesses progression through four health states until death; these health states and mortality were not captured within the clinical trial data.

12.5.3 ***Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.***

The probability of a patient (using the paediatric cohort as an example) being in one of the four primary health states, short end stage or death over time is presented in Table 79 for velmanase alfa and Table 80 for BSC. Of note, at 10 years (aged 16), 19.53% of patients under BSC alone have died, in contrast to 12.08% of the cohort treated with velmanase alfa.

Table 79: Proportion of paediatric cohort in each health state – velmanase alfa

Year	WU	WWA	WC	SI	SES	Dead
1	76.36%	21.63%	1.41%	0.36%	0.00%	0.24%
2	73.38%	22.40%	2.60%	0.89%	0.17%	0.57%
5	59.06%	28.14%	6.61%	2.28%	0.62%	3.29%
10	40.42%	30.23%	12.24%	4.33%	1.12%	11.67%
20	17.98%	22.34%	15.39%	5.90%	1.47%	36.92%
30	7.67%	12.87%	11.85%	4.80%	1.16%	61.65%
40	3.18%	6.55%	7.29%	3.06%	0.73%	79.19%
50	1.29%	3.07%	3.91%	1.68%	0.39%	89.67%
Lifetime	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%

Abbreviations: SES, short end stage; SI, severe immobility; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

Table 80: Proportion of paediatric cohort in each health state – BSC

Year	WU	WWA	WC	SI	SES	Dead
1	70.32%	26.19%	2.08%	0.94%	0.00%	0.48%
2	64.35%	28.06%	3.82%	1.65%	0.98%	1.14%
5	48.96%	30.97%	8.61%	3.42%	1.24%	6.79%
10	31.07%	29.04%	13.56%	5.26%	1.54%	19.53%
20	12.48%	18.20%	13.93%	5.61%	1.44%	48.33%
30	5.00%	9.45%	9.43%	3.95%	0.96%	71.20%
40	1.99%	4.47%	5.29%	2.28%	0.54%	85.43%
50	0.78%	1.98%	2.64%	1.16%	0.27%	93.18%
Lifetime	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%

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

12.5.4 *Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.*

The QALYs accrued over time for a paediatric patient (aged 6, as an example) treated with velmanase alfa or BSC is shown in Table 81 and Table 82, respectively.

Table 81: QALYs accrued per health state in the paediatric cohort model (discounted) – velmanase alfa

Year	WU	WWA	WC	SI	SES
1	0.694	0.085	-0.002	0.000	0.000
2	1.345	0.165	-0.008	0.001	0.000
5	2.987	0.422	-0.051	0.006	0.000
10	4.864	0.861	-0.206	0.018	0.000
20	6.730	1.526	-0.661	0.047	0.001
30	7.419	1.881	-1.049	0.070	0.002
40	7.668	2.043	-1.282	0.084	0.002
50	7.755	2.112	-1.398	0.091	0.002
Lifetime	7.798	2.151	-1.476	0.096	0.003

Abbreviations: QALY, quality adjusted life years; SES, short end stage; SI, severe immobility; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

Table 82: QALYs accrued per health state in the paediatric cohort model (discounted) – BSC

Year	WU	WWA	WC	SI	SES
1	0.594	0.070	-0.004	0.000	0.000
2	1.121	0.145	-0.016	0.001	0.000
5	2.409	0.387	-0.088	0.006	0.000
10	3.824	0.774	-0.297	0.018	0.001
20	5.148	1.317	-0.776	0.046	0.002
30	5.606	1.583	-1.113	0.065	0.002
40	5.764	1.697	-1.292	0.076	0.003
50	5.817	1.742	-1.375	0.081	0.003
Lifetime	5.842	1.766	-1.425	0.084	0.003

Abbreviations: BSC, best supportive care; QALY, quality adjusted life years; SES, short end stage; SI, severe immobility; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

12.5.5 *Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:*

Not applicable.

12.5.6 *Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.*

The disaggregation of incremental QALYs (velmanase alfa vs BSC) by health state are presented in Table 83, using the paediatric cohort (aged 6, as an example).

Table 83: Summary of QALY gain by health state – paediatrics cohort model

Health state QALYs	QALY		Increment	Absolute increment	Absolute increment, %
	VA	BSC			
WU	6.780	4.870	1.910	1.910	39%
WWA	1.778	1.419	0.360	0.360	25%
WC	-1.088	-1.016	-0.071	0.071	-7%
SI	-0.037	-0.041	0.004	0.004	11%
WU + SInf	0.925	0.899	0.027	0.027	3%
WWA + SInf	0.235	0.223	0.012	0.012	6%
WC + SInf	-0.578	-0.583	0.005	0.005	1%
SI + SInf	-0.072	-0.073	0.001	0.001	2%
SES	-0.048	-0.051	0.003	0.003	7%
Total	7.897	5.646	2.251	2.394	40%

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

12.5.7 *Please provide undiscounted incremental QALYs for the intervention compared with each comparator*

The undiscounted incremental QALYs (velmanase alfa vs BSC) by health state are presented in Table 84, using the paediatric cohort (aged 6, as an example).

Table 84: Summary of QALY gain by health state – paediatrics cohort model (undiscounted)

Health state QALYs	QALY		Increment	Absolute increment	Absolute increment, %
	VA	BSC			
WU	7.879	5.612	2.268	2.268	40%
WWA	2.258	1.772	0.485	0.485	27%
WC	-1.564	-1.402	-0.162	0.162	-12%
SI	-0.055	-0.057	0.002	0.002	3%
WU + SInf	1.110	1.042	0.069	0.069	7%
WWA + SInf	0.308	0.281	0.027	0.027	10%
WC + SInf	-0.854	-0.815	-0.038	0.038	-5%
SI + SInf	-0.107	-0.103	-0.004	0.004	-4%
SES	-0.070	-0.070	0.000	0.000	0%
Total	8.906	6.260	2.646	3.056	42%

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

12.5.8 *Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.*

A summary of costs by type is shown in Table 85, using the paediatric cohort (aged 6, as an example).

Table 85: Summary of costs by type in the paediatric cohort (discounted)

Health state costs	Costs		Increment	Absolute increment	Absolute increment, %
	VA	BSC			
Total treatment costs	[redacted]	£0	[redacted]	[redacted]	NA
Intervention cost	[redacted]	£0	[redacted]	[redacted]	NA
Administration cost	[redacted]	£0	[redacted]	[redacted]	NA
Monitoring cost	[redacted]	£0	[redacted]	[redacted]	NA
Adverse event cost	[redacted]	£0	[redacted]	[redacted]	NA
Health state cost	[redacted]	£133,162	[redacted]	[redacted]	[redacted]
PSS cost	[redacted]	£761,007	[redacted]	[redacted]	[redacted]
Societal cost	[redacted]	£0	[redacted]	[redacted]	NA
Carer productivity loss	[redacted]	£0	[redacted]	[redacted]	NA
Personal and caregiver expenditure	[redacted]	£0	[redacted]	[redacted]	NA
Total cost	[redacted]	£894,169	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; NA, not applicable; PSS, personal social services; QALY, quality adjusted life years; VA, velmanase alfa.

12.5.9 ***If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.***

A summary of costs by health state is shown in Table 86, using the paediatric cohort (aged 6, as an example).

Table 86: Summary of costs by health state in the paediatric cohort (discounted)

Health state costs	Costs		Increment	Absolute increment	Absolute increment, %
	VA	BSC			
WU	[redacted]	£26,659	[redacted]	[redacted]	[redacted]
WWA	[redacted]	£21,033	[redacted]	[redacted]	[redacted]
WC	[redacted]	£8,728	[redacted]	[redacted]	[redacted]
SI	[redacted]	£1,874	[redacted]	[redacted]	[redacted]
WU + SInf	[redacted]	£17,467	[redacted]	[redacted]	[redacted]
WWA + SInf	[redacted]	£16,062	[redacted]	[redacted]	[redacted]
WC + SInf	[redacted]	£17,539	[redacted]	[redacted]	[redacted]
SI + SInf	[redacted]	£8,483	[redacted]	[redacted]	[redacted]
SES	[redacted]	£15,317	[redacted]	[redacted]	[redacted]
Total	[redacted]	£133,162	[redacted]	[redacted]	[redacted]

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

12.5.10 ***If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.***

While IRRs are included as an AE, they are assumed not to be associated with a cost (Section 12.2.4).

Sensitivity analysis results

12.5.11 ***Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.***

12.5.11.1 Paediatric cohort

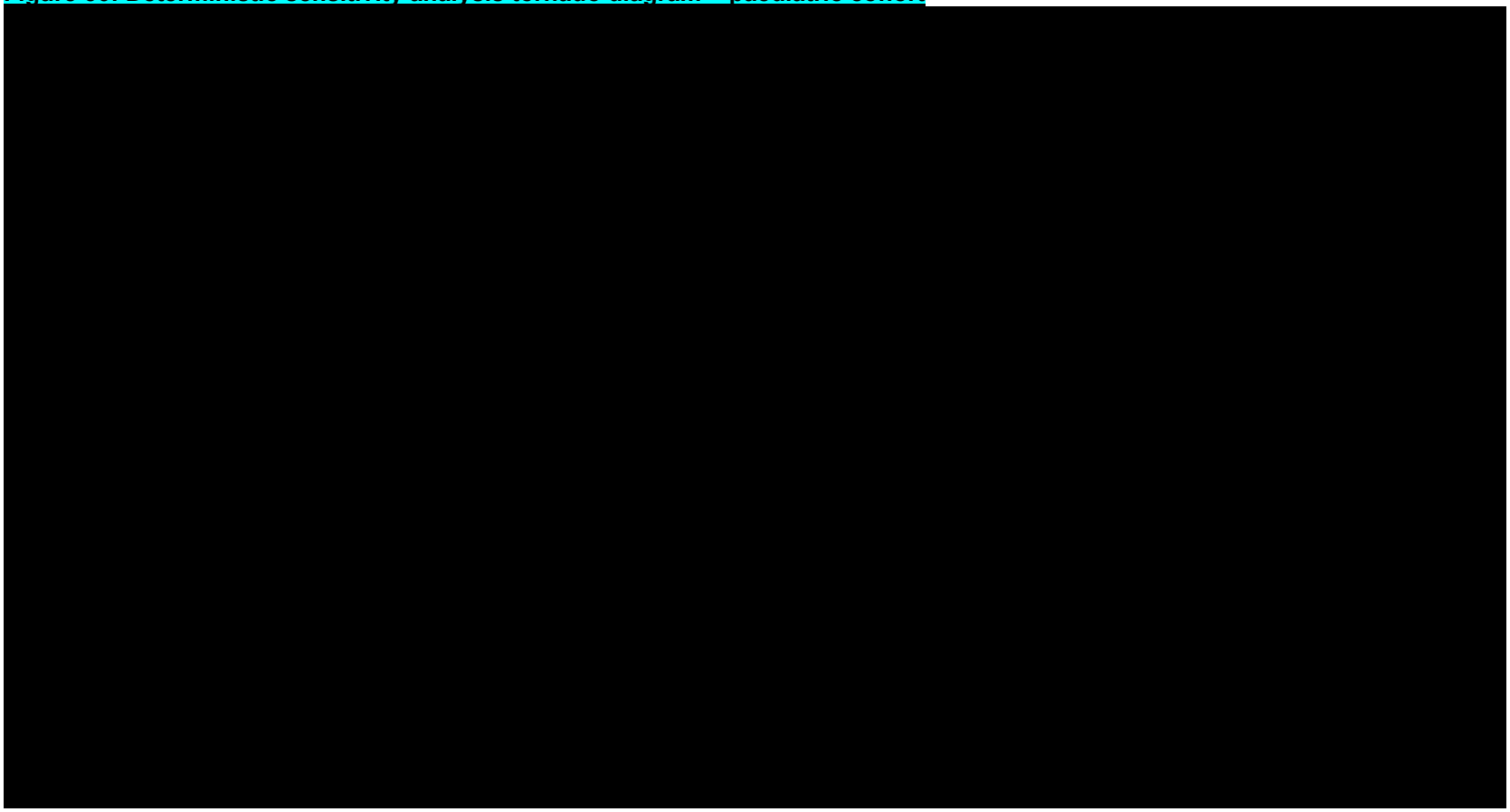
The results of the deterministic, one-way sensitivity analysis for the paediatric cohort are presented in Table 87 and Figure 30. The base case ICER was most sensitive to the cost of velmanase alfa, followed by discount rate (outcomes), and the annual risk of withdrawal.

Table 87: Deterministic sensitivity analysis – paediatric cohort

Parameter	Value			Outcome		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	£887	£665	£1,108	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10.0%	7.5%	12.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	11.44	1.70	23.23	[redacted]	[redacted]	[redacted]
Progression (added years in state) – VA – Paediatric – WU to WWA	£10,259	£7,694	£12,824	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ - WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]

Abbreviations: VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

Figure 30: Deterministic sensitivity analysis tornado diagram – paediatric cohort



Abbreviations: VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

12.5.11.2 Adolescent cohort

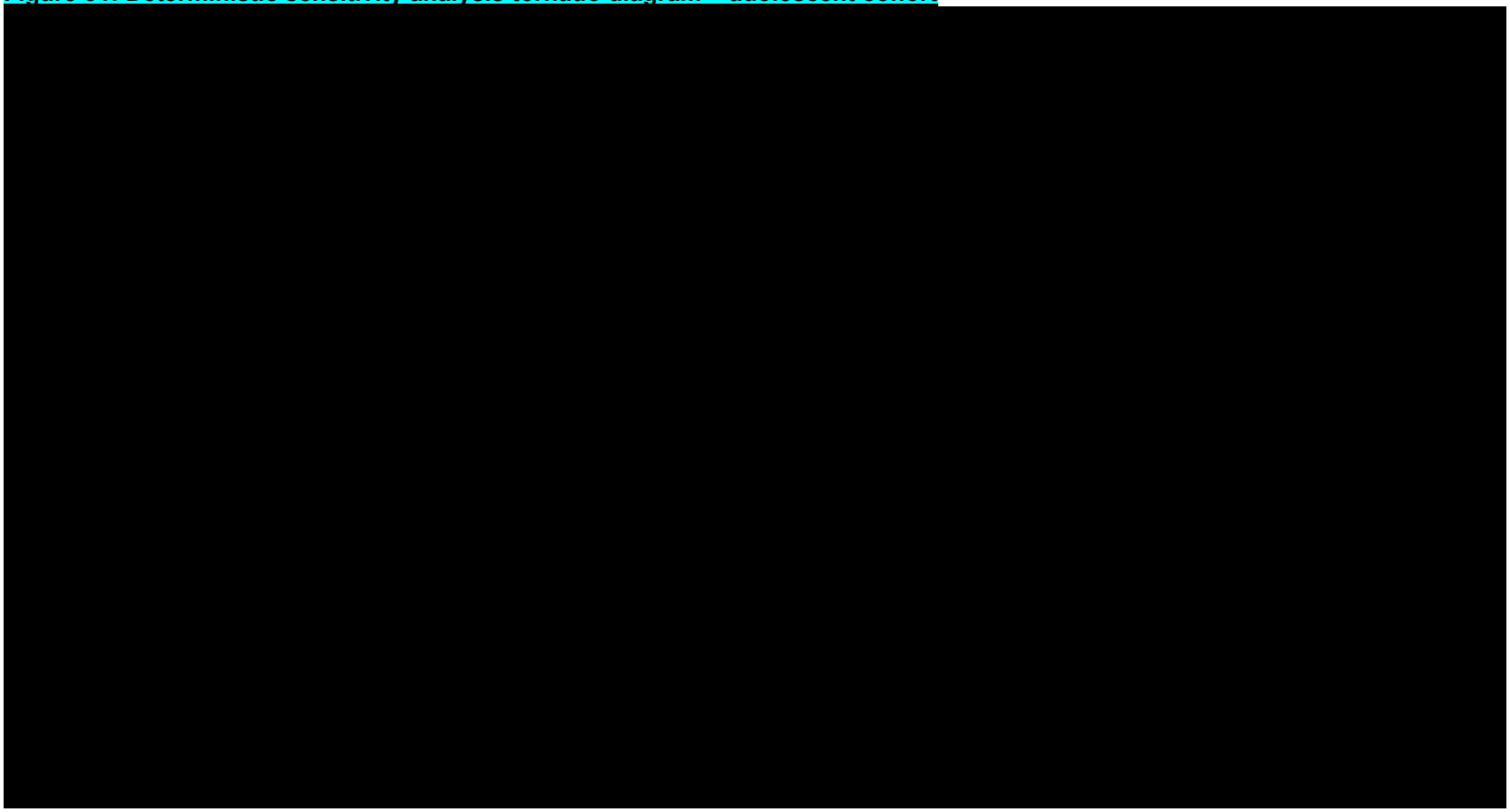
The results of the deterministic, one-way sensitivity analysis for the adolescent cohort are presented in Table 88 and Figure 31. The base case ICER was most sensitive to the cost of velmanase alfa, followed by discount rate (outcomes), and Year 1 backwards transition from walking with assistance to walking unassisted with velmanase alfa.

Table 88: Deterministic sensitivity analysis – adolescent cohort

Parameter	Value			Outcome		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	£887	£665	£1,108	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	11.44	1.70	23.23	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10.0%	7.5%	12.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Population – Weight adjustment	0%	-10%	10%	[redacted]	[redacted]	[redacted]

Abbreviations: VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

Figure 31: Deterministic sensitivity analysis tornado diagram – adolescent cohort



Abbreviations: VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

12.5.11.3 Adult cohort

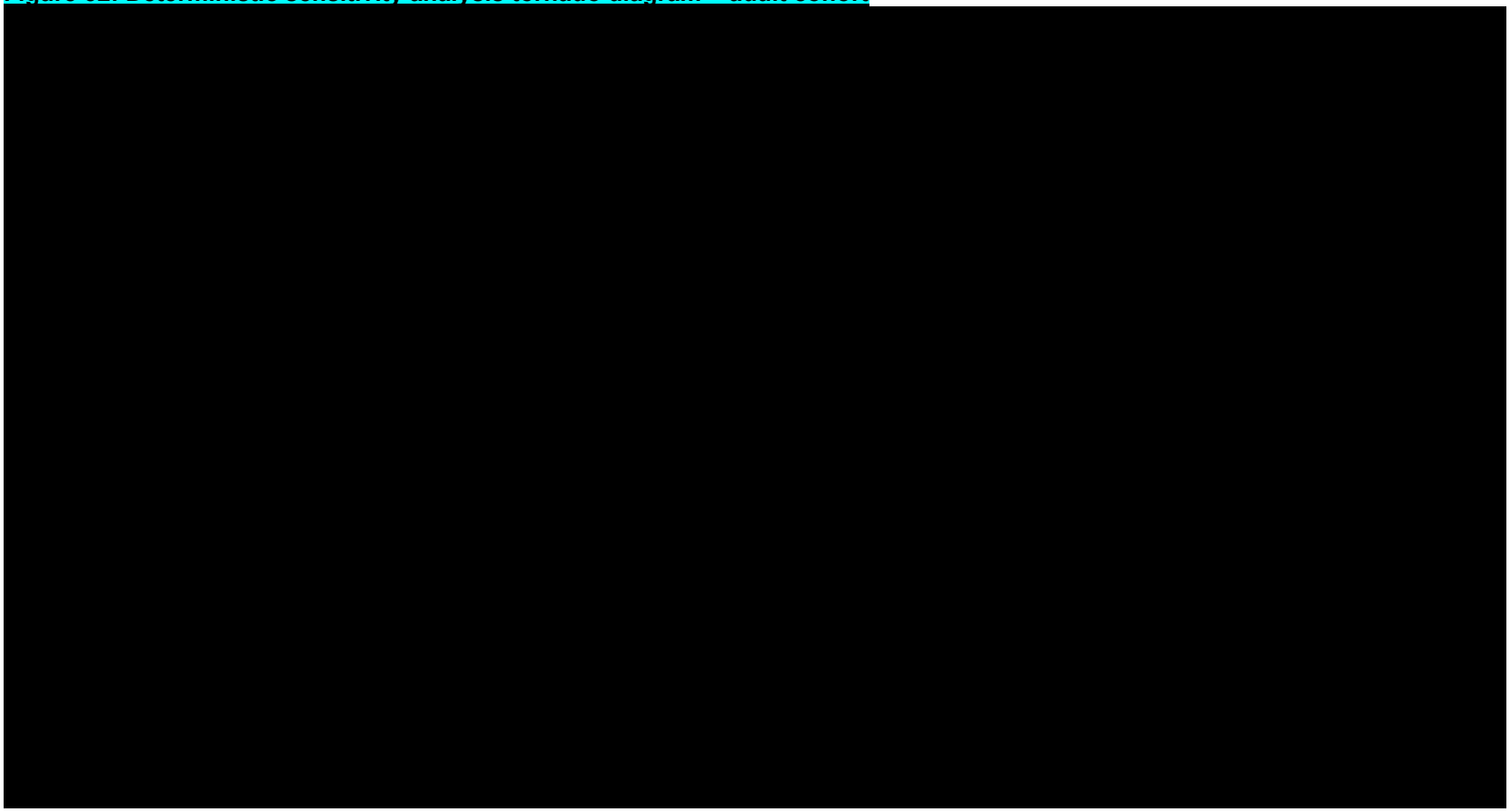
The results of the deterministic, one-way sensitivity analysis for the adult cohort are presented in Table 89 and Figure 32. The base case ICER was most sensitive to the cost of velmanase alfa, followed by the rate of progression while on BSC from ‘walking unassisted’ to ‘walking with assistance’, and Year 1 backwards transition from walking with assistance to walking unassisted with velmanase alfa.

Table 89: Deterministic sensitivity analysis – adult cohort

Parameter	Value			Outcome		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	£887	£665	£1,108	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	11.44	1.70	23.23	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10.0%	7.5%	12.5%	[redacted]	[redacted]	[redacted]
Population – Weight adjustment	0%	-10%	10%	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; TE, treatment effect; VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

Figure 32: Deterministic sensitivity analysis tornado diagram – adult cohort



Abbreviations: BSC, best supportive care; TE, treatment effect; VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

12.5.12 *Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.*

12.5.12.1 Efficacy of velmanase alfa

The current model estimates the efficacy of velmanase alfa with regards to its ability to delay disease progression across four health states and its potential to promote reverse transitions, reflecting an improvement in mobility. While basing disease progression on ambulatory status was determined to be the most suitable approach for the model, there is a paucity of data available to support the efficacy of velmanase alfa within the confines of the model structure. Furthermore, the current knowledge of the efficacy of velmanase alfa is limited to <5 years of follow-up. To address the uncertainty around the efficacy of velmanase alfa in the model, a series of sensitivity analyses were performed.

Disease progression using upper estimates from elicitation panel

The estimates of disease progression while receiving BSC or velmanase alfa were provided by KOLs during an UK-EEP and their uncertainty in the estimates were reflected by a 95% CI (Section 12.2.1.2). A scenario analysis was thereby conducted using the upper estimates of velmanase alfa efficacy (additional years in health state compared with BSC). When compared with the base case results (Section 12.5.1), the ICER for the:

- Paediatric cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 90
- Adolescent cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 91
- Adult cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 92

Table 90: Disease progression using upper estimates of velmanase alfa efficacy from elicitation panel – scenario analysis results for the paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£894,169	18.89	5.65	-	-	-	-
Velmanase alfa	[redacted]	21.95	8.23	[redacted]	3.07	2.58	[redacted]

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

Table 91: Disease progression using upper estimates of velmanase alfa efficacy from elicitation panel – scenario analysis results for the adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£899,375	18.54	5.26	-	-	-	-
Velmanase alfa	[redacted]	21.56	7.77	[redacted]	3.02	2.50	[redacted]

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

Table 92: Disease progression using upper estimates of velmanase alfa efficacy from elicitation panel – scenario analysis results for the adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£914,049	17.85	4.41	-	-	-	-
Velmanase alfa	[redacted]	20.91	7.03	[redacted]	3.06	2.62	[redacted]

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

Disease progression reduced by 50% with velmanase alfa compared with BSC

The possibility that velmanase alfa could reduce disease progression by 50% compared with BSC was assessed in a scenario analysis. When compared with the base case results (Section 12.5.1), the ICER for the:

- Paediatric cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 93
- Adolescent cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 94
- Adult cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 95

Table 93: Disease progression reduced by 50% with velmanase alfa compared with BSC – scenario analysis results for the paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£894,169	18.89	5.65	-	-	-	-
Velmanase alfa	[redacted]	22.60	8.50	[redacted]	3.71	2.85	[redacted]

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

Table 94: Disease progression reduced by 50% with velmanase alfa compared with BSC – scenario analysis results for the adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£899,375	18.54	5.26	-	-	-	-
Velmanase alfa	[redacted]	22.28	8.16	[redacted]	3.74	2.90	[redacted]

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

Table 95: Disease progression reduced by 50% with velmanase alfa compared with BSC – scenario analysis results for the adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£914,049	17.85	4.41	-	-	-	-
Velmanase alfa	[redacted]	21.67	7.42	[redacted]	3.82	3.00	[redacted]

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

Velmanase alfa prevents disease progression compared with BSC

The possibility that velmanase alfa could prevent (halt) disease progression compared with BSC was assessed in a scenario analysis. When compared with the base case results (Section 12.5.1), the ICER for the:

- Paediatric cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 96
- Adolescent cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 97
- Adult cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 98

Table 96: Velmanase alfa prevents disease progression compared with BSC – scenario analysis results for the paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£894,169	18.89	5.65	-	-	-	-
Velmanase alfa	[redacted]	26.18	10.96	[redacted]	7.29	5.32	[redacted]

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

Table 97: Velmanase alfa prevents disease progression compared with BSC – scenario analysis results for the adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£899,375	18.54	5.26	-	-	-	-
Velmanase alfa	[redacted]	25.79	10.59	[redacted]	7.24	5.33	[redacted]

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

Table 98: Velmanase alfa prevents disease progression compared with BSC – scenario analysis results for the adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£914,049	17.85	4.41	-	-	-	-
Velmanase alfa	[redacted]	25.12	9.78	[redacted]	7.27	5.37	[redacted]

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

Backwards transitions from Year 3 onwards

The model currently allows for the possibility of backwards transitions with velmanase alfa from Year 3 onwards at a rate of 2.5%. Scenario analyses were performed to assess the impact on the ICER when backwards transitions:

- are assumed occur at a rate of 5% after Year 3. When compared with the base case results (Section 12.5.1), the ICER for the:
    - Paediatric cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 99
    - Adolescent cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 100
    - Adult cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 101
- are assumed to be not possible after Year 3. When compared with the base case results (Section 12.5.1), the ICER for the:
    - Paediatric cohort was increased by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 102
    - Adolescent cohort was increased by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 103
    - Adult cohort was increased by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 104

Table 99: Backwards transitions occur at a rate of 5% from Year 3 onwards – scenario analysis results for the paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£894,169	18.89	5.65	-	-	-	-
Velmanase alfa	[redacted]	21.89	8.18	[redacted]	3.00	2.54	[redacted]

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

Table 100: Backwards transitions occur at a rate of 5% from Year 3 onwards – scenario analysis results for the adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£899,375	18.54	5.26	-	-	-	-
Velmanase alfa	[redacted]	21.62	7.94	[redacted]	3.07	2.68	[redacted]

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

Table 101: Backwards transitions occur at a rate of 5% from Year 3 onwards – scenario analysis results for the adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£914,049	17.85	4.41	-	-	-	-
Velmanase alfa	[redacted]	20.93	7.12	[redacted]	3.08	2.70	[redacted]

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

Table 102: Backwards transitions are not possible from Year 3 onwards – scenario analysis results for the paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£894,169	18.89	5.65	-	-	-	-
Velmanase alfa	[redacted]	21.46	7.58	[redacted]	2.57	1.94	[redacted]

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

Table 103: Backwards transitions are not possible from Year 3 onwards – scenario analysis results for the adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£899,375	18.54	5.26	-	-	-	-
Velmanase alfa	[redacted]	21.19	7.32	[redacted]	2.64	2.06	[redacted]

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

Table 104: Backwards transitions are not possible from Year 3 onwards – scenario analysis results for the adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£914,049	17.85	4.41	-	-	-	-
Velmanase alfa	[redacted]	20.47	6.46	[redacted]	2.62	2.05	[redacted]

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

12.5.12.2 Health state utilities

In the absence of available/appropriate HSUVs from the trial data or the SR for the four primary health states in the model, HSUVs derived from a KOL-derived, unpublished audit of n=7 AM patients were employed in the base case. This approach resulted in a lower HSUV for the 'wheelchair dependent' health state compared with the 'severely immobile' health state; it was perceived that patients may have a greater self-awareness of the severity of their condition in the 'wheelchair dependent' health state than the 'severely immobile' health state. This assumption was assessed in a scenario analysis, where the HSUV for the 'wheelchair dependent' health state was equal to the HSUV for the 'severely immobile' health state. When compared with the base case results (Section 12.5.1), the ICER for the:

- Paediatric cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 105
- Adolescent cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 106
- Adult cohort was reduced by [redacted] (ICER vs BSC in scenario analysis: [redacted]) – Table 107

Table 105: The health state utility for WC is equal to SI – scenario analysis results for the paediatric cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£894,169	18.89	4.97	-	-	-	
Velmanase alfa	[redacted]	21.69	9.66	[redacted]	2.80	2.39	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; SI, severely immobile; WC, wheelchair dependent.

Table 106: The health state utility for WC is equal to SI scenario analysis results for the adolescent cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£899,375	18.54	4.59	-	-	-	
Velmanase alfa	[redacted]	21.41	9.42	[redacted]	2.87	2.51	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; SI, severely immobile; WC, wheelchair dependent.

Table 107: The health state utility for WC is equal to SI – scenario analysis results for the adult cohort

Technologies	Total			Incremental			ICER vs BSC
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£914,049	17.85	3.73	-	-	-	
Velmanase alfa	[redacted]	20.71	8.64	[redacted]	2.86	2.51	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; SI, severely immobile; WC, wheelchair dependent.

12.5.13 *Present results of the probabilistic sensitivity analysis described in table D10.3.*

12.5.13.1 Paediatric cohort

The results of the PSA (based on 1,000 simulations for the paediatric cohort are shown in Table 108 and Figure 33. The cost-effectiveness acceptability curve (CEAC) is shown in Figure 34.

Table 108: Base case PSA results – paediatric cohort

Technologies	Total		Incremental		ICER vs BSC (95% CI)
	Costs (95% CI)	QALYs (95% CI)	Costs	QALYs	
BSC	£925,433 (£601,050, £1,425,789)	5.30 (-0.04, 9.21)	-	-	-
Velmanase alfa	[redacted]	7.52 (1.76, 11.95)	[redacted]	2.22	[redacted]

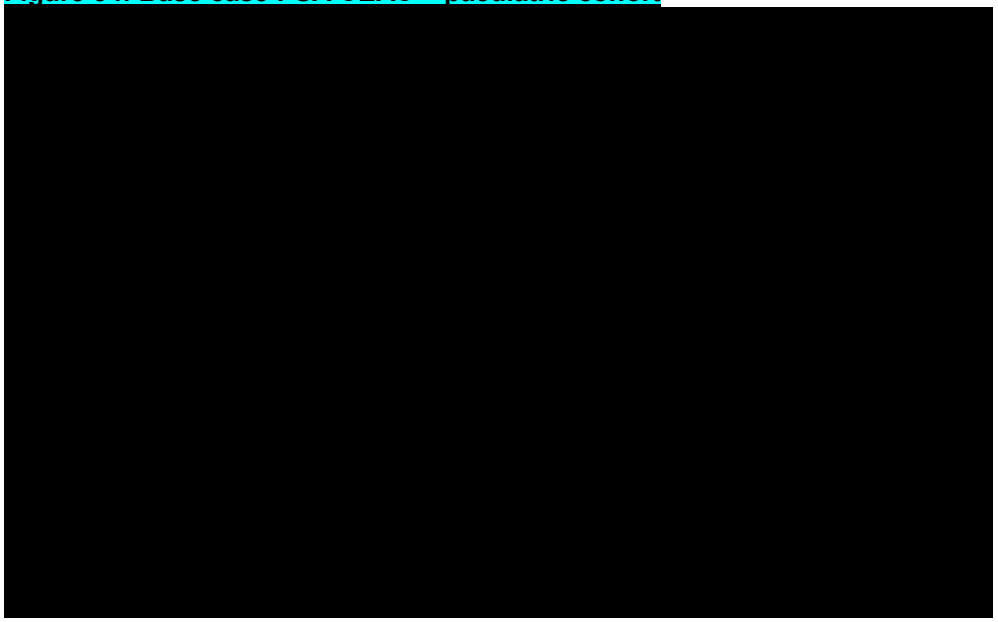
Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life years.

Figure 33: Base case PSA scatterplot of VA vs BSC – paediatric cohort

[redacted]

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

Figure 34: Base case PSA CEAC – paediatric cohort



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

12.5.13.2 Adolescent cohort

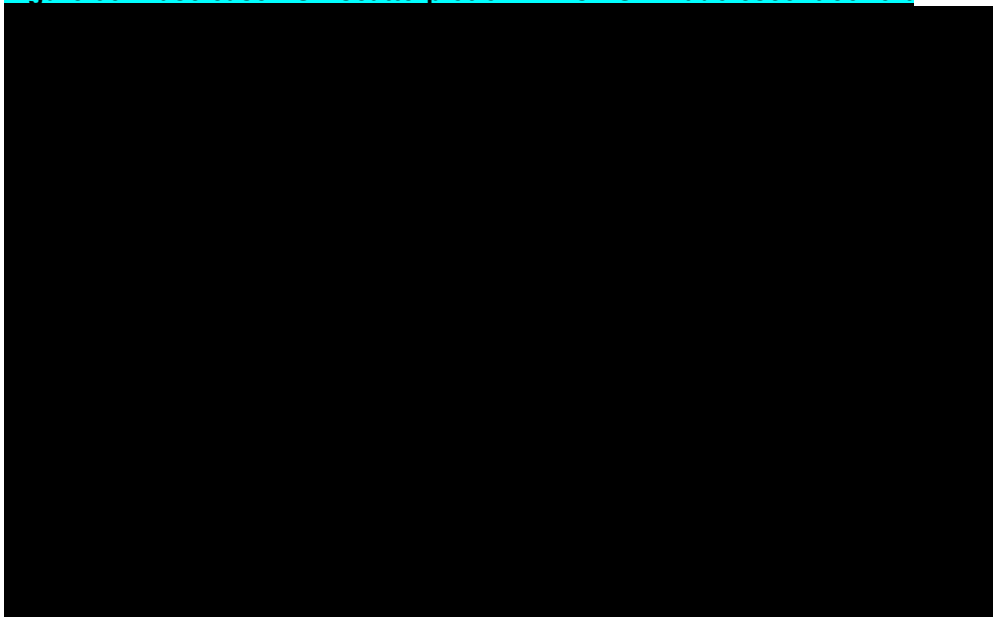
The results of the PSA for the adolescent cohort are shown in Table 109 and Figure 35. The CEAC is shown in Figure 36.

Table 109: Base case PSA results – adolescent cohort

Technologies	Total		Incremental		ICER vs BSC (95% CI)
	Costs (95% CI)	QALYs (95% CI)	Costs	QALYs	
BSC	£929,678 (£612,291, £1,375,196)	4.89 (-0.35, 8.49)	-	-	-
Velmanase alfa	[redacted]	7.24 (1.61, 11.35)	[redacted]	2.35	[redacted]

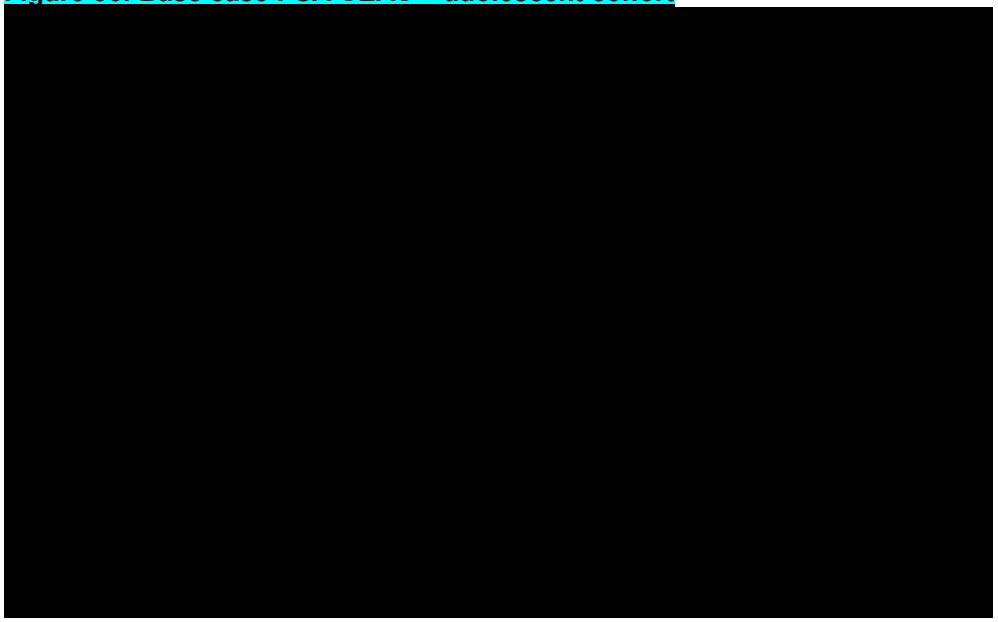
Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life years.

Figure 35: Base case PSA scatterplot of VA vs BSC – adolescent cohort



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

Figure 36: Base case PSA CEAC – adolescent cohort



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

12.5.13.3 Adult cohort

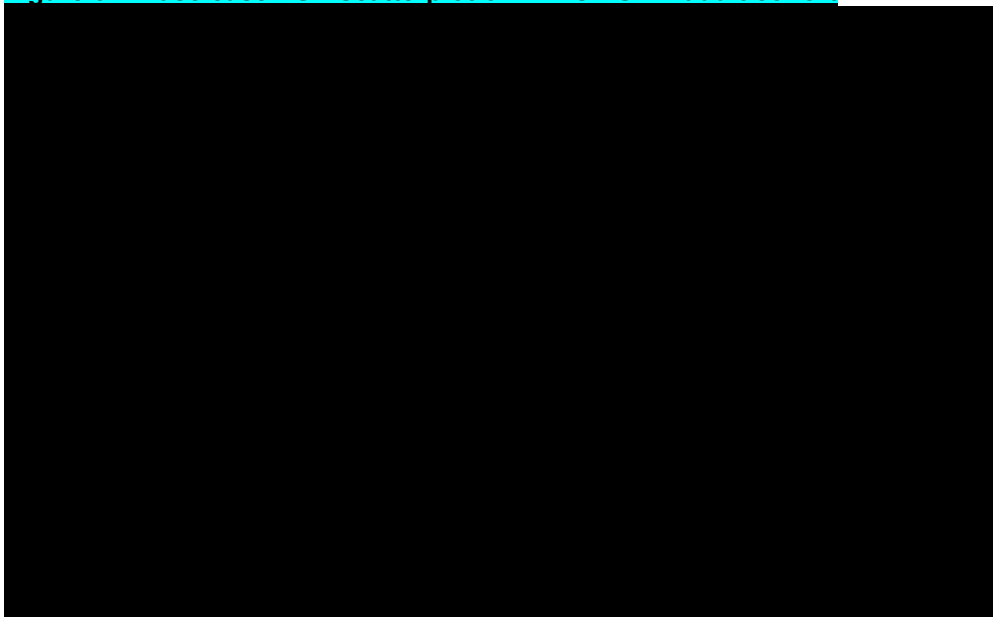
The results of the PSA for the adult cohort are shown in Table 110 and Figure 37. The CEAC is shown in Figure 38.

Table 110: Base case PSA results – adult cohort

Technologies	Total		Incremental		ICER vs BSC (95% CI)
	Costs (95% CI)	QALYs (95% CI)	Costs	QALYs	
BSC	£942,788 (£596,242, £1,423,187)	4.11 (-0.71, 7.80)	-	-	-
Velmanase alfa	[redacted]	6.45 (0.81, 10.95)	[redacted]	2.34	[redacted]

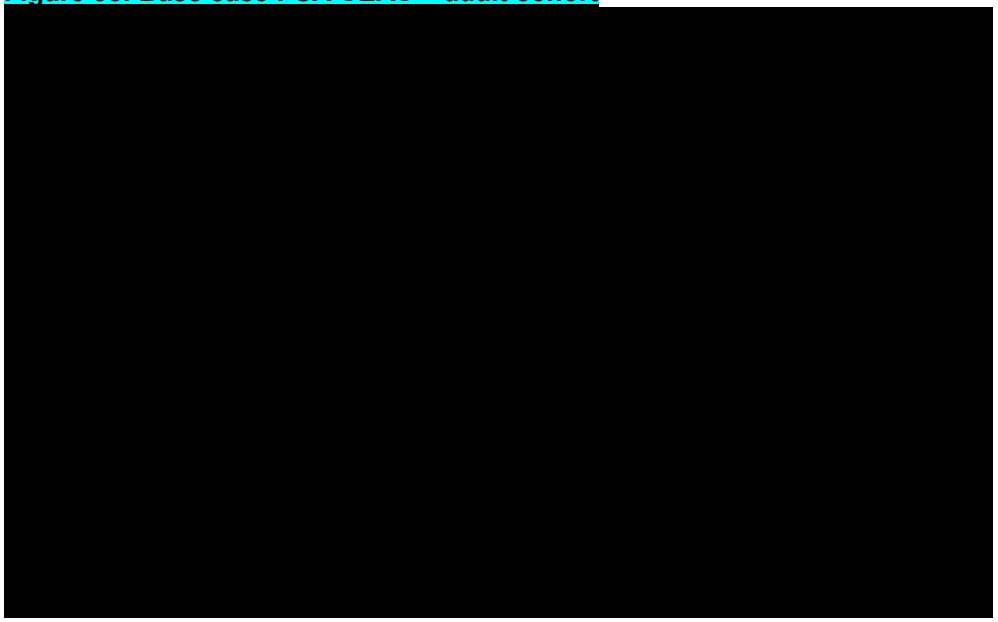
Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life years.

Figure 37: Base case PSA scatterplot of VA vs BSC – adult cohort



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

Figure 38: Base case PSA CEAC – adult cohort



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

12.5.14 *What were the main findings of each of the sensitivity analyses?*

12.5.14.1 Deterministic sensitivity analysis

The DSA across the three age cohorts demonstrated consistency in the parameters that were considered to be the key drivers of the ICER. In all three age cohorts, the ICER was most sensitive to the cost of velmanase alfa and the discount rate (outcomes), with a higher value for both increasing the ICER. The ICER was also sensitive to the rate of backwards transitions at Year 1, Year 2, and Year 3+ across the cohorts, with a lower value increasing the ICER.

12.5.14.2 Probabilistic sensitivity analysis

The PSA demonstrated the combined uncertainty within the model. Overall, the PSA results were similar (in terms of mean results) to the DSA for all three cohorts. The confidence interval around the PSA ICER was broad for each of the cohorts; the PSA ICER with the greatest uncertainty was for the adult cohort [redacted] (95% CI: [redacted]).

12.5.14.3 Scenario analysis

Together, the scenario analyses demonstrate the conservatism employed in the base case results. If the assumptions behind the alternative scenarios are judged as plausible, then the ICER could conceivably be much lower than the base case ICER presented in this submission. The largest impact on the ICER was observed in the analysis which assumed that velmanase alfa could prevent disease progression compared with BSC; from this analysis, the ICER ranged from [redacted] in the paediatric cohort to [redacted] in the adult cohort.

12.5.15 *What are the key drivers of the cost results?*

The key drivers of the cost results are discussed in Section 12.5.14.

Miscellaneous results

12.5.16 *Describe any additional results that have not been specifically requested in this template. If none, please state.*

Due to the heterogeneity of the disease and paucity of evidence, several model parameters were probed to assess the impact on the ICER. The results of these additional scenario analyses performed are shown in Table 111.

Table 111: Additional scenario analyses

Model parameter (base case)	Scenario analysis	Results (£) ICER (incremental cost, incremental QALYs)		
		Paediatric cohort	Adolescent cohort	Adult cohort
Base case results	-	[redacted]	[redacted]	[redacted]
Utilities (England AM audit)	Morquio A proxy utility values adjusted for complications using minimum method and age-adjusted	[redacted]	[redacted]	[redacted]
	Trial data for WU and WWA states	[redacted]	[redacted]	[redacted]
Time horizon (Lifetime)	10 years	[redacted]	[redacted]	[redacted]
	20 years	[redacted]	[redacted]	[redacted]
	30 years	[redacted]	[redacted]	[redacted]
	50 years	[redacted]	[redacted]	[redacted]
Patient age (lowest cohort age (6, 12, 18))	rhLAMAN-10 average age (8, 15, 25)	[redacted]	[redacted]	[redacted]
Discount rates for costs and QALYs (1.5%)	0.00%	[redacted]	[redacted]	[redacted]
	3.50%	[redacted]	[redacted]	[redacted]
Discontinuation (13.3% at year 1, 10% annual, and discontinue at severe immobility	No discontinuation at all	[redacted]	[redacted]	[redacted]
	Annual discontinuation of 20%	[redacted]	[redacted]	[redacted]
	Discontinue once in wheelchair	[redacted]	[redacted]	[redacted]
Caregiver disutility (Gani et al, 2008 (109)). SES state has full year disutility	Acaster et al, 2013 (110)	[redacted]	[redacted]	[redacted]
	No caregiver disutility	[redacted]	[redacted]	[redacted]
	Caregiver disutility in SES applied for 4 weeks	[redacted]	[redacted]	[redacted]

Model parameter (base case)	Scenario analysis	Results (£) ICER (incremental cost, incremental QALYs)		
		Paediatric cohort	Adolescent cohort	Adult cohort
VA on-treatment utility increment (0.1)	0			
	0.2			
VA on-treatment utility increment post discontinuation (0.0)	0.01			
	0.05			
Reduction in probability of major surgery in patients on VA (0.0%)	50%			
VA monitoring (included in routine BSC specialist appointment	Monitoring not part of BSC			
Societal costs (not included)	Include personal & caregiver expenditure			
	Include caregiver productivity loss			
	Include both personal & caregiver expenditure and productivity loss			
Ventilation costs from Noyes (2006) study and VA patients assumed to have 50% lower rate of ventilation/24-hour ventilation in WC and SI health states	Double the costs of ventilation			
	Remove the cost of ventilation			
	VA ventilation equal to BSC ventilation			
	No 24-hour care ventilation required for VA patients			

Abbreviations: AM, alpha-mannosidosis; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

12.6 *Subgroup analysis*

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

Individual utilities for health states and patient preference.

Subgroups based solely on differential treatment costs for individuals according to their social characteristics.

Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 *Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.*

Subgroup analysis has not been undertaken. In accordance with the final scope and as summarised in Table 2, subgroup analysis was not considered appropriate given the paucity of evidence and the ultra-rare nature of the condition. Base case economic results have been presented based on three age cohorts:

- Paediatric cohort: 6–11 years
- Adolescent cohort: 12–17 years
- Adult cohort: ≥18 years

This approach it to account for flexibility in model assumptions relating to the effectiveness of velmanase alfa when initiated in patients of a different age, as well the implications of initiating velmanase alfa in an older patient population with greater functional impairment.

12.6.2 *Define the characteristics of patients in the subgroup(s).*

Not applicable.

12.6.3 *Describe how the subgroups were included in the cost-effectiveness analysis.*

Not applicable.

12.6.4 *What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7*

Not applicable.

12.6.5 *Were any subgroups not included in the submission? If so, which ones, and why were they not considered?*

Not applicable.

12.7 *Validation*

12.7.1 *Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.*

Given the paucity of long-term studies both on the natural history of AM and the effectiveness of velmanase alfa on long-term disease progression, it was not possible to cross-validate the outcomes of the economic model to external data sources.

As part of the validation of the economic model, the mean (undiscounted) age at death was assessed for BSC. In the paediatric cohort, patients lived on average until the age of 34 years. [redacted] Therefore, the model estimate of age at death is broadly consistent with the known age of death in England and Wales, given the very few patients who are able to validate this estimate. These findings, which were also validated by UK KOLs, provide some confirmation about the validity of the economic model.

The model underwent internal validation to quality-assure and verify the model calculations. This validation step was undertaken by a senior independent academic health economist. The manual checking of formulae and model code was conducted to verify the model calculations. Additionally, the model write-up and assumptions were critiqued, and the model and report were compared to ensure consistency and accuracy.

The model also underwent a second internal validation. This validation step was undertaken by a colleague of the model development team lead. Two specific tasks were conducted. Firstly, the model was assessed using the Phillips et al, 2004 (129) checklist. Secondly, logic tests were applied to verify the internal calculations and logic in the model. These tests included:

- Changing mortality parameters and checking life years accrued
- Setting both arms (Markov models) equal and checking the results were the same
- Setting utility values to one and checking QALYs were calculated correctly
- Modifying cost parameters and checking the results were logical
- Checking that values entered for a plausible range did not cause any Excel error messages
- Checking that probabilities could not sum above 1, or that warnings were provided in the model when illogical parameters were being used

The model and the report were updated after these validation activities.

12.8 *Interpretation of economic evidence*

12.8.1 *Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

Not applicable as no relevant economic literature was identified in the SR (Section 11).

12.8.2 *Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?*

The cost-effectiveness analysis is aligned with the licensed indication of velmanase alfa.

12.8.3 *What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?*

The modelling approach was deemed the most adequate to reflect the natural history of AM. By choosing a Markov model, the costs, QALYs and clinical effectiveness can be modelled to determine the long-term impact of velmanase alfa. The primary strength of this economic analysis is that the structure and parameterisation of the model has been informed by expert KOL input, enabling the model to account for the multi-morbid and progressive nature of AM. This expert clinical input has been elicited using formal elicitation panel methods, and structured interviews, to maximise the value of their input and to minimise bias. The lack of clinical and economic long-term published evidence for AM means that expert clinical input was crucial in ensuring that the major drivers of costs and outcomes were captured in the model. The model formally accounts for functional impairment, which is a major driver of morbidity in patients with AM. Severe infections and major surgeries are also explicitly modelled as they are also key drivers of both morbidity and mortality.

Clinical trial data are incorporated in the model to account for appropriate, clinically-led discontinuation of velmanase alfa when a patient is demonstrated to be a non-responder. Specifically, patient discontinuation due to non-response at Year 1 is informed by the post-hoc, multi-domain responder analysis from rhLAMAN-05 (Section 9.6.1.3). The discontinuation of velmanase alfa for patients in the severe immobility or short end stage health state is also supported by UK KOL opinion (17). The model also accounts for the chronic nature of the condition by taking a lifetime perspective, and accommodates the entire spectrum of disease states, from ‘walking unassisted’ to ‘severe immobility’ to end stage.

The model is developed with flexibility around major structural and parameter assumptions, and is programmed to allow for the quick and comprehensive running of sensitivity and scenario analyses. These include the ability to incorporate a societal perspective and account for personal/caregiver expenditure and caregiver lost productivity. The model can estimate multi-morbid and age-adjusted utility values based on proxy condition data, and all parameter values can be easily overwritten and then restored to default values.

The model and the data supporting it have several limitations which should be noted. Even with the availability of clinical experts to validate assumptions, extreme difficulties exist when attempting to use standard HTA and modelling approaches in an ultra-orphan condition. This is mainly due to the paucity of data on current clinical practice, the lack of treatment-specific data, and the extremely low patient numbers in the clinical trials, which preclude any form of statistical analysis and extrapolation of outcomes.

Although the model accounts for the major drivers of the disease (as validated by UK KOLs (17)), it is recognised that the model may not fully account for the multi-morbid impact of AM. AM is known to be a very heterogeneous condition and a 'typical patient' for the purpose of modelling may not exist in reality. There are a wide range of clinical features that may be additional drivers of morbidity and/or mortality including (but not limited to) hearing, psychiatric problems, visual impairment, respiratory function, pain, musculoskeletal impairment, learning difficulties, and dental problems. However, developing a model to explicitly account for these with no supporting data is impossible; therefore, a pragmatic model has been developed to account for major drivers reported by clinical experts. Furthermore, the model does not account for 'intra-ambulatory health state' improvements/progression; for example, the cost and/or utility changes that a patient may experience when moving from requiring one aid for walking (e.g. footwear for stability) to requiring multiple aids/assistance for walking.

While the model uses the key UK-EEP to inform many key model parameters, including disease progression, other clinical expert engagements have been via structured teleconference interviews. These are not the ideal format for engaging with KOLs, but were necessary given that there are very few clinicians who have experience of caring for people with AM. Where gaps remained in the model, proxy data from other related or similar conditions has been used, and these have been validated by UK KOLs (17).

Due to the scarcity of evidence, the cost and economic implications of AM have not been fully captured. Minor infections are not fully costed; therefore, any benefit of velmanase alfa in reducing minor infections has not been formally modelled. Similarly, the model does not capture educational attainment and its link to any future productivity benefits. While velmanase alfa is unlikely to provide direct neurological benefits, a child with greater functional capacity may be able to attend school more frequently. This in turn may provide both economic and QoL benefits. 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 large. In addition, the costing of caregiver productivity losses is based on several assumptions and was therefore not included in the base case analysis. Finally, there are potential budget savings outside of the NICE reference case perspective that treatment with velmanase alfa could achieve, including educational budgets, local government budgets, and welfare budgets. These are discussed further in Section 14.2.

12.8.4 *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

Given the paucity of long-term evidence, the highly ultra-rare nature of the condition, and the limited clinical experience of velmanase alfa, the economic model is reliant on

UK KOL expert opinion and assumptions. All assumptions have been tested and validated by clinical experts and (where possible) informed by clinical studies and experiences from relevant proxy conditions. However, the use of clinical expert opinion and assumptions does lead to uncertainty in the model and can limit its usefulness in informing decision-making regarding the cost-effectiveness of velmanase alfa. From the substantial amount of sensitivity analyses conducted, the main uncertainties in the model relate to:

- the long-term disease progression
- the impact of velmanase alfa on delaying and/or halting disease progression
- the impact of velmanase alfa on improving (reversing) the disease
- the quality of life of patients with AM
- the impact of velmanase alfa in changing the clinical management of AM

It is expected that ongoing clinical outcomes studies and the UK MPS Society registry activities will collect and collate evidence over time that will help to address some of these uncertainties. Chiesi are working with the UK MPS Society to conduct a patient/carer survey to gain qualitative and quantitative data on the quality of life (QoL) of patients/carers with AM in the UK, and the financial burden faced by patients/carers (Section 7.2.4). This survey is currently ongoing and additional evidence likely to be available in the next 12 months.

Furthermore, the development of an economic model with a substantial paucity of both clinical and economic evidence places even more emphasis on the importance of conceptual modelling and early engagement with UK KOLs to inform model structures. We have looked to follow published best-practice to ensure the development of a robust conceptual model and economic model. We would recommend that the academic modelling community continue to support the development and acceptance of innovative modelling methods (including expert elicitation) to enable the development and parameterisation of robust economic models for ultra-rare conditions.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 *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.*

[redacted] Together, European studies estimate 0.17 cases per 100,000 births (130-133), resulting in 1.15 new AM cases per year based on 696,271 live births in England and Wales (6). For pragmatism, we have assumed [redacted] new AM case per year as a midpoint estimate. [redacted]

Annual mortality probabilities for paediatrics (0.02%), adolescents (1.35%) and adults (2.17%) are taken from the economic model. The budget impact calculations assume that 13.3% of incident patients will discontinue due to being a non-responder, along with all Year 1 prevalent patients, and all patients will have an annual probability of discontinuing of 10%, as assumed in the economic model. The total numbers of patients eligible for treatment are provided in Table 112, with these numbers of patients presented by each age group in Table 113-Table 115.

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

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

The total number of patients/treated patients is presented in Table 112. It is estimated that in Year 1, five patients will be treated with velmanase alfa, increasing to seven patients in Year 5. Full patient numbers by age group, including the number of treated patients, are provided in Table 113–Table 115.

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

Table 112: Total patient population

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]6	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 113: Paediatric patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	0.00	0.00	0.00	0.00	0.00
Net number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation – non-responder	0.07	0.07	0.07	0.07	0.07
Discontinuation – annual risk	0.28	0.26	0.31	0.36	0.41
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 114: Adolescent patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	0.04	0.04	0.05	0.05	0.05
Net number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation – non-responder	0.01	0.01	0.01	0.01	0.01
Discontinuation – annual risk	0.16	0.12	0.13	0.13	0.14
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 115: Adult patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	0.37	0.37	0.36	0.36	0.35
Net number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation – non-responder	0.00	0.00	0.00	0.00	0.00
Discontinuation – annual risk	0.34	0.25	0.25	0.24	0.24
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

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

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

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

Chiesi are not aware of any other opportunities.

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

It is anticipated that significant savings could accrue for welfare, education and local government budgets. Further details are provided in Section 14.

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

Budget impact calculations for the total, paediatric, adolescent, and adult cohorts are provided in Table 116–Table 119.

These calculations take into account the increase in treatment cost as weight increases in the paediatric and adolescent cohorts. Administration costs follow the assumptions used in the economic model, with an annual cost of £3,411 in the first year (incident population) and £1,110 in subsequent years due to the switch to homecare provision.

The total annual budget impact is £1.3m in Year 1, rising to £1.9m in Year 5. The total cumulative budget impact over 5 years is £7.8m.

Table 116: Budget impact – total cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	£1,285,098	£1,392,156	£1,506,143	£1,718,238	£1,857,992
Administration cost	£4,727	£1,695	£1,796	£1,897	£1,998
Annual budget impact	£1,289,825	£1,393,852	£1,507,939	£1,720,136	£1,859,991
Cumulative budget impact	£1,289,825	£2,683,677	£4,191,616	£5,911,751	£7,771,742

Table 117: Budget impact – paediatric cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	£312,407	£384,424	£446,733	£658,681	£741,727
Administration cost	£1,911	£887	£987	£1,087	£1,186
Annual budget impact	£314,319	£385,311	£447,720	£659,767	£742,913
Cumulative budget impact	£314,319	£699,630	£1,147,350	£1,807,117	£2,550,030

Table 118: Budget impact – adolescent cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	£251,757	£269,344	£330,813	£340,569	£406,652
Administration cost	£924	£290	£298	£306	£313
Annual budget impact	£252,681	£269,634	£331,111	£340,875	£406,965
Cumulative budget impact	£252,681	£522,315	£853,426	£1,194,301	£1,601,266

Table 119: Budget impact – adult cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	£720,946	£738,414	£728,631	£719,059	£709,695
Administration cost	£1,891	£518	£512	£505	£499
Annual budget impact	£722,837	£738,933	£729,142	£719,564	£710,194
Cumulative budget impact	£722,837	£1,461,770	£2,190,912	£2,910,476	£3,620,671

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

Table 120: Total population assuming no discontinuation or mortality

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 121: Budget impact assuming no discontinuation or mortality in the total cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated – incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated – prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment cost	£1,482,748	£1,572,194	£1,722,382	£1,980,808	£2,162,023
Administration cost	£5,455	£1,918	£2,047	£2,175	£2,304
Annual budget impact	£1,488,203	£1,574,112	£1,724,429	£1,982,983	£2,164,327
Cumulative budget impact	£1,488,203	£3,062,315	£4,786,744	£6,769,727	£8,934,054

In this scenario, the total annual budget impact is £1.5m in Year 1, rising to £2.2m in Year 5. The total cumulative budget impact over 5 years is £8.9m.

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

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

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 *Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.*

Alpha-mannosidosis is a devastating condition with a significant mortality and morbidity impact on patients. As a chronic, multi-morbid, and progressive disease, there are benefits to effective treatment that fall beyond simple costs or improved health. While no patient died during the rhLAMAN trial programme, UK KOL opinion suggests that severe infections and major surgeries are associated with a mortality risk in patients with AM and that effective treatment with velmanase alfa may mitigate these risks.

A targeted search was undertaken to identify evidence regarding the wider cost implications for patients, their carers and their families (Appendix 6, Section 17.6.3 and Section 17.6.4). No data were found that were appropriate for inclusion within the base case economic model. However, it is evident from the UK KOL interviews and the case study derived from the UK MPS Society survey (Section 7) that AM has a substantial, albeit unquantifiable, impact on the financial and social wellbeing of patients and carers. For example, due to the severity of the condition, patients with AM are unlikely to ever obtain full-time employment. Additionally, the amount of care required can limit job opportunities for carers and result in out-of-pocket expenses. Therefore, the substantial and long-term impact on families and carers should not be underestimated.

14.2 *List the costs (or cost savings) to government bodies other than the NHS.*

It is anticipated that treatment with velmanase alfa may result in significant cost savings to the government. Due to the complexity of benefits, support and government services that are potentially available for a person (and their family) with AM, it is not possible to detail every specific area. Furthermore, the uptake of benefits and support will be highly variable due to means testing, awareness of what is available, and geography. It is anticipated that there are three broad ways in which government budgets will be affected:

1. Education benefits – a child with AM will have special educational needs that will require the funding of support, assistance and adaptations to enable the child to receive an education. A child who benefits from velmanase alfa may require reduced educational support.

2. Local government budgets – home adaptations via Disabled Facilities Grant payments may be reduced or postponed due to the benefit of velmanase alfa. These grants cover adaptations such as widening doors and installing ramps, modifying bathrooms and heating, and installing a stair lift. A patient who has a functional improvement or stabilisation may postpone or reduce these home adaptations. Local councils also provide direct payments to enable a patient (or their family) to buy in and arrange care rather than receiving care directly from social services. Patients (or their family) on low income may be entitled to housing benefits and council tax reductions. A patient benefiting from velmanase alfa may not require as many additional local council benefits, and their families may be able to achieve or maintain a higher level of employment.

3. Welfare budgets – central government welfare includes disability and sickness benefits (disability living allowance (DLA) or personal independence payment (PIP), attendance allowances, employment and support allowances, vehicle tax exemption, parking benefits and travel/transport benefits). A patient benefiting from velmanase alfa may not require as many of these benefits. Furthermore, the family of a patient may be able to maintain a higher level of employment which will have income tax benefits.

14.3 *List the costs borne by patients that are not reimbursed by the NHS.*

A targeted search was undertaken to identify evidence regarding the wider cost implications for patients, their carers and their families (Appendix 6, Section 17.6.3 and Section 17.6.4). No data were found that were appropriate for inclusion within the base case model. Chiesi anticipate that patients with AM and their families will require the following out of pocket expenses:

- Modifications to their homes – many will pay out of pocket due to the delays in accessing government benefits and grants
- Modifications to a car, or buying a disabled-accessible vehicle
- Electric wheelchairs, which are not routinely funded by the NHS and enable a patient to maintain social interactions and activities of daily living
- Specialist equipment to aid mobility (sticks, leg braces, orthopaedic boots/footwear for stability etc.)
- Travel costs to and from hospital and specialist schools. Parking charges and subsistence
- Additional time off work
- Private healthcare in an effort to expedite access to specialists
- Private carers and specialist childminders/respite providers

- Paying a ‘top up’ where grant payments are insufficient
- Private tuition, physiotherapy, hydrotherapy, counselling

Some of these costs are discussed in the patient and carer interview detailed in Section 7.2.4.2. A Family Fund study reported that families with a severely disabled child will have a low average income compared with families without a severely disabled child, and that these families will have significant additional expenditure (127). Often families cannot afford to meet these additional needs (estimated at over £5,000 per year [2004 prices]) and usually resort to using various forms of credit (127).

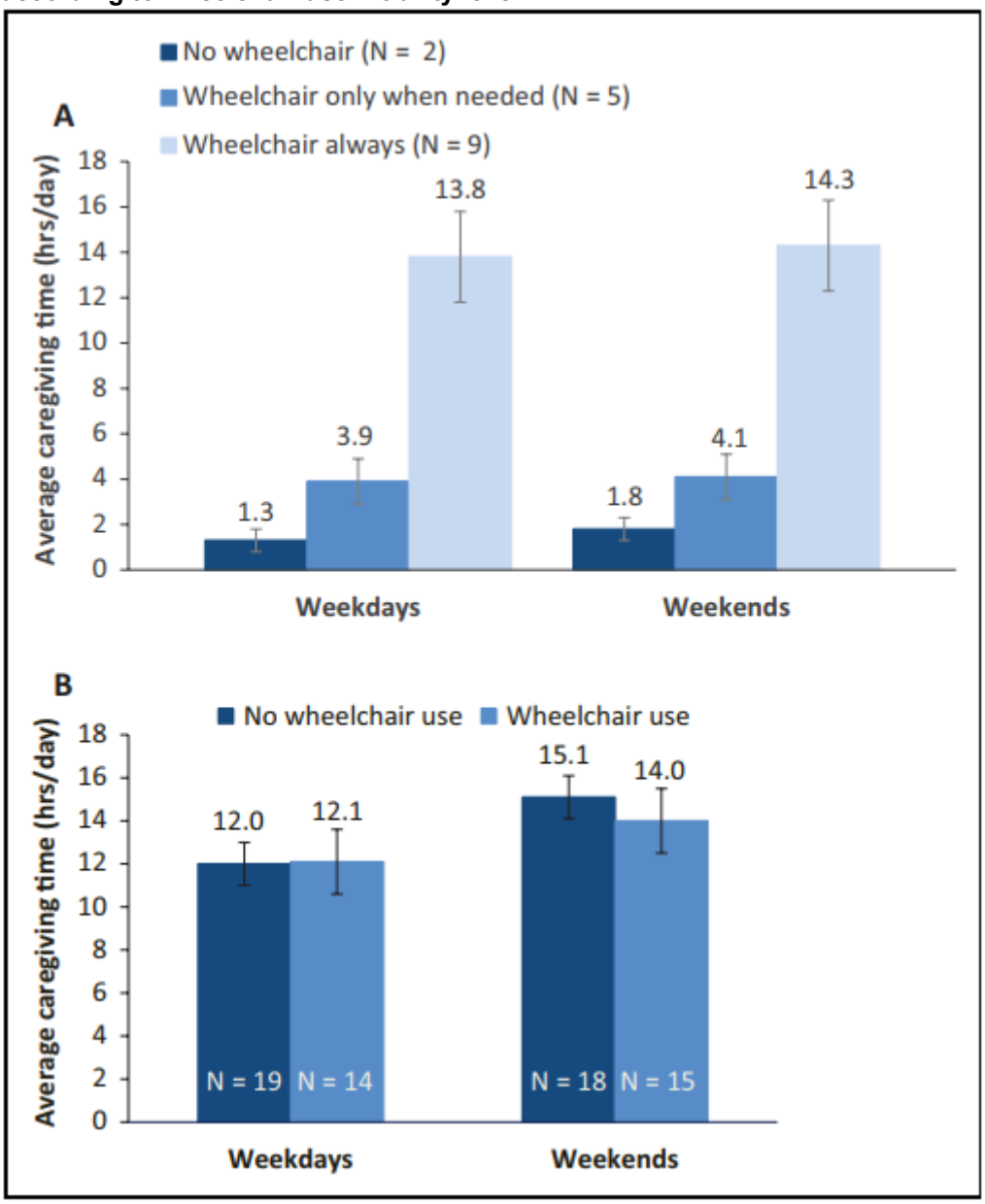
14.4 *Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.*

As reported in Section 14.3, a targeted review was conducted to identify evidence regarding the wider cost implications (including carer time) of AM and that no data were found that were appropriate for inclusion within the base case model. Two papers by Hendriksz et al, report an international survey to evaluate the global burden amongst patients and primary caregivers of patients with MPS IVA (112, 134). It is believed that the burden of AM is at least as severe as caring for a person with MPS IVA; therefore, this study represents a suitable proxy and the results are used in a model sensitivity analysis. The outcomes collected included self-reported time spent on caregiving, the proportion of daily activities requiring caregiver assistance, and how these were affected by age and wheelchair use. In addition, the survey evaluated the impact on caregiving on relationships, physical and mental health, employment status and income. A total of 56 caregivers completed the survey. Two thirds (N=37) cared for a child with MPS IVA, and one third (N=19) for an adult. The results showed that adult patients who were wheelchair dependent required substantially more caregiving time than patients who were more mobile.

In adults, patients who always used a wheelchair required more care time than the other patients. In total, 13.8 and 14.3 hours a day of care were given to an adult who always used a wheelchair on weekdays and weekends, respectively. In contrast, when the wheelchair was used only when needed, only 3.9 and 4.1 hours of care were provided on weekdays and weekends, respectively (Figure 39, Part A). Furthermore, the amount of caregiver time was 1.3 hours on weekdays and 1.8 hours on weekend days for adult patients who did not use a wheelchair. For children, the number of caregiver hours ranged from 12.0 to 15.1 hours depending on the day of the week and if a wheelchair was used (Figure 39, Part B).

The broader impact and burden on caregivers has been described in Section 7.

Figure 39: Mean number of caregiving hours/day on weekdays and weekends for adults (A) and children (B) with Morquio A syndrome, according to wheelchair use/mobility level



Source: Hendriksz et al, 2014 (134). Figure reproduced under the terms of the Creative Commons Attributions 3.0 License.

14.5 *Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.*

Velmanase alfa is the first pharmacological disease-modifying treatment for AM and has been extensively studied in the rhLAMAN clinical development programme (Section 9.4–9.9.5). In addition to the efficacy and safety demonstrated across the clinical trials, the impact (both proven and potential) has been recognised by KOLs in the UK and Europe (Section 7.2). The positioning of velmanase alfa also recognises

the high unmet need for patients ≥6 years, as evidence of clinical intervention is limited in this population.

The long-term efficacy and safety of velmanase alfa will continue to be monitored and assessed in the after-trial studies, rhLAMAN-07 and rhLAMAN-09 (Section 4 and 9.4). A new trial (NCT02998879) investigating the efficacy and safety of velmanase alfa in patients aged <6 years is also ongoing (currently recruiting).

14.6 *Describe the anticipated impact of the technology on innovation in the UK.*

Velmanase alfa is the first pharmacological disease-modifying therapy for patients with AM and represents a step change in clinical management of AM in the UK on the basis of its ability (both proven and potential) to change the natural course of the disease (17).

In addition to the clinical management of disease, the clinical and economic evidence generation programme has provided further innovation to the UK. Conducting robust and informative research in such a small population provides a signal to the UK Life Sciences industry that pursuing research in ultra-rare conditions is possible. It is anticipated that the clinical development programme for velmanase alfa, and its subsequent reimbursement and use in the NHS, could position the UK as a world-leader for rare disease research and investment. It is also anticipated that the use of velmanase alfa will lead to greater understanding of the epidemiology, pathology, and management of rare LSDs. The rhLAMAN clinical development programme is a global collaboration between clinicians, industry and patients, and the UK has been a key participant within the programme and associated evidence generation activities, including KOL interviews, elicitation panel exercises, and the development of an economic model.

14.7 *Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.*

The clinical effectiveness of velmanase alfa will continue to be assessed over the next 5 years in the after-trial studies (rhLAMAN-07 and rhLAMAN-09, see Section 4 and 9.4) and a new trial (NCT02998879, see Section 14.5). A patient registry is planned (unlimited duration with 15 years follow up) as part of the EMA authorisation procedure.

Chiesi are actively collaborating with the UK MPS Society, who operate a patient registry for AM. The effectiveness of velmanase alfa has been captured through a patient-carer survey, which is going at the time of this submission (Section 7.2.4.2). It is anticipated that following the reimbursement and use of velmanase alfa within the NHS, Chiesi will continue to work with the UK MPS Society, and other key stakeholder groups, in order evaluate the long-term effectiveness and safety of velmanase alfa.

14.8 *Describe any plans on how the clinical effectiveness of the technology will be reviewed.*

In order to provide guidance on the appropriate management of patients treated with velmanase alfa, Chiesi have developed a start-stop criteria, in which the clinical effectiveness of the treatment is reviewed (Section 10.1.16). It should be noted that Chiesi are currently in discussion with UK KOLs on the suitability and/or generalisability of these criteria to UK clinical practice; therefore, the details provide on the treatment continuation rules may be subject to further change.

In addition, it is anticipated that Chiesi will continue to work with the UK MPS Society in order to evaluate the long-term effectiveness and safety of velmanase alfa.

14.9 *What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?*

As detailed in Section 8.2.2, patients with LSDs (including AM) are managed at designated LSD specialist centres in Birmingham (one adult centre and one paediatric centre), Cambridge (one adult centre), London (two adult centres and one paediatric centre), and Manchester (one adult centre and one paediatric centre). As shown in Figure 2, these designated LSD specialist centres are responsible for the assessment of patients and the initiation and monitoring of treatments. These centres will have experience of administering ERTs via infusion for other LSDs; therefore, if any training is required for the administration of velmanase alfa, Chiesi expect this to be very minimal.

One of the four national LSD specialist centres (Manchester) was a site for the rhLAMAN clinical programme and has, therefore, recent experience of administering velmanase alfa.

14.10 *Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?*

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

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

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

Discussions are currently ongoing between Chiesi and relevant UK stakeholders (clinicians, patient-society groups and commissioners) about the suitability of a managed access agreement or alternative arrangements, such as the stop-start criteria outlined in Section 10.1.16.

15.2 *Describe the specifics of the MAA proposal, including:*

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

N/A

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

N/A

16 References

1. Chiesi Farmaceutici S.p.A. Clinical Study Report – rhLAMAN-10. A single center, open label clinical trial investigating the long-term efficacy of rhLAMAN-(recombinant human alpha-mannosidase or Lamazym) treatment in subjects with alpha-mannosidosis who previously participated in Lamazym trials. 2016.
2. Malm D, Nilssen O. Alpha-mannosidosis. Orphanet J Rare Dis. 2008 Jul 23;3:21.
3. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999 Jan 20;281(3):249-54.
4. MPS society. Data on file: MPS Society Registry – registered patients in England. 2017.
5. Borgwardt L, Lund AM, Dali CI. Alpha-mannosidosis - a review of genetic, clinical findings and options of treatment. Pediatr Endocrinol Rev. 2014 Sep;12 Suppl 1:185-91.
6. Sun H, Wolfe JH. Recent progress in lysosomal alpha-mannosidase and its deficiency. Exp Mol Med. 2001 Mar 31;33(1):1-7.
7. Malm D, Nilssen O. Alpha-Mannosidosis. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews(R). Seattle (WA); 2001 [Updated 2012].
8. MPS society. Guide to Understanding Alpha Mannosidosis. Available from: http://www.mpssociety.org.uk/wp-content/uploads/2016/07/guide-alphamannosidosis-2013.pdf Accessed: March 2017. 2013.
9. Borgwardt L, Danielsen ER, Thomsen C, Mansson JE, Taouatas N, Thuesen AM, et al. Alpha-mannosidosis: characterization of CNS pathology and correlation between CNS pathology and cognitive function. Clin Genet. 2015 Jul 23.
10. Malm D, Riise Stensland HM, Edvardsen O, Nilssen O. The natural course and complications of alpha-mannosidosis--a retrospective and descriptive study. J Inherit Metab Dis. 2014 Jan;37(1):79-82.
11. University of Tromsø and the University Hospital of North Norway. Alpha-mannosidosis Mutation Database. Available at: https://apex.jupiter.no/apex/f?p=101:1:::::: Accessed: March 2017. 2016.
12. 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 Jun 20;8:88.
13. The International Advocate for Glycoprotein Storage Diseases. Alpha Mannosidosis Fact Sheet. Available at: http://www.ismrd.org/glycoprotein_diseases/alpha_mannosidosis/fact_sheet (Accessed: August 2017).
14. Chiesi Farmaceutici S.p.A. Data on file: Velmanase alfa: clinical trial KOL interviews. 2017.
15. Malm D, Pantel J, Linaker OM. Psychiatric symptoms in alpha-mannosidosis. J Intellect Disabil Res. 2005 Nov;49(Pt 11):865-71.
16. Borgwardt L, Thuesen AM, Olsen KJ, Fogh J, Dali CI, Lund AM. Cognitive profile and activities of daily living: 35 patients with alpha-mannosidosis. J Inherit Metab Dis. 2015 Nov;38(6):1119-27.
17. Chiesi Farmaceutici S.p.A. Data on file: UK key opinion leader interviews. 2017.
18. Chiesi Farmaceutici S.p.A. Chiesi Advisory Board – Saturday 28th January 2017. Enzyme replacement therapy for alpha mannosidosis. 2017.
19. Chiesi Farmaceutici S.p.A. Clinical Study Report – rhLAMAN-02. A single center, open-label, dose escalation study of the safety and pharmacokinetics

of rhLAMAN (recombinant human alpha-mannosidase or Lamazym) for the treatment of patients with alpha-mannosidosis. 2015.
20. Chiesi Farmaceutici S.p.A. Clinical Study Report – rhLAMAN-03. A single center, randomized, open-label, multiple-dose study of the efficacy and long-term safety of rhLAMAN (recombinant human alpha-mannosidase or Lamazym) for the treatment of patients with alpha-mannosidosis. 2015.
21. Chiesi Farmaceutici S.p.A. Clinical Study Report – rhLAMAN-04. A multi-center, open-label trial of the long-term efficacy and safety of Lamazym for the treatment of patients with alpha-Mannosidosis. 2014.
22. Chiesi Farmaceutici S.p.A. Clinical Study Report – rhLAMAN-05. A multi-centre, double-blind, randomized, placebo-controlled, parallel group trial, investigating the efficacy and safety of repeated Lamazym treatment of subjects with alpha-mannosidosis. 2016.
23. Chiesi Farmaceutici S.p.A. Data on file: clinical question 137. 2017.
24. Berg T, King B, Meikle PJ, Nilssen O, Tollersrud OK, Hopwood JJ. Purification and characterization of recombinant human lysosomal alpha-mannosidase. Mol Genet Metab. 2001 May;73(1):18-29.
25. Tollersrud OK, Berg T, Healy P, Evjen G, Ramachandran U, Nilssen O. Purification of bovine lysosomal alpha-mannosidase, characterization of its gene and determination of two mutations that cause alpha-mannosidosis. Eur J Biochem. 1997 Jun 01;246(2):410-9.
26. Crawley AC, Walkley SU. Developmental analysis of CNS pathology in the lysosomal storage disease alpha-mannosidosis. J Neuropathol Exp Neurol. 2007 Aug;66(8):687-97.
27. Blanz J, Stroobants S, Lullmann-Rauch R, Morelle W, Ludemann M, D'Hooge R, et al. Reversal of peripheral and central neural storage and ataxia after recombinant enzyme replacement therapy in alpha-mannosidosis mice. Hum Mol Genet. 2008 Nov 15;17(22):3437-45.
28. National Federation of Voluntary Bodies. Quality of life of young people with an intellectual disability in Ireland. Interim Report: Available at: http://www.fedvol.ie/home/Default.aspx?id=30&search=interim%20report Accessed: March 2017. 2003.
29. Borgwardt L, Stensland HM, Olsen KJ, Wibrand F, Klenow HB, Beck M, et al. Alpha-mannosidosis: correlation between phenotype, genotype and mutant MAN2B1 subcellular localisation. Orphanet J Rare Dis. 2015 Jun 06;10:70.
30. Michalski JC, Klein A. Glycoprotein lysosomal storage disorders: alpha- and beta-mannosidosis, fucosidosis and alpha-N-acetylgalactosaminidase deficiency. Biochim Biophys Acta. 1999 Oct 08;1455(2-3):69-84.
31. Zanetta JPB, R.; Maschke, S.; Strecker, G.; Michalski, J. C. Hypothesis: immunodeficiencies in a-mannosidosis, mycosis, AIDS and cancer—a common mechanism of inhibition of the function of the lectin interleukin 2 by oligomannosides. Glycobiology. 1998;8(3):vi-x.
32. Borgwardt LL, AM; De Meirleir, L; Amraoui, Y; Andersen, O; Dolhem, P; Campos, M. G; Guffon, N; Héron, B; Jameson, E; Jones, S. A. Improvement in pulmonary function and serum immunoglobulin G in long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase) in alpha-mannosidosis patients. Molecular Genetics and Metabolism. 2017;120(1):S29.
33. Malm D, Halvorsen DS, Tranebjaerg L, Sjursen H. Immunodeficiency in alpha-mannosidosis: a matched case-control study on immunoglobulins, complement factors, receptor density, phagocytosis and intracellular killing in leucocytes. Eur J Pediatr. 2000 Sep;159(9):699-703.
34. Chiesi Farmaceutici S.p.A. Data on file: PAREXEL International. Research report Europe. Part A – Patient Concerns. 2016.

35. MPS society. Our main achievements. . Available at: http://www.mpssociety.org.uk/about/our-main-achievements/ (Accessed: August 2017).
36. White-Koning M, Arnaud C, Bourdet-Loubere S, Bazex H, Colver A, Grandjean H. Subjective quality of life in children with intellectual impairment--how can it be assessed? Dev Med Child Neurol. 2005 Apr;47(4):281-5.
37. Genetic Alliance UK. The hidden costs of rare diseases: a feasibility study. Available at: http://www.geneticalliance.org.uk/media/2502/hidden-costs-full-report_21916-v2-1.pdf Accessed: March 2017. 2016.
38. Polz MG, J. α-Mannosidosis – long-term examination of a rare storage disorder. Monatsschr Kinderheilkd. 2001;149:576-8.
39. MPS society. Data on file: MPS Society patient and carer survey. 2017.
40. NHS. 2013/14 NHS standard contract for lysosomal storage disorders service (children and adults). Available at: https://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf (Accessed: December 2017).
41. NHS. NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children). October 2017. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf (Accessed: December 2017).
42. UK BMT Group. Indications for HSCT in Children. Available at: http://bsbmt.org/wp-content/uploads/2015/10/UK-Paed-BMT-Gp-HSCT_Indications_15Oct2015.pdf (Accessed: May 2017). 2015.
43. Parkinson-Lawrence EJ, Shandala T, Prodoehl M, Plew R, Borlace GN, Brooks DA. Lysosomal storage disease: revealing lysosomal function and physiology. Physiology (Bethesda). 2010 Apr;25(2):102-15.
44. Broomfield AA, Chakrapani A, Wraith JE. The effects of early and late bone marrow transplantation in siblings with alpha-mannosidosis. Is early haematopoietic cell transplantation the preferred treatment option? J Inherit Metab Dis. 2010 Dec;33 Suppl 3:S123-7.
45. Bembi B, Zanatta M, Carrozzi M, Baralle F, Gornati R, Berra B, et al. Enzyme replacement treatment in type 1 and type 3 Gaucher's disease. Lancet. 1994 Dec 17;344(8938):1679-82.
46. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. N Engl J Med. 2001 Jul 05;345(1):9-16.
47. Giugliani R, Hwu WL, Tylki-Szymanska A, Whiteman DA, Pano A. A multicenter, open-label study evaluating safety and clinical outcomes in children (1.4-7.5 years) with Hunter syndrome receiving idursulfase enzyme replacement therapy. Genet Med. 2014 Jun;16(6):435-41.
48. Harmatz P, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda MC, et al. Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: Final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase. Mol Genet Metab. 2008 Aug;94(4):469-75.
49. Hendriksz CJ, Burton B, Fleming TR, Harmatz P, Hughes D, Jones SA, et al. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. J Inherit Metab Dis. 2014 Nov;37(6):979-90.
50. Jameson E, Jones S, Wraith JE. Enzyme replacement therapy with laronidase (Aldurazyme((R))) for treating mucopolysaccharidosis type I. Cochrane Database Syst Rev. 2013 Nov 21(11):CD009354.

51. Winkel LP, Van den Hout JM, Kamphoven JH, Disseldorp JA, Remmerswaal M, Arts WF, et al. Enzyme replacement therapy in late-onset Pompe's disease: a three-year follow-up. Ann Neurol. 2004 Apr;55(4):495-502.
52. Chiesi Farmaceutici S.p.A. Data on file: Velmanase alfa. Summary of product characteristics.
53. Borgwardt L, Dali CI, Fogh J, Mansson JE, Olsen KJ, Beck HC, et al. Enzyme replacement therapy for alpha-mannosidosis: 12 months follow-up of a single centre, randomised, multiple dose study. J Inherit Metab Dis. 2013 Nov;36(6):1015-24.
54. Borgwardt LD, C.I.; Fogh, J.; Mansson, J.E.; Olsen, K.J.; Beck, H.C.; . Enzyme replacement therapy in children and adolescents with α-mannosidosis: An 18-month follow-up. Journal of Inborn Errors of Metabolism and Screening. 2014;2:93-4.
55. Guffon N, ; Amraoui, Y.; Cattaneo, F.; Ardigo, D.; Geraci, S.; Gil-Campos, M,; de Meirleir, L.; Van Den Hout, H.; Jones, S.; Lund, A.M.; Borgwardt, L. Improvements in Endurance, Serum Immunoglobulin G Levels, and Quality of Life in Alpha-Mannosidosis Patients Switching From Placebo to Velmanase Alfa Long-Term Enzyme Replacement Therapy. 13th ICIEM. Abstract: 806. 2017.
56. Borgwardt L, Lund AM, Amraoui Y, Andersen O, De Meirleir L, Dolhem P, et al. Long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase) slows disease progression in adult patients suffering from alpha-mannosidosis. Molecular Genetics and Metabolism. 2017;120(1):S30.
57. Borgwardt L, Lund AM, Amraoui Y, Andersen O, De Meirleir L, Dolhem P, et al. Improvement in fine and gross motor proficiency after long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha mannosidase) in alpha-mannosidosis patients. Molecular Genetics and Metabolism. 2017;120(1):S29-S30.
58. Lund AM, Borgwardt L, Amraoui Y, Andersen O, De Meirleir L, Dolhem P, et al. Long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase) improves mobility in alpha-mannosidosis patients. Molecular Genetics and Metabolism. 2017;120(1):S88-S9.
59. Harmatz PC, F.; Ardigo, D.; Geraci, S.; Lund, A.M.; Borgwardt, L. . Toward establishment of a minimal clinically important difference in the treatment of alpha- mannosidosis: first results from velmanase alfa (human recombinant alpha-mannosidase) development program. . 13th ICIEM. Abstract: 804. 2017.
60. Borgwardt LG, N.; Amraoui, Y.; De Meirleir, L.; Campos, M.G. . Impact of Anti-Drug Antibodies (ADA) on safety and efficacy of velmanase alfa (human recombinant alpha-mannosidase) long-term enzyme replacement therapy in patients with alpha-mannosidosis. . 13th ICIEM. Abstract: 805. 2017.
61. Cattaneo FB, L.; Dali, C.; Szymanska, A.T.; Wijburg, F. . Quality of life and activities of daily living in alpha-mannosidosis: Long-term data of enzyme replacement therapy with velmanase alfa (human recombinant alpha mannosidase). . Journal of Inborn Errors of Metabolism & Screening. 2016;4:60-1.
62. Ardigo DB, L.; Dali, C.; Campos, G. Guffon, N. . Enzyme replacement therapy for alpha-mannosidosis: long-term safety data in patients treated with velmanase alfa (recombinant human alpha mannosidase). Journal of Inborn Errors of Metabolism & Screening. 2016;4:47-8.
63. Borgwardt LC, F. Dali, C. Amraoui, Y. Andersen, O. . Long-term follow-up of patients treated with velmanase alfa (recombinant human alpha-mannosidase): a comprehensive evaluation of efficacy of enzyme

replacement therapy in alpha mannosidosis. . Journal of Inborn Errors of Metabolism & Screening. 2016;4:48-9.
64. Furst DE. Serum immunoglobulins and risk of infection: how low can you go? Semin Arthritis Rheum. 2009 Aug;39(1):18-29.
65. Sewell WA, Kerr J, Behr-Gross ME, Peter HH, Kreuth Ig Working G. European consensus proposal for immunoglobulin therapies. Eur J Immunol. 2014 Aug;44(8):2207-14.
66. Harmatz P, Ketteridge D, Giugliani R, Guffon N, Teles EL, Miranda MC, et al. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. Pediatrics. 2005 Jun;115(6):e681-9.
67. Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, et al. The 6-Minute Walk Test and Person-Reported Outcomes in Boys with Duchenne Muscular Dystrophy and Typically Developing Controls: Longitudinal Comparisons and Clinically-Meaningful Changes Over One Year. PLoS Curr. 2013 Jul 08;5.
68. European Medicines Agency. Vimizim® (elosulfase alfa) European Public Assessment Report. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002779/WC500169242.pdf. Accessed: December 2017.
69. Nightingale EJ, Pourkazemi F, Hiller CE. Systematic review of timed stair tests. J Rehabil Res Dev. 2014;51(3):335-50.
70. Bolton JW, Weiman DS, Haynes JL, Hornung CA, Olsen GN, Almond CH. Stair climbing as an indicator of pulmonary function. Chest. 1987 Nov;92(5):783-8.
71. Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest. 1992 Dec;102(6):1774-9.
72. American Thoracic Society.; Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 01;166(1):111-7.
73. Chiesi Farmaceutici S.p.A. Instructions to the Three-Minute Stair Climb Test.
74. Chiesi Farmaceutici S.p.A. Six-Minute Walk Test.
75. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008 Feb 01;177(3):253-60.
76. Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. Eur Respir J. 2010 Jul;36(1):12-9.
77. Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, et al. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. Am J Respir Crit Care Med. 2009 Sep 15;180(6):547-52.
78. Klepper SE. Measures of pediatric function: Child Health Assessment Questionnaire (C-HAQ), Juvenile Arthritis Functional Assessment Scale (JAFAS), Pediatric Outcomes Data Collection Instrument (PODCI), and Activities Scale for Kids (ASK). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S371-82.
79. van Reenen MJ, B. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument. Available from: http://www.euroqol.org/eq-5d-publications/user-guides.html Accessed: March 2017. 2015.

80. Arends M, Hollak CE, Biegstraaten M. Quality of life in patients with Fabry disease: a systematic review of the literature. Orphanet J Rare Dis. 2015 Jun 16;10:77.
81. Cairney J, Schmidt LA, Veldhuizen S, Kurdyak P, Hay J, Faught BE. Left-handedness and developmental coordination disorder. Can J Psychiatry. 2008 Oct;53(10):696-9.
82. Wuang YP, Su CY. Reliability and responsiveness of the Bruininks-Oseretsky Test of Motor Proficiency-Second Edition in children with intellectual disability. Res Dev Disabil. 2009 Sep-Oct;30(5):847-55.
83. Wuang YP, Wang CC, Huang MH, Su CY. Profiles and cognitive predictors of motor functions among early school-age children with mild intellectual disabilities. J Intellect Disabil Res. 2008 Dec;52(12):1048-60.
84. Mazzone E, Martinelli D, Berardinelli A, Messina S, D'Amico A, Vasco G, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2010 Nov;20(11):712-6.
85. Harmatz PW, C.B.; Wang, R.Y.; Bauer, M.; Song, W.; Chesler, S.; Schwartz, E.; Haller, C.; Kakkis, E. A novel, randomized, placebo-controlled, blind-start, single-crossover phase 3 study to assess the efficacy and safety of UX003 (rhGUS) enzyme replacement therapy in patients with MPS VII. . Molecular Genetics and Metabolism. 2017 120(1):S63.
86. Cook CE. Clinimetrics Corner: The Minimal Clinically Important Change Score (MCID): A Necessary Pretense. J Man Manip Ther. 2008;16(4):E82-3.
87. Enright PL. The six-minute walk test. Respir Care. 2003 Aug;48(8):783-5.
88. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD. 2005 Mar;2(1):125-9.
89. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012 Sep 01;186(5):428-33.
90. Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. Cardiopulm Phys Ther J. 2013 Sep;24(3):21-9.
91. McDonald CM, Henricson EK, Abresch RT, Florence J, Eagle M, Gappmaier E, et al. The 6-minute walk test and other clinical endpoints in duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. Muscle Nerve. 2013 Sep;48(3):357-68.
92. Lachmann R, Schoser B. The clinical relevance of outcomes used in late-onset Pompe disease: can we do better? Orphanet J Rare Dis. 2013 Oct 12;8:160.
93. Wells AU, Behr J, Silver R. Outcome measures in the lung. Rheumatology (Oxford). 2008 Oct;47 Suppl 5:v48-50.
94. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011 Dec 15;184(12):1382-9.
95. Dempster H, Porepa M, Young N, Feldman BM. The clinical meaning of functional outcome scores in children with juvenile arthritis. Arthritis Rheum. 2001 Aug;44(8):1768-74.
96. 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 Oct 15;47(5):501-5.
97. Hendriksz CJ, Parini R, AlSayed MD, Raiman J, Giugliani R, Solano Villarreal ML, et al. Long-term endurance and safety of elosulfase alfa enzyme

replacement therapy in patients with Morquio A syndrome. Mol Genet Metab. 2016 Sep;119(1-2):131-43.
98. Cassidy JT, Nordby GL, Dodge HJ. Biologic variation of human serum immunoglobulin concentrations: sex-age specific effects. J Chronic Dis. 1974 Dec;27(11-12):507-16.
99. Phillips DR, I.; Cattaneo, F. Evaluating Health-Related Quality of Life, Disability, and Pain in Alpha-Mannosidosis: long-term data using the EQ-5D-5L and CHAQ to measure the efficacy of velmanase alfa. [in preparation]. 2017.
100. Chiesi Farmaceutici S.p.A. Data on file: age subgroup analysis. 2017.
101. Boudes PF. Clinical studies in lysosomal storage diseases: Past, present, and future. Rare Dis. 2013;1:e26690.
102. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. Eur Respir Rev. 2013 Dec;22(130):487-94.
103. Burton BK, Berger KI, Lewis GD, Tarnopolsky M, Treadwell M, Mitchell JJ, et al. Safety and physiological effects of two different doses of elosulfase alfa in patients with morquio a syndrome: A randomized, double-blind, pilot study. Am J Med Genet A. 2015 Oct;167A(10):2272-81.
104. Noll RB, Kulkarni R, Netzloff ML. Follow-up of language and cognitive development in patients with mannosidosis. Arch Neurol. 1986 Feb;43(2):157-9.
105. Noll RB, Netzloff ML, Kulkarni R. Long-term follow-up of biochemical and cognitive functioning in patients with mannosidosis. Arch Neurol. 1989 May;46(5):507-9.
106. White MKD, J.E.; Gan, C.; Mnkandla, S.; Camero, I.; Batzios, S.; Chakrapani, A.; Footitt, E.; Gissen, P.; Grunewald, S.; Cleary, M.A. G388(P) Enzyme replacement therapy infusion related reactions: a large single-centre review of children with lysosomal storage disorders. Archives of Disease in Childhood. 2017;102:A152-A3.
107. Drabinski AW, G.; Formica, C. . Observational evaluation of health state utilities among a cohort of sepsis patients. . Value in Health. 2001;4(2):128-9.
108. BioMarin Europe Ltd. Highly Specialised Technologies Evaluation Programme. Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA [ID744]. Submission of evidence by BioMarin Europe Limited. Available at: https://www.nice.org.uk/guidance/hst2 (Accessed: November 2017). 2014.
109. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. Pharmacoeconomics. 2008;26(7):617-27.
110. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. BMC Health Serv Res. 2013 Sep 09;13:346.
111. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010 Aug;13(5):509-18.
112. Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. Orphanet J Rare Dis. 2014 Mar 07;9:32.
113. Kanters TA, Redekop WK, Kruijshaar ME, van der Ploeg AT, Rutten-van Molken MP, Hakkaart L. Comparison of EQ-5D and SF-6D utilities in Pompe disease. Qual Life Res. 2015 Apr;24(4):837-44.
114. Currie CJ, Poole CD, Woehl A, Morgan CL, Cawley S, Rousculp MD, et al. The health-related utility and health-related quality of life of hospital-treated

subjects with type 1 or type 2 diabetes with particular reference to differing severity of peripheral neuropathy. Diabetologia. 2006 Oct;49(10):2272-80.
115. Jonsson L, Andreasen N, Kilander L, Soininen H, Waldemar G, Nygaard H, et al. Patient- and proxy-reported utility in Alzheimer disease using the EuroQoL. Alzheimer Dis Assoc Disord. 2006 Jan-Mar;20(1):49-55.
116. Colquitt JL, Jones J, Harris P, Loveman E, Bird A, Clegg AJ, et al. Bone-anchored hearing aids (BAHAs) for people who are bilaterally deaf: a systematic review and economic evaluation. Health Technol Assess. 2011 Jul;15(26):1-200, iii-iv.
117. Chiesi Farmaceutici S.p.A. Data on file: UK Expert Elicitation Panel. 2017.
118. National institute for Health and Care Excellence. NICE Guide to the methods of technology appraisal. Available at: https://www.nice.org.uk/guidance/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (Accessed: November 2017). 2013.
119. Royal College of Paediatrics and Child Health. School age charts and resources. Available at: http://www.rcpch.ac.uk/child-health/research-projects/uk-who-growth-charts/uk-growth-chart-resources-2-18-years/school-age#2-18 (Accessed: August 2017).
120. Oakley JOH, A. . SHELF: The Sheffield Elicitation Framework (version 3.0). Available from: http://tonyohagan.co.uk/shelf. (Accessed Nov 2017). Sheffield, UK: School of Mathematics and Statistics, University of Sheffield, UK, 2016 [updated October 2016; cited].
121. Morris DEO, J.E.; Crowe, J.A. A web-based tool for eliciting probability distributions from experts. Environmental Modelling & Software. 2014;52:1-4.
122. Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. Pediatrics. 2012 Aug;130(2):e273-80.
123. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis. 2012 Dec;12(12):919-24.
124. Department of Health. NHS reference costs 2015-16. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 (Accessed: August 2017).
125. Curtis LB, A. PSSRU. Unit Costs of Health & Social Care. 2016.
126. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. Health Soc Care Community. 2006 Nov;14(6):508-22.
127. Woolley M. Income and expenditure of families with a severely disabled child. York: Family Fund. Available at: http://www.communityequipment.org.uk/wp-content/uploads/How_do_they_manage11.pdf (Accessed: December 2017). 2004.
128. Rowland C, Hanratty B, Pilling M, van den Berg B, Grande G. The contributions of family care-givers at end of life: A national post-bereavement census survey of cancer carers' hours of care and expenditures. Palliat Med. 2017 Apr;31(4):346-55.
129. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004 Sep;8(36):iii-iv, ix-xi, 1-158.
130. Hult M, Darin N, von Dobeln U, Mansson JE. Epidemiology of lysosomal storage diseases in Sweden. Acta Paediatr. 2014 Dec;103(12):1258-63.

131. Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, et al. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet. 2004 Feb;12(2):87-92.
132. Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet. 1999 Jul-Aug;105(1-2):151-6.
133. Poupetova H, Ledvinova J, Berna L, Dvorakova L, Kozich V, Elleder M. The birth prevalence of lysosomal storage disorders in the Czech Republic: comparison with data in different populations. J Inherit Metab Dis. 2010 Aug;33(4):387-96.
134. Hendriksz CJL, C.; Coker, M.; Ucar, S.K.; Jain, M.; Bell, L.; Lampe, C. The Burden Endured by Caregivers of Patients With Morquio A Syndrome: Results From an International Patient-Reported Outcomes Survey. Journal of Inborn Errors of Metabolism & Screening. 2014:1-8.
135. Avenarius DF, Svendsen JS, Malm D. Proton nuclear magnetic resonance spectroscopic detection of oligomannosidic n glycans in alpha-mannosidosis: a method of monitoring treatment. J Inherit Metab Dis. 2011 Oct;34(5):1023-7.
136. Grewal SS, Shapiro EG, Krivit W, Charnas L, Lockman LA, Delaney KA, et al. Effective treatment of alpha-mannosidosis by allogeneic hematopoietic stem cell transplantation. J Pediatr. 2004 May;144(5):569-73.
137. Mulrooney DA, Davies SM, Walk D, Charnas LR. Late occurrence of chronic immune-mediated axonal polyneuropathy following bone marrow transplant for juvenile-onset alpha-mannosidosis. Bone Marrow Transplant. 2003 Nov;32(9):953-5.
138. Mynarek M, Tolar J, Albert MH, Escolar ML, Boelens JJ, Cowan MJ, et al. Allogeneic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients. Bone Marrow Transplant. 2012 Mar;47(3):352-9.
139. Will A, Cooper A, Hatton C, Sardharwalla IB, Evans DI, Stevens RF. Bone marrow transplantation in the treatment of alpha-mannosidosis. Arch Dis Child. 1987 Oct;62(10):1044-9.
140. Yesilipek AM, Akcan M, Karasu G, Uygun V, Kupesiz A, Hazar V. Successful unrelated bone marrow transplantation in two siblings with alpha-mannosidosis. Pediatr Transplant. 2012 Nov;16(7):779-82.
141. Gerards AH, Winia WP, Westerga J, Dijkmans BA, van Soesbergen RM. Destructive joint disease in alpha-mannosidosis. A case report and review of the literature. Clin Rheumatol. 2004 Feb;23(1):40-2.
142. Desai AS, Dramis A, Board TN, Kay PR. Cemented total hip arthroplasty in a patient with alpha-mannosidosis: a case report. Hip Int. 2009 Apr-Jun;19(2):151-4.
143. Eckhoff DG, Garlock JS. Severe destructive polyarthropathy in association with a metabolic storage disease. A case report. J Bone Joint Surg Am. 1992 Sep;74(8):1257-61.
144. Seidl U, Giesel FL, Cantz M, Schmidbauer M, Schroder J, Pantel J. [Unusual course of alpha-mannosidosis with symptoms of paranoid-hallucinatory psychosis]. Nervenarzt. 2005 Mar;76(3):335-8.
145. Kalsi JS, Auplish G, Johnson AR, Darbar UR. Severe periodontal destruction in alpha-mannosidosis: a case series. Pediatr Dent. 2012 Sep-Oct;34(5):140-3.

17 Appendices

The appendices to this manufacturer submission are provided as a separate document.

18 Related procedures for evidence submission

18.1 *Cost- effectiveness models*

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 *Disclosure of information*

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company

representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 *Equality*

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technologies

Velmanase alfa for treating alpha-mannosidosis [ID800]

Dear Julie,

The Evidence Review Group, School of Health Related Research – ScHARR, and the technical team at NICE have looked at the submission received on 12th January from Chiesi. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on 23 February. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on 'NICE Docs/Appraisals'].

Commented [AT1]: Jo to add the link?

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Aminata Thiam, Technical Lead (Aminata.thiam@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Literature searching

A1. The reference lists of included studies were scanned to identify potentially relevant publications (section 9.1.1.1 p75). Please clarify if the company conducted any additional "forward" citation tracking to look for more recent publications making reference to those included?

A2. In the Appendices of the company submission (section 17.1.5.1 p6), details are provided of hand searches of conference proceedings and others (i.e., research registers and search engines). However none of these appear in the PRISMA flow diagram (Fig 40, Appendices section 17.1.7 p9). Please confirm if there were any results found from any of these sources?

A3. The PRISMA flow diagram (Fig 3, section 9.2.2 p78) lists 'Econlit' but this search is not described in the search strategy. Please clarify if the search was done, or whether this relates to the systematic review of cost effectiveness models? Please also clarify what the number of included studies was, as the PRISMA flow diagram says 17 (25 publications) whereas the text in section 9.2.2 says 16 (19 publications).

Systematic Review Methods

A4. a- Please provide a quality assessment for rhLAMAN-05 using a tool for cohort studies (Table 22 p124).
b- Table 22 (p124): The question about allocation concealment appears to have been misinterpreted as asking whether the trial was blinded. Please clarify if the allocation of patients to groups was concealed from the enroller and patient/parent/guardian before the patient was enrolled? Please clarify how randomisation was carried out, e.g. by reference to a table, centralised, automated phone system? Please clarify if blinding was broken for any patients, e.g. in an emergency? Please clarify why reference to the imputations made in rhLAMAN-05 have not been referred to in answer to the question "were appropriate methods use to account for missing data?" and provide an answer to this question, which is currently missing.

A5. Please provide a quality assessment for rhLAMAN-10 using a tool for cohort studies (Table 23 p125).

A6. Please clarify who conducted the study selection and data extraction processes of the studies described in section 9.4.1 p90 (e.g., one or more than reviewer?). Please also clarify who conducted the critical appraisals in section 9.5 p121 (e.g. one or more than reviewer?)

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A7. Please clarify why the studies from Japan were excluded, when this is not listed as an exclusion criterion? Please provide the references for these studies and a rationale for why they are not relevant.

A8. The selection criteria appear to include all interventions for alpha-mannosidosis (AM), but only studies relating to velmanase alfa (VA) are included. Please clarify what the excluded studies relate to, and what the criteria for selecting includable studies was (e.g. whether any VA study was included, or if restrictions were placed relating to posology or dose). Please clarify if any studies of VA were excluded, and if so, for what reason?

Population

A9. **Priority Question**: Please clarify if patients aged younger than 6 years are to be included in the licence and what impact that has on this evaluation? (Section 1 p33)

A10. **Priority Question**: Given that *'each patient's' symptom profile and ... impact of QoL is heterogeneous*' (p52) and that *'patient heterogeneity*' (p164) is a recognised issue, please clarify what determines progression / rate of progression, if known, and whether the groups in the rhLAMAN-05 trial are balanced for these factors.

A11. **Priority Question**: Please provide any further information on whether the treatment initiation and continuation rules are likely to change following consultation with UK KOLs (section 10.1.16 p182).

A12. **Priority Question**: Please clarify how patients with *'mild to moderate AM*' (p38) and *'for whom allogeneic HSCT is unsuitable and/or not possible*' (p42 and p67) are defined / identified for the purposes of being ineligible for VA treatment and thus haematopoietic stem cell transplantation (HSCT) is not relevant as a comparator (Table 2 p33). How many of the patients in the trial would have been eligible for HSCT in accordance with UK practice and /or Chiesi's definition of eligibility? Does the exclusion of these patients affect the outcomes described in the decision problem?

A13. Treatment continuation rules (p.26): How would the current treatment 'start-stop criteria' affect the evidence base? Would any patients who participated in the clinical trials have been excluded on the basis of these rules? How would this affect the outcomes reported?

A14. Please clarify if there was only one patient not naïve to velmanase in rhLAMAN-05 (p110)? What is the evidence to support a 3-month wash out period in the inclusion criteria (p97)?

A15. Please clarify why patients with IgE >800 IU/ml were excluded from rhLAMAN-05?

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A16. Please clarify if treatment was unblinded for any participants of rhLAMAN-05? Which group were they allocated to? (p98)

Comparator

A17. **Priority Question**: Please clarify the number and the age of patients in the UK that have received an HSCT. Please also clarify what data exist on the effectiveness and safety data of HSCT.

Study Design

A18. a- Please clarify why some patients were enrolled in a compassionate use programme, whilst some were enrolled in rhLAMAN-07 and -09? (p99)
b- What are studies rhLAMAN-07 and rhLAMAN-09 designed to test?

Outcomes

A19. **Priority Question**: Please clarify what was the EMA's reason for requesting a multi-domain analysis?

A20. **Priority Question**: Please clarify what evidence exists for a relationship between surrogate markers, such as serum oligosaccharides and IgG and clinical outcomes. (i.e. have the surrogate markers been validated?)

A21. **Priority Question**: Serum IgG is a proxy for the clinical outcome "infections". Please clarify why infection rates were not measured and analysed as a clinical outcome (they are measured as an adverse event). If they were measured, please provide the data.

A22. **Priority Question**: Please provide evidence to support the minimum clinically important difference (MCID) for all outcomes within the scope of the NICE assessment. Please also clarify how the cut-offs for serum oligosaccharide levels and childhood health assessment questionnaire (CHAQ) were determined.

A23. Please clarify why the '3-MSCT' was selected as the co-primary outcome rather than the '6-MWT' outcome measure (p72).

A24. Please clarify who completed the CHAQ disability index and CHAQ Pain (VAS) tools and how those were completed (p88). The text states *'All patients' legally authorised guardian(s) were asked to complete the following CHAQ topics*', but also suggests that the tools are appropriate for gaining responses from patients themselves. Please

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clarify why CHAQ was used if the questionnaire was being completed by a proxy adult/guardian? What evidence is there that the measures are valid when completed by a parent/guardian?

A25. Please provide evidence to support the statement that there may have been a 'ceiling effect' for 3-MSCT and 6-MWT, in the context of normal values for these measures.

A26. Please clarify what evidence is available to link mobility and quality of life.

A27. Please clarify if there is there an update on the MPS Society survey (section 12.8.4 p291).

A28. Please clarify if the 3-MSCT and 6-MWT are adjusted for age and height, or have predicted values for age and height. This is not described in summaries of the studies (e.g. Table 7, p87, p105-106 or in the results for rhLAMAN-05), although the results for rhLAMAN-10 refer to % of predicted (p142, p143). If available, please provide both distance and % of predicted data for rhLAMAN-05 and rhLAMAN-10 for all analyses. If % predicted data are not available, please indicate the likely impact of age and height on these scores, and of normal growth, especially in paediatric patients.

A29. Please confirm whether the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines define which reference values for lung function should be used, and if these were used (p88).

A30. Please clarify why the strength subtest was not collected? Please also clarify what evidence there is to support this approach, and the likely effect on the scores collected? (p89)

A31. Please clarify exactly how *'impairment categories*' have been determined (e.g. literature to support thresholds) and whether they were pre-planned or post-hoc (section 9.4.4.2 p116)

Adverse events

A32. **Priority Question**: Please clarify what the protocols were for recording adverse events in all trials?

A33. Please clarify why the patient mentioned on page 146 required an amputation. Was this due to AM?

A34. Please clarify where infusion-related reaction (IRR) appears in the adverse event tables and whether it was established why the small number of patients with IRRs experience multiple events (p158).

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Results

A35. **Priority Question**: Please clarify how many patients have discontinued the use of VA and for what reasons. Please relate this to the numbers at each time point given in Table 14, p103.

A36. **Priority Question**: Please clarify whether interaction tests have been performed to ascertain if there are different effects between subgroups. For example, in the ANCOVA and between results observed for those aged under 18 years and those aged 18 years and over. (e.g. Table 25, Figures 18-24). Provide similar tests for the post-hoc analyses undertaken when categorising three age groups, for instance with the data contained in Table 27.

A37. Please clarify how missing data were accounted for in the intention-to-treat analysis in rhLAMAN-10.

A38 Please provide ranges, as well as mean and standard deviation, for rhLAMAN-05 for the following measures (where missing): 3-MSCT, 6-MWT, FVC and serum oligosaccharides (Table 16 p110). Also, there appears to be a typo in the placebo column of this table (6-MWT placebo ≥500m). Please clarify this data.

A39. Please provide absolute values at baseline and at each assessment for all outcomes, particularly for CHAQ and EQ-5D, in both rhLAMAN-05 and rhLAMAN-10.

A40. Please provide N for all outcomes reported in rhLAMAN-05 and rhLAMAN-10.

A41. Please clarify the changes in EQ-5D values, classified by multi-domain response, for patients receiving VA and placebo in rhLAMAN-5.

A42. Please clarify if there is evidence for whether or not the efficacy of VA will be maintained as treatment duration increases considerably?

A43. Please clarify what the impact on the clinical effectiveness evidence would be if the MCID thresholds for each response criteria were varied by ±10%.

A44. Please clarify what proportions of patients receiving VA and placebo in rhLAMAN-05 transitioned between the health states that are used in the economic model (that is the health states based on ambulatory status – walking unassisted, walking with assistance, wheelchair dependent, and severe immobility)

A45. Please clarify how the adjusted mean difference in the change from baseline in serum oligosaccharides has been generated for each treatment in rhLAMAN-05 and explain

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the discrepancy in the point estimate for the treatment effect in the following (Table 24 p126):

- o VA -77.60% (95% CI: -81.58, -72.76)
- o Placebo -24.14% (95% CI: -40.31, -3.59)
- o Difference -70.47% (95% CI: -78.35, -59.72)

A47. For the post hoc analysis of serum IgG, please clarify if the 10 patients who had normal IgG at baseline in the VA group maintained a normal value at month 12 (p135)?

Section B: Clarification on cost-effectiveness data

Model Conceptualisation

B1. **Priority Question**: Please clarify whether patients in the following states are intended to be treated with VA and if so, clarify whether the time on treatment was as intended.
   a. The Severe Immobility (SI) state
   b. The Short End state

In the SI state patients who are treated apparently receive treatment for exactly one year. In the short end state, patients will apparently receive treatment for one year despite dying after 4 weeks (see Appendix B1)

B2. **Priority Question**: If patients treated with VA are intended to be treated in the SI state, please clarify whether patients receiving VA in the SI state can have severe infections and how this is implemented in the model. It appears as though patients are not at risk of severe infection in the year that they are in the SI on treatment health state (see Appendix B2)

B3. **Priority Question**: Please clarify the likely impact of the simplification of not allowing backward transitions in the placebo arm. It is not the case that the incremental costs and QALYs remain constant when a fixed value is removed from both interventions and added to the transitions to other health states. Ideally, please include the possibility for improvement on standard of care within the model.

B4. **Priority Question**: Please provide the incremental cost-effectiveness ratio (ICER) of VA vs best supportive care (BSC) if all the patients were assumed to reside in a chosen health state at a time at the start of the model (e.g. 100% of patients reside in the Walking Unassisted health state, 100%of patients reside in the Walking with assistance health state…).

B5. Please clarify why no relationship was assumed within the model between the level of formal carer costs and the utility loss and productivity loss assumed for individual

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carers. Please clarify whether you consider the present method would lead to double counting.

B6. Please clarify the potential level of double-counting that could occur when using three independent sources for disutility as detailed in Table 43 p316. For instance, having hearing difficulties may be correlated with cognitive limitations and if so applying both disutilities in full would be invalid.

B7. Please clarify why the model does not adjust the utilities for age and comment on the likely impact of this on the ICERs.

Potential Model Implementation Errors

B8. **Priority Question**: It is believed that there are errors relating to the life years, and costs associated with the Short End state: please see appendix B8. Please clarify if this is correct. Most notable, it appears that patients are treated with VA for 52 weeks despite dying within 4 weeks (see question B1).

B9. Please clarify whether there is an inconsistency between treatment discontinuation and surgical-related mortality as applied for VA and as applied for BSC (see Appendix B9).

B10. Please clarify whether there is an inconsistency within the VA arm relating to on treatment discontinuation (see Appendix B10).

B11. Please clarify why costs for first attendance at each consultation are included in each year for health state costs, rather than only for the first attendance as an adult or child (see Appendix B11).

B12. Please clarify the source of paediatric ophthalmology visit costs, as these appear to be the same as adults. Paediatric costs are available in NHS reference costs (see Appendix B12).

B13. Please clarify why the year 1 administration costs are applied in the model for all years of treatment. It is anticipated that these will reduce after the initial hospitalisation visits within year 1 (see Appendix B13).

B14. Please clarify whether cell E20 of the 'Treatment' sheet in the Excel model was deliberately left blank. This cell is used in numerous calculations, for example in K15 of the 'Matrices' sheet.

Model Parameterisation - Utility

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B15. **Priority Question**: Please clarify how the VA utility increment of 0.1 was derived.

B16. **Priority Question**: The submission states that the utilities produced by the 'minimum' method are aligned to those published in the literature from proxy diseases (p179). Please provide details of the published studies to support this statement, including the diseases on which they are based and the utility values they report.

B17. **Priority Question**: Please clarify why the proxy-reported EQ-5D values for 'Walking Unassisted' and 'Walking With Assistance' from rhLAMAN-10 were not used in base case economic analyses.

B18. **Priority Question**: Please clarify why the 'minimum' method (p179) has not been used in the base case analyses when it has been stated that 'Overall, using the 'minimum' method would appear to be the most appropriate/conservative approach, as this method produces utilities that are more aligned to those published in the literature (from proxy diseases) as well as the utilities derived from the EQ-5D data from the rhLAMAN trials.'

B19. Please clarify how the studies for the multi-morbid utility calculations were chosen and whether the approach taken was systematic.

Model Parameterisation – Resource Use

B20. **Priority Question**: The model appears to calculate the weight for males and females and takes the average then calculates the number of vials required, rather than calculating the number of vials required for males and females and taking the average. Please clarify why a more accurate approach of considering a distribution of patient weights within the population to estimate the number of vials required was not undertaken. Please provide an indication of the impact on the costs of VA were a distribution to be used (see Appendix B20).

B21. The ventilation costs assumed in the model are taken from Noyes et al (2006) and are total support costs, which include other hospital, community health, social services and education costs. Please clarify whether using these values introduces double counting? Please provide analyses using only these costs (excluding health state and carer costs) and provide analyses using the ventilation costs reported from MPS IVA as reported in http://www.gov.scot/Resource/Doc/293936/0090811.pdf.

B22. Please provide the HRG code assumed to represent the administration cost of VA

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B23. Please clarify how uncertainty distributions were derived for NHS reference costs. It appears that the Standard Error, calculating using the number of data submissions and the inter-quartile range, has not been used.

B24. Please clarify why the values calculated for severe infection costs used in the model (which have been calculated using severe sepsis costs) are preferable to the cost that can be estimated from NHS Reference costs (using non-elective long stay codes WJ05A, WJ05AB, WJ06A, WJ06B, WJ06C, WJ06D, WJ06E, WJ06F, WJ06G, WJ06H, WJ06J,). These are £2742 with an average length of stay of 6.39 days when weighted by the number of Finished Consultant Episodes.

B25. Please clarify the mean, maximum and minimum infusion times related to VA treatment.

B26. Please clarify why resource use is not varied in sensitivity analysis.

Model Parameterisation – General

B27. **Priority Question**: Please justify the distributions used, including the use of +/- 25% as the 95% confidence interval in parameters that were not formally elicited.

B28. **Priority Question**: Please clarify what evidence exists to support the modelling assumption that values for the following parameters must be greater than 0:

- the reduction in the rate of severe infections;
- the reduction in recovery period post severe infections;
- the reduction in mortality post-infection;
- the reduction in surgical-related mortality;
- the reduction in surgical-related complications;
- the reduction in recovery period post severe infections.

We note that Table 32 p158 indicates that there were more infections and infestations in the VA arm than in the placebo arm.

B29. **Priority Question:** Please clarify why the number of additional years in 'Walking Unassisted' 'with VA (Table 73) is [redacted]

B30. Please clarify, with reference to the NICE methods guide, why a discount rate of 1.5% was used.

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B31. Please clarify why the baseline age of paediatric, adolescent and adult patients was assumed to be the lowest age of each band, rather than the average age (which is an option in the model).

B32. Please clarify the source of the following parameters, and associated uncertainty, with details of questions asked and responses at the Expert Elicitation Panel or KOL interviews:

a. Backward transitions / improvement for VA
b. 10% annual VA discontinuation
c. Surgery-related mortality
d. Surgery-related complications
e. Minor surgery probabilities
f. Duration of short end-stage state
g. Proportion of care provided by formal carer in each health state
h. Reduction in Severe infections due to VA

B33. Please clarify whether the default distribution of all parameters (e.g. disease progression) matches that of patients currently with AM in England.

B34. Please provide the parameter values for the distributions contained in Table 74 p245.

B35. Please comment on the apparent discrepancy between the carer time required for children in Morquio A syndrome (Figure 39 p301: little difference between patients who do and do not require wheelchair use), and the data provided in Table 68 p235 (Hendriksz: sharp increase in care-giving requirements when a patient enters the wheelchair state).

B36. Please provide, as appropriate, the following with respect to Table 74 p245:

- confirmation that the use of normal distributions gives effectively zero probability of negative values for uncertain values that are strictly positive
- a justification for the use of gamma distributions for relative estimates of treatment effects that could take negative values

Elicitation Exercise / KOL interviews

B37 **Priority Question**: Please comment on the face validity of the utility value for being wheelchair dependent, particularly in reference to the description of the health state provided in Table 47. Please comment on whether this value indicates that the values provided by the KOLs are not reliable.

B38. **Priority Question**: Please provide the exact questions asked at the elicitation exercise. Please also clarify whether the clinicians explicitly took into account potential

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improvements in health state, such as moving from walking with aids to walking unaided, when the estimate of the increased years in walking without aids due to VA treatment was elicited. Unless the question explicitly excluded patients who improved, it is likely that the clinicians assessed the typical patient progressing to the next health state and that the gains modelled will be an overestimate of the benefit of VA.

B39. Please clarify the approach used to generate the clinician proxy utility values, including how many clinicians provided answers, what information was used to define the health states, which EQ-5D valuation set was used (3L or 5L), and the associated uncertainty.

B40. Please clarify how the resource use data and the associated uncertainty presented in Table 66 p232 was derived from KOLs.

B41. Please clarify whether KOLs/experts were given a training exercise before the elicitation process and also if the clinicians were provided with an evidence dossier. Please also clarify whether any clinician strongly objected to the 'consensus' distribution (note the final distribution should align with that of a rational impartial observer privy to all discussions not a consensus and therefore strong disagreement is possible).

Model Output

B42. **Priority Question**: Please provide an example of how the weighted ICER was calculated.

B43. **Priority Question**: Please provide an example of how the credible intervals associated with each ICER were calculated.

B44. **Priority Question**: Please clarify the estimated incremental undiscounted QALYs gained t associated with the use of VA compared with BSC.

Other

B45. **Priority Question**: Please clarify the likely distribution of health states that a cohort of people with AM diagnosed in the future would reside in, and the likely age distribution of these patients.

B46. Please provide information on the age of patients in the UK MPS Society registry.

B47. Please clarify what utility data the UK MPS Society survey is expected to provide and which model health states it will populate.

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B48. Please clarify whether any resource use data was recorded in rhLAMAN-05 or rhLAMAN-10. If yes, clarify why this was not considered within the modelling.

Section C: Textual clarifications and additional points

C1. Has any follow-up been undertaken on the patient who suspended VA treatment in September 2016 (p38)?

C2. Please clarify the source of the quotation, "It is the simple things ...” and provide a reference to support the statement: 'Mobility was identified as a key factor in the overall health and QoL of patients with AM' (section 7.1.3.1 p.52).

C3. Please clarify if the total patient population is 33 (as stated on p23) or 34 (as stated on p72)?

C4. Please confirm that patients in rhLAMAN-10 came from other locations than just Denmark (Table 13 p.100).

C5. There appears to be a typo in Table 26 p137: the last banded row states “serum IgG” but the data underneath states 12 month CHAQ disability index score. Please clarify which is the correct data, and provide any missing data.

C6. There appears to be a lack of consistency between the statements “This limitation is known as a ‘ceiling effect’ and suggests that improvement is more difficult to observe in patients who have baseline values approaching the normal range.” and “The results for the 3-MSCT and 6-MWT may have also been confounded by the lack of patient selection at baseline according to mobility and motor performance. This led to a potential unbalance in the severity of patients in favour of placebo, with a higher proportion of more compromised patients randomised to the velmanase alfa group; however, as previously mentioned, all patients were reasonably mobile and recorded as being able to walk (with or without aids/assistance) at baseline. Ultimately, the treatment effect may have been eroded by a combination of the ceiling effect, limiting the ability to observe improvement in the velmanase alfa group, and higher-functioning patients in the placebo group who may have possessed a greater ability to perform well in these tests.” If the first statement is true, the velmanase alfa group should have the potential to show more effect compared to the placebo group, not less, and this would appear to suggest that the velmanase alfa group has an advantageous bias in comparative analyses between treatment and placebo. Please clarify your interpretation of the evidence.

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C7. Please clarify why the text in section 12.5.3 (p250) states “at 10 years (aged 16), 19.53% of patients under BSC alone have died, in contrast to 12.08% of the cohort treated with velmanase alfa” whereas the results for VA in Table 79 gives this as 11.67%.

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23 February 2018

RE: Highly Specialised Technologies Evaluation Programme
Velmanase alfa for treating alpha-mannosidosis (ID800)

Dear Sheela,

Chiesi would like to thank you for undertaking a review of the timelines in order for us to be able to process our responses.

In reply to your recent request for further clarification on specific aspects of the clinical and cost-effectiveness data contained in the above company submission, please find enclosed the 'Tier 2' and 'Tier 3' responses from Chiesi. We trust that these responses will assist the ERG and the technical team at NICE to address these issues in their reports.

As requested, two versions of Chiesi's final ERG clarification responses are submitted; one with academic/commercial-in-confidence information clearly marked and one with this information redacted. The checklist for confidential information has also been completed and is enclosed describing data that are not already referenced in the main body of our submission and that are academic/commercial in confidence.

In addition to the final ERG clarification response, Chiesi has provided the following supporting documentation:

- Appendix A: UK MPS Society Survey Report (Word file)
- Appendix B: Updated base case and sensitivity analyses (Word file)
- Appendix C: Updated cost-utility analysis model – list price (Excel file)
- Appendix D: [redacted]
- Appendix E: [redacted]

If you have any further queries or require any additional clarification on the issues raised, then please do not hesitate to contact me.

Yours sincerely,
Julie De-Almeida
Head of Market Access UK & Ireland

Contents

Abbreviations

3-MSCT	3-minute stair climb test
6-MWT	6-minute walk test
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIC	Academic in confidence
AM	Alpha-mannosidosis
AME	Attention and memory
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
BOT-2	Bruininks-Oseretsky test of motor proficiency, second edition
BMI	Body-mass index
BSC	Best supportive care
CEV	Clinical evaluation visit
CHAQ	Childhood health assessment questionnaire
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIC	Commercial in confidence
CMO	Contract manufacturing organisation
CRO	Clinical research organisation
CS	Company submission
CSI	Caregiver Strain Index
CSF	Cerebral spinal fluid
CSR	Clinical study report
CUA	Cost-utility analysis
DOF	Data on file
DMD	Duchenne muscular dystrophy
EMA	European Medicines Agency
ERG	Evidence Review Group
EQ-5D	EuroQol five-dimension questionnaire
EQ-5D-5L	EuroQol-5 Dimension-5 Level questionnaire
EQ-5D-Y	EuroQol-5 Dimension-Youth questionnaire
ER	Endoplasmic reticulum

ERS	European Respiratory Society
ERT	Enzyme replacement therapy
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HADS	The Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HST	Highly specialised technology
HSUV	Health state utility value
HUI	Health utilities index
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IRR	Infusion-related reaction
IMP	Investigational medicinal product
KOL	Key opinion leader
LS	Least squares
LSD	Lysosomal storage disorder
MAA	Marketing Authorisation Application
MCID	Minimal clinically important difference
MPS	Mucopolysaccharidosis
NHS	National Health Service
NA	Not available
NR	Non response
NICE	National Institute for Health and Care Excellence
PD	Pharmacodynamic
PEF	Peak expiratory flow
PIP	Paediatric Investigational Plan
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PTA	Pure tone audiometry
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial

SAE	Serious adverse events
SD	Standard deviation
SI	Severe immobility
SUSAR	Suspected, unexpected, serious adverse drug reactions
TEA	Total equivalence age
UK MPS Society	UK Society for Mucopolysaccharide Diseases
VA	Velmanase alfa
VAS	Visual analogue scale
VR	Visualisation and reasoning
WC	Wheelchair dependent
WU	Walking unassisted
WWA	Walking with assistance

Confidential marking

Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

ERG Clarification Questions

Section A: Clarification on effectiveness data

Literature searching

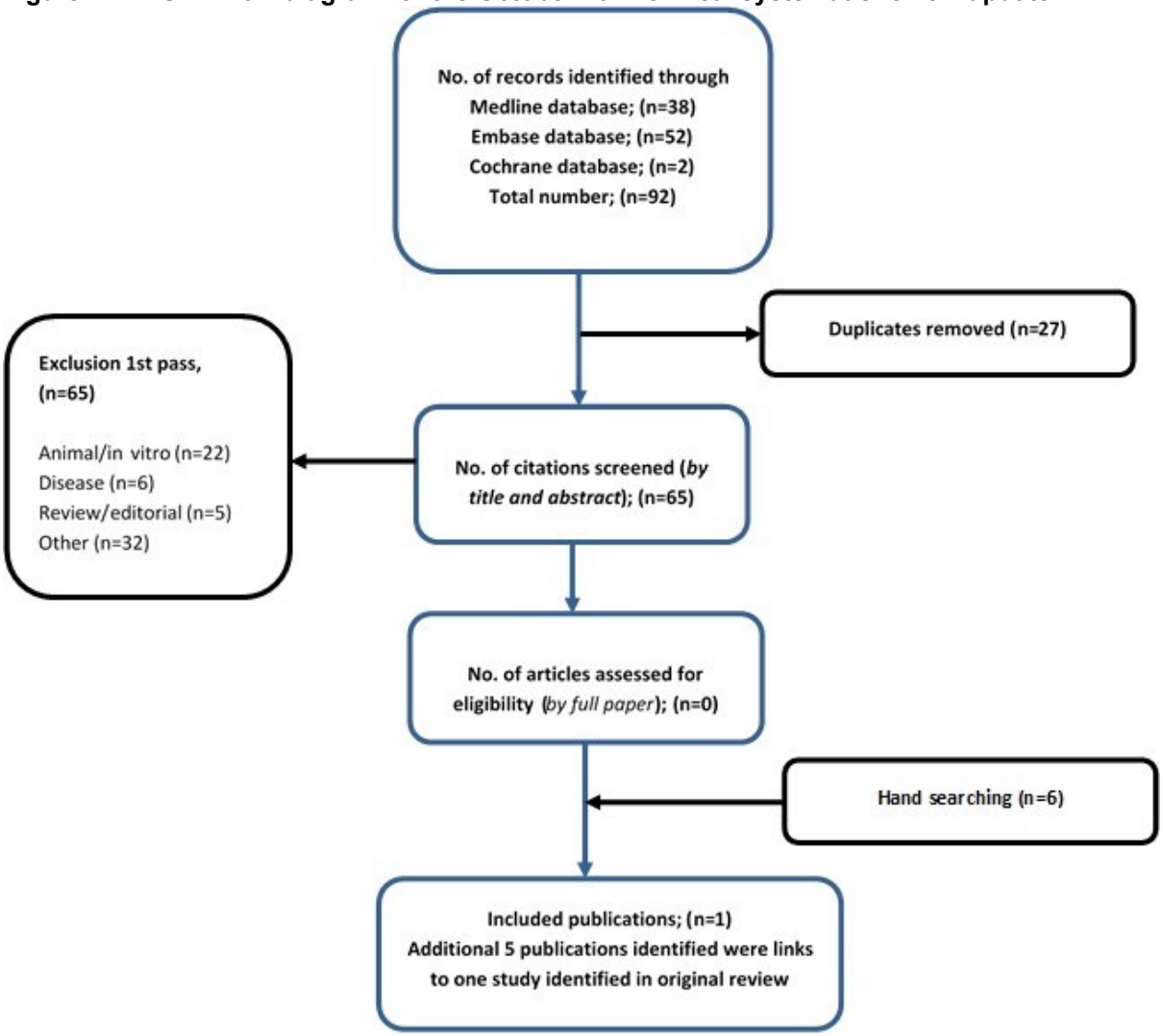
A1. The reference lists of included studies were scanned to identify potentially relevant publications (section 9.1.1.1 p75). Please clarify if the company conducted any additional "forward" citation tracking to look for more recent publications making reference to those included?

As a part of the systematic review process, the reference lists of included studies were scanned for any additional relevant publications. The company did not conduct any "forward" citation tracking to look any recent publications.

A2. In the Appendices of the company submission (section 17.1.5.1 p6), details are provided of hand searches of conference proceedings and others (i.e., research registers and search engines). However, none of these appear in the PRISMA flow diagram (Fig 40, Appendices section 17.1.7 p9). Please confirm if there were any results found from any of these sources?

Figure 40 in the company submission (CS) Appendices (Section 17.1.7 p9) refers to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram for searches that were conducted in October 2017. During this update, a total of six studies were identified from hand searching as mentioned in text of the CS Section 9.2.2 (second paragraph). A box from the PRISMA flow diagram was erroneously removed, an updated PRISMA diagram is provided in Figure 1.

Figure 1: PRISMA flow diagram for the October 2017 clinical systematic review update



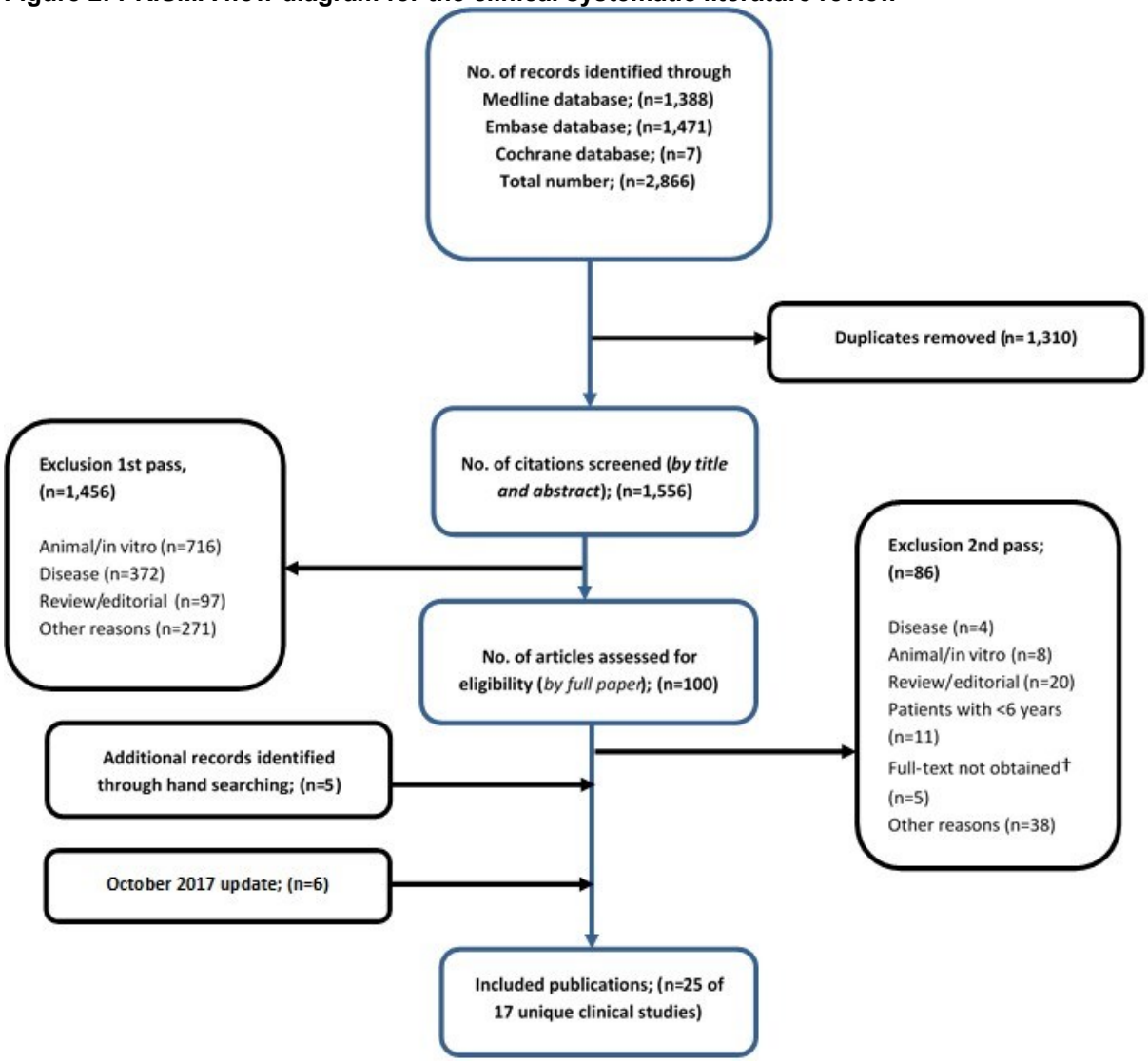
A3. The PRISMA flow diagram (Fig 3, section 9.2.2 p78) lists 'EconLit' but this search is not described in the search strategy. Please clarify if the search was done, or whether this relates to the systematic review of cost effectiveness models? Please also clarify what the number of included studies was, as the PRISMA flow diagram says 17 (25 publications) whereas the text in section 9.2.2 says 16 (19 publications).

The inclusion of EconLit is a typographical error in the PRISMA diagram – this database was not searched as part of the clinical effectiveness analysis.

In the original review, a total of 16 studies were identified from 19 publications. The text refers to the number of studies identified as part of the original review. Furthermore, six publications were identified in the October 2017 update, out of which one was a unique study and five publications were additional links to studies already included in the original review. Hence, a total of 17 studies from 25 publications were identified. Figure 3 (CS Section 9.2.2) refers to the overall PRISMA flow diagram including (original review and update review). A separate diagram for update review is provided in Figure 40 (CS Appendix Section 17.1.7). Also, in Figure 3 (CS Section 9.2.2) a box for studies identified during

update searches was erroneously removed. An updated PRISMA flow diagram is provided in Figure 2.

Figure 2: PRISMA flow diagram for the clinical systematic literature review



Systematic Review Methods

A4. a- Please provide a quality assessment for rhLAMAN-05 using a tool for cohort studies (Table 22 p124).

b- Table 22 (p124): The question about allocation concealment appears to have been misinterpreted as asking whether the trial was blinded. Please clarify if the allocation of patients to groups was concealed from the enroller and patient/parent/guardian before the patient was enrolled? Please clarify how randomisation was carried out, e.g. by reference to a table, centralised, automated phone system? Please clarify if blinding was broken for any patients, e.g. in an emergency? Please clarify why reference to the imputations made in rhLAMAN-05 have not been referred to in answer to the question "were appropriate methods use to account for missing data?" and provide an answer to this question, which is currently missing.

a. The Evidence Review Group (ERG) confirmed during the ERG clarification teleconference call (12 Feb 2018) that this question no longer required an answer.

b. In rhLAMAN-05, the randomisation (in a 3:2 ratio) into active or placebo group was stratified on age and was used to allocate the patients into blocks. Within the blocks, a standard randomisation into active and placebo was performed. The subject number, identification and randomisation were documented by the Clinical Research Organisation (CRO). Three sets of sealed code/label with the randomisation number containing information about the treatment for the particular subject were prepared for each subject. One set was kept at the dosing site (during the entire trial period), one set was kept at the CRO and one set was kept at the Sponsors Quality Assurance. The randomisation code list was kept at the CRO and was disclosed to the contract manufacturing organisation (CMO) performing the packaging of the trial. The code for a particular subject could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject. However, blinding was not broken for any patient in the trial.

   Appropriate methods were employed to account for missing data. For the analysis of covariance (ANCOVA) models, in case of missing data, under the assumption of missing at random, a multiple imputation method was applied before performing the analysis. This approach assumes that measures for withdrawn patients follow the pattern of patients who remained in the study. Imputation was performed by proc multiple imputation in SAS using the Markov Chain Monte Carlo approach by treatment. Each record included baseline, 26 weeks and 52 weeks in addition to the baseline age. A total of 1,000 imputations were created and the imputed data sets are then analysed with PROC MIANALYSE.

A5. Please provide a quality assessment for rhLAMAN-10 using a tool for cohort studies (Table 23 p125).

The quality assessment preformed for rhLAMAN-10 using a cohort checklist is provided in Table 1.

Table 1: Critical appraisal of observational studies

Study name: rhLAMAN-10		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients were enrolled from the previous rhLAMAN studies
Was the exposure accurately measured to minimise bias?	Yes	
Was the outcome accurately measured to minimise bias?	Yes	A clear definition of all measured outcomes were reported
Have the authors identified all important confounding factors?	Not clear	Identification of potential confounding factors was difficult due to disease heterogeneity, exemplified by variation in severity across the numerous disease manifestations, together with the small population size of the trial.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	
Was the follow-up of patients complete?	Yes	The follow-up period ranged from 1 to 4 years
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	For all efficacy outcome results, p-values and variances were reported wherever applicable
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

A6. Please clarify who conducted the study selection and data extraction processes of the studies described in section 9.4.1 p90 (e.g., one or more than reviewer?). Please also clarify who conducted the critical appraisals in section 9.5 p121 (e.g. one or more than reviewer?)

As a part of the systematic review process, a review of titles and abstracts of all identified citations was performed by two independent researchers. Any judgement based on titles/abstracts where there was no consensus were reviewed again by both researchers and then by a third independent researcher if agreement could not be reached. Similarly, full-text publications were assessed by two independent reviewers against the pre-defined eligibility criteria. Disputes as to eligibility were referred to a third independent researcher.

Data extraction of included studies was performed by two independent researchers and any disputes were resolved by a third independent researcher. A similar process was followed for conducting the critical appraisal checklist.

A7. Please clarify why the studies from Japan were excluded, when this is not listed as an exclusion criterion? Please provide the references for these studies and a rationale for why they are not relevant.

A total of five Japanese studies were excluded from systematic review considering:

- The population would be less generalisable to UK population
- The studies were published prior to 2002

A list of these references is provided below:

1) Arashima, S. Fucosidosis and mannosidosis. [Japanese]. Nippon rinsho. 1978: 1404-1405

2) Sakai, N. Mannosidosis. [Japanese]. Ryoikibetsu shokogun shirizu. 2001. 34 Pt 2: 135-136

3) Yamaguchi, S. Alpha-mannosidosis. [Japanese]. Ryoikibetsu shokogun shirizu. 1998. 19 Pt 2: 455-457

4) Yamaguchi, S. Mannosidosis. [Japanese]. Ryoikibetsu shokogun shirizu. 2000. 32: 340-342

5) Kawai H, Nishida Y, Nishino H, Inui T, Saito S, Takeda E, et al. Two sisters with mannosidosis: clinical manifestations and pathologic findings of the skeletal muscle. [Japanese]. Nihon Naika Gakkai zasshi. 1986. 5: 638-64

A8. The selection criteria appear to include all interventions for alpha-mannosidosis (AM), but only studies relating to velmanase alfa (VA) are included. Please clarify what the excluded studies relate to, and what the criteria for selecting includable studies was (e.g. whether any VA study was included, or if restrictions were placed relating to posology or dose). Please clarify if any studies of VA were excluded, and if so, for what reason?

In the systematic review of clinical evidence, 25 publications relating to 17 studies were identified. The details of the included studies are presented in Appendix 2, Section 17.2.1 of the CS: Table 123 outlines the baseline characteristics, Table 124 provides a summary of the reported efficacy data, Table 125 provides a summary of the reported safety data. Of these studies:

- Four studies[a] were related to the efficacy and safety of velmanase alfa
    - No studies assessing velmanase alfa were excluded
- Seven studies/case reports were related to allogeneic haematopoietic stem cell transplantation (HSCT)
- Six studies were related to the treatment of the consequences of alpha-mannosidosis (AM)

Only studies that assessed the clinical effectiveness of velmanase alfa in humans were deemed relevant to the decision problem, and therefore presented in Section 9.3 of the CS onwards.

[a] The four studies covered the three Phase I/II trials (rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04), and two Phase III trials (rhLAMAN-05 and rhLAMAN-10). Individual, company-supplied clinical study reports (CSRs) are available for each of the five trials as supplied in the company submission reference pack.

Population

A9. <u>Priority Question</u>: Please clarify if patients aged younger than 6 years are to be included in the licence and what impact that has on this evaluation? (Section 1 p33)

The European Medicines Agency (EMA) has adopted a positive opinion to velmanase alfa with a therapeutic indication not restricted by age, so as to no longer exclude patients aged under 6 years. This decision, in part, is due to the EMA recognising that early treatment with velmanase alfa is likely to benefit the patient. As part of the Paediatric Investigational Plan (PIP) for the product, there is an ongoing trial on the safety and efficacy of velmanase alfa treatment in paediatric patients with AM aged 0 to 5 years at enrolment (study rhLAMAN-08), with an estimated primary completion date of February 2020 and a target study size of at least three patients.

At the time of the Marketing Authorisation Application (MAA), and currently, no clinical trial data concerning the efficacy and safety of velmanase alfa are available for patients aged 5 years and under; therefore, a clinical and economic case is put forward in this highly specialised technology (HST) evaluation for an AM population aged 6 years and older. This AM population is also aligned to the final National Institute for Health and Care Excellence (NICE) scope.

A10. <u>Priority Question</u>: Given that 'each patient's' symptom profile and ... impact of QoL is heterogeneous' (p52) and that 'patient heterogeneity' (p164) is a recognised issue, please clarify what determines progression / rate of progression, if known, and whether the groups in the rhLAMAN-05 trial are balanced for these factors.

No real prognostic or stratification factors are known for AM. In addition, the heterogeneity of the disease between patients and in different disease manifestations even within the same patients is such that no disease severity factor has ever been established. As a consequence, patients enrolled in rhLAMAN-05 trial were stratified only by age, which appears to be the only clear clinical variable somehow associated with disease severity.

AM is a monogenic disease characterised by significant heterogeneity in terms of clinical presentation and the spectrum of underlying mutations. This heterogeneity has led to attempts to define separate clinical phenotypes according to the severity of the manifestations. Initially, the disease was described to have two distinct phenotypes:

- Type I: an extremely severe form with onset in early childhood, with clear neuro-psychiatric manifestations, and death
- Type II: a less severe form, constituting the vast majority of AM patients

A second classification by Malm et al (2008) was also proposed, based on three phenotypes, defined as “Mild” (Type 1), “Moderate” (Type 2), and “Severe” (Type 3) (1). However, this classification appears not to be based on clinical evidence and is not helpful in classifying AM patients. In fact, when an attempt was made (post hoc) to classify patients from the rhLAMAN-10 integrated analysis according to the Malm classification on the basis of the patient’s medical history, a total of 11 patients (33.3%) were clearly identifiable as putative Type 1 patients given the clear absence of both ataxia and skeletal abnormalities.

However, the vast majority of these patients (10 out of 11 patients) had clinically-relevant impairment in manifestations not included in Malm's classification, such as motor (nine patients) or pulmonary (five patients) dysfunction, and all presented with some degree of mental impairment.

Seven patients (21.2%) could be reasonably allocated to Type 2 due to the simultaneous presence of both ataxia and skeletal abnormalities. It is of note that ataxia was present in almost all paediatric cases (four out of five patients); however, the Malm classification limits the onset of ataxia to adults only. All patients had motor impairment and two had pulmonary dysfunction, and some degree of mental impairment was present across the board. Interestingly, three of these seven cases (all paediatric) had more serious impairments.

For 15 patients (45.5%), it was not possible to assign one of the two phenotypes as they presented with conflicting results between the two clinical parameters used in the classification. Of these patients, five patients were suffering from ataxia, but exhibited no relevant skeletal abnormalities. Conversely, 10 adults had skeletal abnormalities but no ataxia. Based on these data, Malm's classification fails to identify clear-cut phenotypes in almost 50% of cases. This is consistent with the high degree of inter-patient variability known for the disease, which makes classification based on severity problematic.

In other rare conditions such as Fabry disease, Gaucher, Pompe, and mucopolysaccharidosis (MPS) I, clear distinctions can be drawn between sub-populations that are remarkably different for either target organs, severity, or progression. This distinction is often based on clear differences mainly based on gender and underlying mutation.

Gender

Data on disease course stratified by gender are not available in the Tromsø database or from the relevant publications arising from the database (1-4). The main literature sources include a retrospective and descriptive study of 125 patients, and several case reports of individual patients. In addition, no conclusive data on clinical disease outcome based on gender emerged from case reports in patients bearing the same mutation. Two case reports of siblings of different genders are presented in the literature, allowing for a comparison of patients with the same mutation. In one case, the female sibling presented with a more severe phenotype while the male sibling had a less severe disease (Govender et al, 2014 (5)), while in the other case report, the situation was reversed (Michelakakis et al, 1992 (6)).

Genetic mutation

AM is caused by pathogenic sequence variants in MAN2B1 leading to loss of lysosomal alpha-mannosidase activity. Depending on the causative MAN2B1 mutation, mutant MAN2B1 proteins have been detected in subcellular compartments such as the endoplasmic reticulum (ER) and lysosomes. For instance, the protein can be folded incorrectly and arrested in the ER, or it can be folded correctly and transported to the lysosomes in an inactive form. A total of 127 MAN2B1 disease-associated mutations have been reported. The mutations are scattered throughout the coding region and include missense mutations, nonsense mutations, frameshifting small insertions/duplications/deletions, in-frame duplications, intronic splice site mutations and large deletions. Existing studies indicate that there is no apparent correlation between mutations and clinical phenotypes (7, 8). Phenotypic variability is high, even between siblings with identical genotypes.

A11. <u>Priority Question</u>: Please provide any further information on whether the treatment initiation and continuation rules are likely to change following consultation with UK KOLs (section 10.1.16 p182).

The treatment initiation and continuation rules presented are derived from the post-hoc, multi-domain responder analysis conducted as part of the EMA submission. The results of this multi-domain responder analysis are used in the submitted cost utility model (to inform the rate of discontinuation at year 1). However, to ensure monitoring of patients is practical in the clinical setting, several UK key opinion leaders (KOLs) have already been consulted regarding these criteria. Therefore, the treatment initiation and continuation rules may be subject to change as a result of this UK KOL consultation.

A12. <u>Priority Question</u>: Please clarify how patients with *'mild to moderate AM*' (p38) and *'for whom allogeneic HSCT is unsuitable and/or not possible*' (p42 and p67) are defined / identified for the purposes of being eligible for VA treatment and thus haematopoietic stem cell transplantation (HSCT) is not relevant as a comparator (Table 2 p33). How many of the patients in the trial would have been eligible for HSCT in accordance with UK practice and /or Chiesi's definition of eligibility? Does the exclusion of these patients affect the outcomes described in the decision problem?

Patients with mild to moderate AM

The typical profile of an AM patient who would be classified as 'severe' according to the three-phenotype classification (1) is characterised by a very young age and rapidly progressive involvement of the central nervous system, and who would typically be candidates for allogeneic HSCT if available and clinically indicated to receive it. The EMA's expected approved therapeutic indication (based on the recently published positive Committee for Medicinal Products for Human Use [CHMP] opinion) excludes this type of 'severe' patient. None of the patients involved in the rhLAMAN trials displayed such 'severe' phenotypic presentation; the patients enrolled in the rhLAMAN clinical trial programme presented with 'mild to moderate AM' and therefore fall outside the 'severe' phenotype.

Patients for whom allogeneic HSCT is unsuitable and/or not possible

Eligibility and suitability for allogeneic HSCT would be considered on a case-by-case basis, and would depend on the availability of a suitably matched donor, the age of presentation and diagnosis of the patient and the impact of this on the perceived risk-benefit of allogeneic HSCT treatment, in addition to the impact of any comorbidities.

It is assumed that any patients in the rhLAMAN clinical trial programme who were suitable for allogeneic HSCT would have been previously treated; therefore, the population within the trial programme would be those patients only unsuitable for allogeneic HSCT and should not have any impact on the outcomes described within the decision problem.

As stated above, those patients with a severe, rapidly progressing disease course are also typical candidates for allogeneic HSCT and would not be eligible for velmanase alfa following the expected EMA approved therapeutic licensed indication based on the recent CHMP positive opinion.

A13. Treatment continuation rules (p.26): How would the current treatment 'start-stop criteria' affect the evidence base? Would any patients who participated in the clinical trials have been excluded on the basis of these rules? How would this affect the outcomes reported?

The current treatment start-stop criteria were based primarily on the eligibility criteria of the rhLAMAN trials and the outcome of the post-hoc, multi-domain responder analysis results from rhLAMAN-05 and rhLAMAN-10. Therefore, there would be no effect on the number of patients included in the study or those at the Month 12 review point. There may be some effect on the results seen at longer term follow up for patients in rhLAMAN-10 in that only the patients meeting the endpoints at Month 12 would have continued with treatment; therefore, outcomes at later time-points are likely to be more favourable if only this group of patients were to be examined.

A14. Please clarify if there was only one patient not naïve to velmanase in rhLAMAN-05 (p110)? What is the evidence to support a 3-month wash out period in the inclusion criteria (p97)?

In rhLAMAN-05, a total of 25 patients were enrolled and assigned to either velmanase alfa (N=15) or placebo (N=10). Of these subjects, 24 had never received velmanase alfa before entering rhLAMAN-05 (i.e. were naïve to treatment). The remaining patient was initially enrolled in rhLAMAN-02 (ID# 520) and continued to rhLAMAN-03 before discontinuing treatment and dropping out from the study due to adverse drug reactions (i.e. repeated infusion-related reactions [IRRs]). After more than 2 years without treatment, the patient was enrolled in study rhLAMAN-05 (ID# 403) and has been treated with velmanase alfa without further discontinuations ever since.

The length of the wash out period was set in order to ensure that a sufficient amount of time had elapsed since the last administration of an investigational medicinal product (IMP) in a previous trial. At the time of the study design, the most probable experimental treatments for a lysosomal storage disorder (LSD) were enzyme replacement therapies (ERTs). Given that most ERTs are given as weekly or bi-weekly infusions, a total of 12 weeks since the last infusion would ensure that a time significantly longer than 5 times the longest theoretical half-life would have elapsed, ensuring a complete drug wash out.

A15. Please clarify why patients with IgE >800 IU/mL were excluded from rhLAMAN-05?

At the time of trial design, it was decided to exclude patients with significant atopic predisposition, at high risk of anaphylactic reactions, or for whom the high background concentrations of immunoglobulin E (IgE) would make it difficult to clearly identify an increase due to a reaction to velmanase alfa. The threshold was arbitrarily chosen; however, 800 UI/mL is representative of highly pathological levels of circulating IgE.

A16. Please clarify if treatment was unblinded for any participants of rhLAMAN-05? Which group were they allocated to? (p98)

No case of unblinding occurred during the conduct of the study in rhLAMAN-05 trial. Blinding was open for all 25 patients after database lock, as foreseen by the statistical analysis plan.

Comparator

A17. <u>Priority Question</u>: Please clarify the number and the age of patients in the UK that have received an HSCT. Please also clarify what data exist on the effectiveness and safety data of HSCT.

Based on the data collected in the recent UK Society for Mucopolysaccharide Diseases (UK MPS Society) Survey, Chiesi is aware of [redacted] patients that have received allogeneic HSCT for the treatment of AM in England. Summary information for these [redacted] patients are provided in Table 2, with full details of the data collected for these [redacted] patients described in **Appendix A**.

Table 2: UK MPS Society Survey patients in receipt of allogeneic HSCT for AM

MPS Survey patient code	Current age (years)†	Age at diagnosis (years, months)‡	Weight (kg)‡	Walking ability‡	Age at receipt of allogeneic HSCT§
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AM, alpha-mannosidosis; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; UK, United Kingdom.
†At time of survey completion; ‡Responses taken from phase 3 of the survey responses, as they are the most up to date data; §Treatment described as bone marrow transplant in survey responses
Source: Data on file: UK MPS Society patient and carer survey, 2018 (9).

As described in Section 8.3.3 of the CS, there is limited evidence on the safety and efficacy of allogeneic HSCT in the treatment of AM in the UK. Following a clinical systematic review (see Appendix 2, Section 17.2.1 of the CS), only seven studies investigating allogeneic HSCT as a treatment for AM in those aged ≥6 years old were identified (10-16). Only data for an AM patient population aged ≥6 years receiving allogeneic HSCT were extracted as the economic case for velmanase alfa is presented in this age group only (see Section 12.1.1 of the CS for further rationale). None of the identified studies for allogeneic HSCT were randomised controlled trials (RCTs) and all studies enrolled a small sample size with a maximum of three patients aged ≥6 years old. Only two of the seven studies identified included AM patients from the UK (10, 14); however, in the study by Mynarek et al, 2012 it is unclear which of the reported patients in the study (n=17) were from the UK, as the data were derived from multiple countries in a retrospective multi-institutional analysis (UK, Germany, United States, Norway and the Netherlands). Please consult the following tables in Appendix 2, Section 17.2.1 of the CS for further information regarding the identified effectiveness and safety data for allogeneic HSCT in AM patients aged ≥6 years old:

- Table 123: Baseline characteristics of the studies included in the clinical efficacy review (original review and update)
- Table 124: Summary of clinical efficacy results reported in studies included in the clinical efficacy review

- Table 125: Summary of safety results reported in studies included in the clinical efficacy review

As stated in Section 8.3.3 of the CS, velmanase alfa is to be positioned in patients with AM alongside best supportive care (BSC) for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible. Therefore, allogeneic HSCT is not considered as a relevant comparator for velmanase alfa.

The results of the aforementioned clinical effectiveness systematic literature review also indicate that there are very limited effectiveness data for the use of allogeneic HSCT in a UK AM patient population, which limits the potential for a robust comparison to velmanase alfa if it (allogeneic HSCT) were to be deemed an appropriate comparator.

Study Design

A18. a- Please clarify why some patients were enrolled in a compassionate use programme, whilst some were enrolled in rhLAMAN-07 and -09? (p99)

b- What are studies rhLAMAN-07 and rhLAMAN-09 designed to test?

a. The initial development plan for velmanase alfa envisaged that all patients completing the Phase II trial rhLAMAN-04 and the Phase III trial rhLAMAN-05 were to transition to a multi-national compassionate care program to provide continuation of treatment until local availability of the commercial product. Relevant authorities and ethical committees of the concerned countries were engaged to verify local acceptability and feasibility of such plan. The authorities of some countries were not open to support the switch to compassionate care and preferred the inclusion of national patients into a long-term open-label treatment study, mainly focused on safety. This situation occurred in France, Norway, and Poland. In all these countries, where a compassionate care programme was not recommended or feasible, a nation-wide trial was opened:

   1) rhLAMAN-07: included French patients only, who reported to a single clinical centre in Lyon (national principal investigator: Nathalie Guffon). In this study, patients are treated and assessed for safety in Lyon, France. In addition, patients are referred to the international coordinator centre of Copenhagen (Rigshospitalet, principal investigator: Allan Meldgaard Lund) for a yearly efficacy assessment.

   2) rhLAMAN-09: included all patients from Norway and Poland. In this study, patients are treated and followed-up for both safety and efficacy in Copenhagen.

   Patients from the other countries were transitioned to a local compassionate care programme.

b. The two studies rhLAMAN-07 and rhLAMAN-09 are primarily designed to ensure continuity of treatment in patients who are resident of countries where a national compassionate care programme was not acceptable or feasible, and to monitor the safety of velmanase alfa administration. In addition, all patients are assessed yearly in the coordinating centre in Copenhagen. No formal hypothesis testing or sample size calculation was considered for these long-term, open-label extension studies.

Outcomes

A19. Priority Question: Please clarify what was the European Medicines Agency's (EMA's) reason for requesting a multi-domain analysis?

At D120 of the MAA review procedure, the Rapporteur and co-Rapporteur requested Chiesi to provide further information and data analysis to enable better quantification of the clinical relevance of the observed results, with a particular focus on the individual patient's change from baseline in relation to a clinically important difference defined for each relevant efficacy endpoint.

The abovementioned question (Q137D) requested the following (17):

"*The clinical relevance of the various changes compared to baseline or compared to placebo cannot be assessed for all endpoints due to the lack of predefined clinically important changes. Clinically relevant changes based on experience with comparable conditions for the various endpoints should be identified based on relevant literature. For example 3MSCT and 6MWT might be related to the experience in patients with JIA. Responder analyses based on these clinically relevant differences should be submitted. Also the 3MSTC and 6MWT results should be presented as scatter plots of change (style shown in fig 11-6 in study report rhLAMAN-05) in order to further appreciate the individual responses."* [verbatim from Q137D of D120 List of Questions]

To address this question in a complete manner, Chiesi (1) defined a minimal clinically important difference (MCID) for each of the somatic efficacy parameters measured in both the Phase I/II and Phase III trials; (2) provided a response analysis based on the response to treatment for each variable according to the defined MCID; and (3) generated a global treatment response model based on domains of clustered biochemical and clinical variables to combine all variables in a single response to treatment score.

The MCIDs for the clinical endpoints tested in the velmanase alfa trial were not previously defined for AM. Therefore, Chiesi conducted a literature review and consulted with experts in the field in an attempt to define MCIDs for serum oligosaccharides, the 6-minute walk test (6-MWT), the 3-minute stair climb test (3-MSCT), forced vital capacity (FVC) and quality of life (QoL) endpoints.

The disease heterogeneity, exemplified by large variation in severity across the numerous disease manifestations, together with the small population size, leads to very large variability at baseline for many measures of efficacy and limits the sensitivity of the classical metric application (such as mean or median values) to detect the overall clinically significant treatment effect. As such, the interpretation of analyses using mean values are limited in this context, while a responder analysis might represent an alternative way to measure treatment effects across multiple clinical parameters. In fact, the strategy of combining disease-specific response domains is emerging in rare diseases. For example, in a recent study in Duchenne muscular dystrophy (DMD) (18), it was found that a combination of outcome measures (North Star Assessment and the 6-MWT) can be effectively used in ambulant DMD boys and provides information on different aspects of motor function, which may not be captured by using a single measure alone. In Classic Late Infantile Neuronal Ceroid Lipofuscinosis, a disease score has been generated based on mobility and language (Oral presentation at 2016 SSIEM Annual Symposium, Rome 2016). In MPS VII, response has been measured

using an index of aggregated scores for 6-MWT, FVC, shoulder flexion, visual acuity and Bruininks-Oseretsky test of motor proficiency, second edition (BOT-2) (19).

In the velmanase alfa multi-domain, responder analysis, the endpoints were grouped into three domains, one biochemical domain and two clinical (functional and QoL) domains:

- a pharmacodynamic domain including serum oligosaccharide response
- a muscular-functional domain including the 3-MSCT, the 6-MWT and FVC % of predicted. As muscular weakness is a key symptom of the disease, FVC % of predicted was included as representative of muscular effort
- a QoL domain, including two different scores extracted from the childhood health assessment questionnaire (CHAQ; CHAQ disability index and CHAQ visual analogue scale [VAS] pain).

A patient was considered a responder in a domain if they achieved a response to at least one efficacy parameter within that domain. In the overall responder analysis, a patient qualified as a responder to treatment if the response criteria was reached in at least two domains.

A20. <u>Priority Question</u>: Please clarify what evidence exists for a relationship between surrogate markers, such as serum oligosaccharides and IgG and clinical outcomes. (i.e. have the surrogate markers been validated?)

Serum oligosaccharides

Full details of the data submitted to the EMA in relation to the relationship between changes in serum oligosaccharide and changes in clinical parameters are documented in the provided data on file (DOF) reference – 'DOF – Chiesi – Response to Clinical Question 137C.pdf' (20). The key themes of the available evidence base are:

Surrogate biomarkers to predict clinical benefit – relevant in the assessment of rare, chronic and progressive diseases

AM is a progressive disease with substantial accumulation of irreversible damage to tissues and organs. This progression may be slow, depending on the presentation of the disease on an individual basis. Unpredictable timeframes of progression cause difficulty in conducting studies within a reasonable timeframe, which creates a compelling need for the use of alternative biomarker endpoints. Additionally, if the clinical manifestations of the disease are irreversible and the goal of the therapy is stabilisation, achieving sufficient power to detect the difference between placebo and treated patients is far more difficult. In this situation, biomarkers that are directly in the line of the pathophysiologic process provide a valuable assessment of treatment effect that can reasonably predict clinical benefit.

AM is characterised by a deficiency of the enzyme alpha-mannosidase. Lack or deficiency of alpha-mannosidase results in lysosomal accumulation of mannose-rich oligosaccharides in all tissues. The progressive accumulation of oligosaccharides is toxic and induces impaired cell function and apoptosis. Serum oligosaccharides were therefore chosen as the primary pharmacodynamic (PD) biomarker in the rhLAMAN clinical programme. A reduction in serum oligosaccharides is representative of the intracellular lysosomal activity of alpha-mannosidase and therefore the oligosaccharide content in the serum of patients

before and after ERT is considered an important PD biomarker to assess the efficacy of ERT in AM patients.

Relationship between serum oligosaccharides and clinical endpoints

Pearson's correlation

Changes in serum oligosaccharides were assessed in relation to the changes from baseline after 12 months of treatment and at the last observation during rhLAMAN-10 for the co-primary endpoint (3-MSCT), and for the secondary endpoints of 6-MWT and FVC % of predicted.

Pearson's correlation was calculated to determine the relationship between serum oligosaccharides and clinical parameters (changes from baseline to Month 12 and last observation in both). The results are presented in Table 3. The desired result is a strong negative correlation, i.e. as serum oligosaccharides decrease, the results of the clinical measures increase (improve). At Month 12, a marginal negative correlation was seen between serum oligosaccharides and two of the clinical parameters; the 3-MSCT (r= –0.23301, p=0.2071) and the 6-MWT (r= –0.22183, p=0.2304). A negligible negative correlation was seen between serum oligosaccharides and FVC % of predicted. At last observation, a marginal negative correlation was seen between serum oligosaccharides and all three clinical parameters; the 3-MSCT (r= –0.23231, p=0.1933), the 6-MWT (r= –0.32689, p=0.0633) and FVC % of predicted (r= –0.19375, p=0.3139).

Table 3: Correlation between serum oligosaccharides and clinical parameters (change from Baseline to Month 12 and last observation)

Endpoint	Month 12	Last observation
3-MSCT		
Pearson Correlation Coefficient	–0.23301	–0.23231
p value	0.2071	0.1933
N	31	33
6-MWT		
Pearson Correlation Coefficient	–0.22183	–0.32689
p value	0.2304	0.0633
N	31	33
FVC % of Predicted		
Pearson Correlation Coefficient	–0.06684	–0.19375
p value	0.7354	0.3139
N	28	29

Abbreviations: FVC, forced vital capacity; 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test.

It is apparent from these results that a trend for a stronger negative correlation between changes in serum oligosaccharides and changes in clinical parameters emerges as time progresses. At last observation, the negative correlation with 6-MWT increased in strength vs Month 12 and a marginal negative correlation with predicted FVC % arose (at Month 12 the correlation was negligible). Further details of the association between serum

oligosaccharides and each clinical parameters (3-MSCT, 6-MWT and FVC % predicted) are provided in the DOF reference (20).

The correlation between changes in the PD biomarker and changes in the clinical endpoints should be considered in the context of disease-specific hallmarks that, acting as confounding factors, may mask a correlation. In particular, when this correlation is examined at the level of a single clinical endpoint, the following confounding factors may interfere: 1) limited treatment duration, 2) a heterogeneous population which was not pre-selected in favour of younger patients in the early phases of the disease, and 3) heterogeneity of disease presentation across clinical parameters. In addition, given the results of the natural history study (21) and the long-term data from patients treated with velmanase alfa in rhLAMAN-10, it is plausible that clinically relevant changes in motor function (3-MSCT and 6-MWT) and pulmonary function (FVC % predicted), may take more than 2 years of treatment to emerge.

Multi-domain responder analysis

As AM is a complex, ultra-rare disease which involves multiple body systems, it is likely that more than one clinical endpoint for each domain is required to adequately assess an effective treatment. The large variation in severity, disease stage, irreversibility and age of onset led to large variability at study baseline for many measures of efficacy. This limits the value of classical descriptive statistics (such as mean or median values) to detect whether the overall treatment is clinically significant. As presented in the CS, a post-hoc analyses combining multiple disease-specific domains after 12 months of treatment and at last observation was conducted. This analysis supports that, given a stable significant reduction of serum oligosaccharides, overall clinical response to treatment emerges over time, paralleling the clearance of serum oligosaccharides which is the preliminary requirement for clinical benefit.

The results of the multi-domain responder analysis, which considers multiple domains relevant to AM (PD, functional and QoL domains), demonstrated that the majority of patients were responders (≥2 domains) to velmanase alfa treatment with a greater trend for response following prolonged treatment. From Month 12 to last observation, following an extended period of treatment with velmanase alfa, there was a clear shift to a larger proportion of patients showing improvement in all three domains, i.e. normalisation was reached in the PD (serum oligosaccharides) and MCID in the functional domain (3-MSCT, 6-MWT and FVC % of predicted) as well as the QoL domain. In the domain-specific responder analysis, serum oligosaccharide clearance was maintained over time while improvement in the motor and QoL domains became more apparent at last observation. These results support that there is a relationship between clinically relevant serum oligosaccharide clearance and clinically relevant improvement in clinical parameters, but that this relationship only becomes clearly apparent after prolonged treatment with velmanase alfa.

Serum IgG

Full details of the data submitted to the EMA concerning the relationship between changes in serum immunoglobulin G (IgG) and infection rates are documented in the provided DOF reference – 'DOF – Chiesi – Response to Clinical Question 149' (22). The key themes of the available evidence base are:

Serum IgG – a relevant biomarker for infection rates in AM

Immunodeficiency and recurrent infections are hallmarks of AM. Literature on longevity in AM is limited, but sources available demonstrate a progressive clinical deterioration resulting in life-threatening illness in adult patients who have a reduced life expectancy. This morbidity and mortality can in part be attributed to immunodeficiency where patients experience recurrent systemic infections.

The biomarker of serum IgG is well accepted as a surrogate for humoral deficiency and for patients with hypogammaglobulinaemia. Patients with AM may have serum IgG levels below the normal range. The standard therapy for hypogammaglobulinaemia is replacement with immunoglobulins, a treatment which has been demonstrated to reduce infections. An increase in IgG following treatment with velmanase alfa is therefore considered a positive effect.

The effect of serum IgG status on antibiotic use

The dataset available recapitulating the entire clinical programme with velmanase alfa cannot robustly demonstrate a positive effect of the treatment with velmanase alfa on infection rate, as the rate of infections was not systematically investigated as an efficacy endpoint or as an adverse event of special interest (AESI). However, there are multiple indicators that point to the beneficial clinical effect experienced by patients treated with velmanase alfa.

One such indicator is a post hoc analysis of infections requiring antibiotics in those patients with hypogammaglobulinaemia in rhLAMAN-05. The number of infections that required antibiotic use in patients with low serum IgG levels in rhLAMAN-05 was assessed, with a comparison between velmanase alfa vs placebo made. In total, 5/15 patients (33.3%) receiving velmanase alfa and 4/10 patients (40.0%) receiving placebo were reported to have serum IgG levels below the normal range for their age and gender. Of these patients, a slightly larger proportion of patients receiving placebo experienced infections that required antibiotic use vs velmanase alfa treatment – 2/4 patients (50.0%) receiving placebo vs 2/5 patients (40.0%) receiving velmanase alfa (Table 4). Over 12 months, the overall rate of infections requiring antibiotic use per patient was higher under placebo vs active treatment (2 vs 1). If only those events that occurred after 1 month of treatment are included (after such time that velmanase alfa would be assumed to be effective), the rate of infection per infected patient was 1.5 under placebo vs 0 under active treatment.

Analysis of concomitant medication use (infections that required antibiotic use) and safety data (infection and infestation treatment emergent adverse events), which was regularly collected, revealed supportive evidence that no infections from encapsulated bacteria affected patients who were originally identified as having hypogammaglobulinaemia and received velmanase alfa for at least 1 month. In contrast, continuing occurrence of infections was reported for patients under placebo with low IgG levels. The timing of the infection events in particular support the immune-protective, beneficial impact of velmanase alfa, as no infections were experienced after 1 month of treatment, while patients under placebo were persistently affected during the year of study observation. This is believed to be due to velmanase alfa reversing hypogammaglobulinaemia or at least improving IgG status.

Caregivers report reduced infection rates after treatment

A questionnaire was administered to the caregivers of the patients included in the rhLAMAN studies at the time of the comprehensive evaluation visit (CEV) during rhLAMAN-10 to

explore where the burden of disease was for each patient and to indirectly estimate the occurrence of infections. One of the sections questioned the changes in social life problems before and after treatment. The large majority of caregivers reported the recurrent infections as a pre-treatment burden, which limited the social life of the patients, and a reduction in the rate of infections following treatment with velmanase alfa (Table 5). Although the exact number of infections was not collected, of the 32 patients with completed questionnaires, 22 (68.8%) were reported by their caregivers as having fewer or almost no infections after treatment. This observation supports the favourable effect of velmanase alfa on infection rates in all rhLAMAN studies, including the early phase studies for which no serum IgG values were collected. As these benefits were seen in the majority of patients, including those patients in rhLAMAN-05 who were not identified as having below normal IgG status, even patients with normal IgG status may experience an increase in IgG levels which improves their resistance to infection.

Table 4: Number of patients with low IgG levels experiencing infections requiring antibiotics during the 12 months of rhLAMAN-05

	Velmanase alfa n=15		**Placebo n=10**	
	Number of patients (%)	**Number of events**	**Number of patients (%)**	**Number of events**
Number of patients with low IgG	5/15 (33.3)	-	4/10 (40.0)	-
Low IgG patients with infections requiring antibiotic use				
Overall	2/5 (40.0)†	2	2/4 (50.0)	4
>1 month	0/2 (0)	0	2/2 (100.0)	3
Rate of Infections requiring antibiotics per infected patient				
Overall	1		2	
>1 month	0		1.5	

Source: CSR Study rhLAMAN-05, Table 11-19, Appendix 16.2.4. Listing 16.2.4.4
†Patient 518 received Cefazolin on Day 234 for use during genua valga surgery has been excluded as the antibiotic use was preventative and not to treat an infection.
IgG, immunoglobulin G.

Table 5: Changes in social life problems: Occurrence of infections before and after treatment with velmanase alfa

Patient	**Before Treatment**	**Last Observation in rhLAMAN-10**	
		Positive Change	**No Change/ No Comment**
401	No comment on infections		No comment on infections
402	Often sick with fever	Less infections – almost none	
404	Often lung infections	Seldom lung infection	
405	No social life problems reported		No social life problems reported
406	Many infections	Fewer infections	

Patient	Before Treatment	Last Observation in rhLAMAN-10	
		Positive Change	No Change/ No Comment
407	Many infections	Fewer infections	
408	Many infections	Fewer infections	
409	Several infections	Fewer infections. Better healing.	
410	No social life problems reported		No social life problems reported
503	No comment on infections	Fewer infections	
504	No social life problems		No social life problems
505	A lot of infections, especially ear infections and common colds	Less infections, no infection last year	
506	Often infections, especially upper airways	No infections	
507	Many ear infections, abscesses on body and face	No ear infections since study start	Still has fungal infection on upper body
508	Many infections	Fewer infections this year	
509	Many infections per year	Fewer infections, very noticeable change	
510	Many infections	Fewer infections. Heals better.	
511	No social life problems reported		No comment on infections
512	No comment on infections		No comment on infections
513	Before study start many infections, often upper airway infections requiring antibiotic treatment and otitis	Rarely infected. Has not experienced a throat infection since study start. Otitis 2-3 times a year	
514	Often infections (nose), worse as a child	Fewer infections. Not been sick since last [year]	
515	No comment on infections		No comment on infections
516	Severe infections	Still takes a long time recovering from illness, but milder course of disease	Still some tendency to common colds/sore throat
517	No social life problems reported		No social life problems reported
518	No social life problems reported		No comment on infections
519	No social life problems reported		No social life problems reported
520†	Many infections	Fewer infections	
521	Fairly many infections	Fewer infections, rarely sick	

Patient	Before Treatment	Last Observation in rhLAMAN-10	
		Positive Change	No Change/ No Comment
522	Many ear infections. Had flu in the winter for long periods of time	Fewer infections the last two years	
523	Many infections, often fever	Normal seasonal infections, no fever	
524	Colds, many infections	One cold per year	
525	Many infections, often antibiotic treatment. Upper airway infections, otitis media, stomatitis	Most notable difference for the parents is fewer infections since treatment start	

Source: CSR Study rhLAMAN-10, Appendix 16.2.6. Listing 16.2.35
Note: There are no data available for Patients 501 and 502.
†Participated in Study rhLAMAN-02, -03 as Patient 403.
Wording reported as in source.

A21. <u>Priority Question</u>: Serum IgG is a proxy for the clinical outcome "infections". Please clarify why infection rates were not measured and analysed as a clinical outcome (they are measured as an adverse event). If they were measured, please provide the data.

Although immunodeficiency and recurrent infections are hallmarks of AM, at the time of designing the clinical trials for velmanase alfa the expected size of the trial population was considered too small to envisage the possibility to collect meaningful clinical data on the change of infection rate after treatment. No specific parameters were assessed in relationship to immune deficiency and/or infection rate or severity; both the occurrence of infections and the levels of IgG were collected as part of the routine safety assessment.

However, at the time of rhLAMAN-05 data analysis, a clear difference in IgG concentration behaviour was observed between treatment and placebo groups raising the hypothesis that treatment with velmanase alfa could lead to improved cellular response to infections. In a post-hoc analysis, a statistically significant difference in mean serum IgG between velmanase alfa and the placebo group ($p<0.0001$) was observed, with an increase in the serum values apparent in the velmanase alfa group at Month 12 (adjusted mean difference vs placebo: 3.47 g/L; 95% confidence interval [CI]: 2.12, 4.81).

Unfortunately, serum IgG were only routinely measured as part of the trial assessments in rhLAMAN-05; therefore, baseline data are missing for the phase I/II patients. Within the Phase III study rhLAMAN-05, only a very limited number of patients had relevant hypogammaglobulinaemia at baseline. In fact, 9 out of 25 patients were classified as having low serum IgG based on age and gender (five randomised to velmanase alfa and four to placebo). Notably, the majority of patients treated with velmanase alfa (3 of 5 patients, 60%) reverted to a normal immunological pattern. In contrast, no improvement in the placebo arm (all four patients) was observed. The two patients in the velmanase alfa arm who did not revert to normal did experience a remarkable improvement in serum IgG status, even though serum IgG was below the normal value for their age and gender.

This sub-group of nine patients is the only group where a potential correlation between an increase in serum IgG due to treatment and improvement in rate and/or severity of infections could be formally demonstrated. In particular, of the five patients with low IgG at baseline allocated to velmanase alfa treatment, two (40%) had at least one infection requiring the use of antibiotics for a total of 2 events (1 per-patient). These two events occurred within the first month of treatment (4 administrations); no further events occurred from Month 2 to 12. Conversely, of the four patients with low IgG at baseline allocated to placebo, two (50%) had at least one infection requiring the use of antibiotics for a total of four events. Of these four events, three occurred after the first month of trial; the results are summarised in Table 4.

A copy of the response to a similar question submitted to the EMA in relationship between IgG and infections is provided as DOF reference – 'DOF – Chiesi – Response to Clinical Question 149 (22). The document also provides narratives of these nine patients as well as an overall commentary on the infection data available from the rhLAMAN-05 and rhLAMAN-10 studies.

A22. <u>Priority Question</u>: Please provide evidence to support the minimum clinically important difference (MCID) for all outcomes within the scope of the NICE assessment. Please also clarify how the cut-offs for serum oligosaccharide levels and childhood health assessment questionnaire (CHAQ) were determined.

Full details of the data submitted to the EMA in relation to the MCID and multi-domain responder analysis are documented in the provided DOF reference – 'DOF – Chiesi – Response to Clinical Question 137D (17). Chiesi conducted a literature review and consulted with experts in the field to define MCID for serum oligosaccharide, 6-MWT, 3-MSCT, and FCV and QoL endpoints included in the multi-domain response analysis model. Chiesi is not aware of any other MCIDs specific to AM for the remaining, additional outcomes described in the NICE scope. Key evidence to support the MCID for these five outcomes included in the multi-domain responder analysis are described below:

Serum oligosaccharides

The adopted MCID for patients with AM was defined as a cut off of ≤4 µmol/L.

This was based on the data from rhLAMAN-05, in which all patients had pre-treatment serum oligosaccharide levels >4.0 µmol/L. The lower limit of quantification of the assay was 0.5 µmol/L and the patient value at baseline ranged from 4.4 µmol/L to 10.2 µmol/L.

3-MSCT

The adopted MCID for patients with AM was defined as an increase in ≥7 steps/min.

The use of the 3-MSCT as a measure of efficacy is limited in the context of LSDs. The 3-MSCT has been previously used in a study (MOR-004) assessing the effect of elosulfase alfa in patients with MPS IVA over 6 months (23). An attempt was made to define a pre-specified MCID for each of the outcomes of interest using a combination of literature review and a Delphi consensus panel prior to the unblinding of the trial; however, these efforts proved unsuccessful, such that the responder analyses that were ultimately carried out were conducted post hoc. In MOR-004, there was a mean change (standard deviation) from baseline of 4.8 (8.1) steps/min in the elosulfase alfa group compared with 3.6 (8.5) steps/min in the placebo group (least squares [LS] mean difference: 1.1 [95% CI: –2.1 to 4.4]). In MPS

IVA, a change of 20% from baseline was adopted for the threshold in the relative risk. With a baseline in MPS IVA of 27–35 steps/min, 20% was approximately 7 steps/minute.

In the absence of any existing MCID, an absolute change of ≥7 steps/minute can be considered appropriate to apply to AM patients, based on the clinical plausibility claimed with other LSDs. No additional references emerged from a literature search or consultation with the experts in the field.

6-MWT

The adopted MCID for patients with AM was defined as an absolute increase of ≥30 metres.

This endurance test was originally developed to measure the submaximal level of functional capacity in adult patients with moderate to severe heart or lung diseases, and is a predictor of morbidity and mortality in these patients. The test has been adopted to assess functional outcome in other patient populations, such as cystic fibrosis, obesity, and MPS. The 6--MWT results are associated with pulmonary function, health related QoL, maximum exercise capacity, and mortality. The MCID for the 6-MWT has been reported as 54–80 metres in chronic lung disease patients (24, 25), as 33 metres in patients with pulmonary hypertension (26) and as 30.1 metres in patients with chronic heart failure (27). In Duchenne muscular dystrophy, the MCID for the 6-MWT was reported as 28.5 to 31.7 metres based on two statistical distribution methods (28). A literature-based combined predictive model of the 6-MWT in healthy subjects was used to derive 6-MWT as percentage of predicted normative value (adjusted for age, height and gender).

For elosulfase alfa in the treatment of MPS IVA, an increase in the 6-MWT was considered clinically significant where the magnitude of change from baseline over 24 weeks compared with placebo was 22.5 metres (23). As the baseline functional status of patients with AM was better (466 metres) compared with MPS IVA (200 metres), this makes a definition of MCID more challenging given the confounding ceiling effect, i.e. as patients with AM were generally well functioning at baseline, there is limited ability to observe further improvement; consequently, demonstrating that treatment with velmanase alfa results in a significant improvement in 6-MWT compared with placebo is challenging. Furthermore, a longer treatment duration is required in higher-functioning patients in order to observe a meaningful effect; the variable progression of physical function in AM also requires the assessment of efficacy over a prolonged period when considering a single efficacy measure.

When Lachmann and Schoser, 2013 (29) analysed the MCID for endpoints in Pompe disease, they conducted a literature search on the MCID for the 6-MWT in different diseases. When these absolute and relative MCIDs for the 6-MWT were applied to clinical trials of late-onset Pompe disease, the majority of studies (9 out of 10) reported absolute changes from baseline in 6-MWT that lay within or above the absolute MCID level (24–54 metres). As Pompe disease is a rare LSD associated with progressive proximal myopathy, causing a gradual loss of muscular function and respiratory insufficiency, Pompe disease is considered a proxy disease for understanding of clinical endpoints and their relevance in AM. The results from the Lachmann and Schoser review support the assumption that an absolute MCID of 30 metres is also applicable to AM; the distance of 30 metres may have real-world significance in terms of keeping up with peers and traversing the distances required to perform activities of daily living.

Notably, when accepted MCID relative thresholds of other diseases (as low as 5% change) are applied to the mean baseline 6-MWT, a 23.35-metre change would be considered clinically meaningful for AM. This further emphasises that ≥30 metres would be a robust measure of clinical meaningfulness in evaluation of 6-MWT and would exceed the MCID for 6-MWT from multiple accepted methodologies in other diseases.

FVC percentage of predicted

The adopted MCID for patients with AM was an absolute increase of ≥10% of FVC (% of predicted).

When FVC is used as a measure of respiratory function, predicted FVC values >80% are considered to be within the normal range. In patients with chronic lung diseases, change in FVC over time is a valid outcome measure. Guidelines for the assessment of patients with systemic scleroderma cite that an improvement or reduction of 10% from baseline values is required to ensure that the variation in lung capacity can be ascribed to a change in disease severity rather than measurement error (30). In a large study of 1,156 patients with idiopathic pulmonary fibrosis, the MCID in FVC (% of predicted) was defined as an absolute change of 2–6% of predicted (equivalent to a 3–9% relative change from baseline) and changes from baseline in FVC (% of predicted) reflected changes in global health status (31). However, the definition of a relevant change from baseline in FVC in late-onset Pompe disease is variable compared with the MCID described for idiopathic pulmonary fibrosis; despite an observed change below the MCID, patients still reported feeling either “somewhat better” or “much better” in their overall health. In two-thirds of the studies in which late-onset Pompe patients were treated with alglucosidase alfa, the changes from baseline in FVC (% of predicted) were above or within the MCID established in respiratory diseases aforementioned (absolute MCID 2–6%; or 3–9% relative MCID), and the difference was perceived as either an improvement or stabilisation by patients.

The MCID adopted for patients with AM is a challenging target given that the overall study population had predominantly normal values at baseline (mean values were 85% of predicted). Therefore, the study population may be subject to a ceiling effect, where the ability to observe further improvement is limited. Consequently, demonstrating that treatment with velmanase alfa results in a significant improvement in FVC (% of predicted) compared with placebo is challenging.

CHAQ disability index

The adopted MCID for patients with AM was a reduction of ≥0.13.

Disability index scores range from 0 to 3 with higher scores indicating greater disability and the MCID has been reported as -0.13 in Juvenile Arthritis (32). Similarly, AM patients with arthritis present with pain, muscle weakness, skeletal abnormalities and challenges with activities of daily living; 35.7% of the adult patients included in the rhLAMAN-10 integrated data set presented with arthralgia at baseline.

CHAQ pain (VAS)

The adopted MCID for patients with AM was a reduction of ≥0.246.

The MCID for Pain (VAS) has been reported as a reduction of magnitude ≥8.2% (0.82 cm on a 10 cm VAS (33)) in patients with juvenile arthritis, which is a disease with physical impact

on the musculoskeletal system and joints similar to that experienced in AM; this corresponds to a reduction of ≥0.246 on the 0–3 scale. Similar to patients with AM, patients with arthritis present with pain, muscle weakness, skeletal abnormalities and challenges with activities of daily living.

A23. Please clarify why the '3-MSCT' was selected as the co-primary outcome rather than the '6-MWT' outcome measure (p72).

Efficacy was assessed in rhLAMAN-05 and in the rhLAMAN-10 integrated analysis on the basis of two co-primary endpoints: oligosaccharides in serum and the 3-MSCT. Secondary efficacy endpoints included other measures of functional capacity, including the 6-MWT.

Both the 3-MSCT and the 6-MWT have been widely adopted to assess endurance in LSDs (34, 35), and the results have been used as clinical endpoints to support the approval of ERT products for MPS I, MPS II, MPS VI, and MPS IVA. Improvement in these tests of endurance provides a robust measure of clinical benefit.

The 3-MSCT was selected as primary variable to evaluate the effects of velmanase alfa on clinical functioning because it measures the limiting factors amongst multiple systems such as the musculoskeletal, neurological and cardiovascular systems (36). Stair climbing also provides a functional measure that is commonly performed in daily life and relates to level of the independence and community participation. Skeletal abnormalities and myopathy are common disease manifestations in AM and the stair climbing test is associated with measures of lower limb strength and power (37). Stair climbing also requires a greater range of motion from the joints of the lower limbs and greater strength than level walking.

The test was performed in accordance with guidelines (38, 39) by a trained physiotherapist. In the clinical studies in AM patients, the test is limited by the lack of availability of normative data (by age and gender). The assessment is effort-dependent which is significantly problematic in paediatric or neurologically-affected patients whose performance is often influenced by their developmental stage, understanding of instructions and willingness to cooperate, reflecting in inter- and intra-patient variability. However, the test was executed at the same site, in the same conditions (the same stairs) and evaluated by the same trained physiotherapists.

The rarity of AM precludes a formal validation of 3-MSCT in this disease, but its use to test motor function in patients for whom musculoskeletal disease constitutes a major limitation is justified in this condition. KOLs and clinicians who treat these patients consider the 3-MSCT an appropriate test of efficacy for AM treatment (40). This also consider the test as relatively challenging test for patients with sufficient walking proficiency and less influenced by differences in height than the 6-MWT. This greater independence from height makes the test also suitable to test endurance across a relatively large age group with less influence due to age and therefore less dependence from normative age- and gender-adjusted data. The EMA agreed these co-primary endpoints for the Phase III study at the 30 November 2011 protocol assistance meeting.

In addition, Phase II data (N=9) showed a clear and clinically-relevant response in the change from baseline of 3-MSCT of 30 steps in the 3 minutes both at 6 and 12 months of follow up starting from a baseline of 157.9 steps. Results were statistically-significant. The 6-

MWT also showed a relevant increase from baseline of more than 35 meters in average both at 6 and 12 months, although the results were not statistically significant.

Given all these considerations, the 3-MSCT was preferred as the primary outcome measure as it is more challenging from the point of view of the overall performance, potentially more representative of a muscle effort, and based on preliminary trial data.

A24. Please clarify who completed the CHAQ disability index and CHAQ Pain (VAS) tools and how those were completed (p88). The text states *'All patients' legally authorised guardian(s) were asked to complete the following CHAQ topics*', but also suggests that the tools are appropriate for gaining responses from patients themselves. Please clarify why CHAQ was used if the questionnaire was being completed by a proxy adult/guardian? What evidence is there that the measures are valid when completed by a parent/ guardian?

All patients' legally authorised guardian(s) were asked to complete CHAQ disability index and CHAQ Pain (VAS), due to the mental impairment of the patients. It is common for the CHAQ to be given to both parents and children. Concordance between the two are moderately high using an intraclass correlation (41, 42). Several articles on the CHAQ have been published demonstrating the validity of parent report. In fact, parent report appears to be more highly correlated with other measures and the physician's report, when compared with that of the child. In addition, parent report correlates with other measures such as the Paediatrics Outcomes Data Collection Instrument (PODCI) and QoL measures. Parent report is important as it is known that children often underreport their symptoms (43). Several research studies on juvenile arthritis are relevant to this issue.

References of the most important papers assessing parent proxy reporting: Lam C et al, 2004 (41), Brunner H et al, 2004 (42), Klepper S et al, 2003 (44), Ding T et al, 2008 (45), and Kolko D et al, 1993 (43).

A25. Please provide evidence to support the statement that there may have been a 'ceiling effect' for 3-MSCT and 6-MWT, in the context of normal values for these measures.

The evidence to support this statement is from a comparison of rhLAMAN-05 with trials in related, proxy diseases. Ceiling effects are common across functional outcomes (36) and have been previously observed for the 6-MWT (46, 47). To overcome this limitation, one study of ERT for the treatment of MPS IVA (Morquio A syndrome) restricted the patient population to those who had a baseline 6-MWT distance of 30 to 325 metres in order to 'identify patients most likely to show improvement' (48). Consequently, the study successfully demonstrated a significant improvement in 6-MWT compared with placebo following ERT (48). In contrast, the mean 6-MWT distance of patients in rhLAMAN-05 was 460–466 metres; therefore, the rhLAMAN-05 population may have had less potential for improvement.

A26. Please clarify what evidence is available to link mobility and quality of life.

There are four main evidence sources that link mobility and QoL:

1. UK MPS Society Survey data in AM patients

As described in full in **Appendix A** and in further detail in response to clarification question **B47**, the QoL of patients with AM in the UK was assessed qualitatively and quantitatively via a UK MPS Society Survey completed by AM patients and/or their carers.

[redacted] Full details of patients' utility, as reported by carers (by proxy) and by patients (by self-report) are provided in **Appendix A**, with results presented at a patient-level and at a health-state level (i.e. after data pooling for stratification by patients' walking ability).

2. UK KOL AM patient (n=7) audit data

As described in Section 10.1.9.1 of the CS and in response to clarification question **B39**, AM patient utility data (n=7) from EQ-5D-5L questionnaires completed by their treating clinician (i.e. completed by proxy) also provides evidence that AM patients' QoL diminishes as their walking ability worsens.

The data from this UK KOL AM patient audit suggests that a transition to wheelchair dependency is associated with the largest reduction in patients' QoL, as the 'wheelchair dependent' health state had the lowest level of utility of the four ambulatory states assessed. One rationale for this observation, as provided by the treating clinician, is because this is the stage of the disease when patients become self-aware of the severity of their situation in relation to their (lack of) mobility. Another explanation is that if a patient's level of cognition declines further once they move into a 'severe immobility' state, their anxiety/discomfort goes away as they are no longer aware, or less aware, of their disease state, resulting in an apparent utility increase between the 'wheelchair dependent' and 'severe immobility' health states. However, it was noted by the clinician providing the audit data that this QoL trend (where a 'wheelchair dependent' state is associated with the lowest level of utility of the four health states assessed) may not be replicated in all patients, as each patient's symptom profile (in particular their level of cognition and disease/burden awareness) and subsequent impact on QoL is likely to be heterogeneous.

3. UK KOL opinion

As described in Section 7.1.3.1 of the CS, UK KOL interviews were conducted with UK KOLs to gain further understanding on the impact that AM has on QoL of patients. Among other symptoms, reduced mobility was cited as particularly burdensome to patients and that the largest reduction in QoL is thought to be related to a deterioration in ambulatory status. In addition, a rapid decline in QoL can occur following a clinical event that has a profound impact on the patient (e.g. a fall, or ligament damage). Mobility was identified as a key factor in the overall health and QoL of patients with AM. For example, patients who remain mobile for longer may experience fewer infections. Mobile patients will also remain socially integrated, have a better perception of wellbeing and retain a certain level of independence. Consequently, a loss of mobility can have a substantial impact on health and QoL. Please consult the UK KOL interview DOF (49) for further information (for example, responses to

questions in Section 2.2 of the Stage 3 interviews [from page 140/225 onwards in the DOF]), which was provided in the CS.

4. Data from proxy diseases

As described in Section 10.1.9.2 of the CS, data from other LSD diseases, which share some similarities to AM in relation to patients' musculoskeletal clinical features and subsequent (lack of) ambulation, indicate that patients' QoL is linked to their walking ability. As described in Table 6, overall patients' QoL decreases as their ability to walk deteriorates for the proxy conditions of MPS IVA and Pompe disease.

Table 6: Disutility incurred due to functional impairment in proxy disease

Primary health state	Hendriksz 2014 – MPS IVA	Kanters 2015 – Pompe disease
Walking unassisted	-0.07	-0.11
Walking with assistance	-0.33	-0.20
Wheelchair	-0.86	-0.30
Severe immobility	-0.86	-0.30

Source: Hendriksz et al, (2014) (50) and Kanters et al, (2015) (51)

A27. Please clarify if there is there an update on the MPS Society survey (section 12.8.4 p291).

At the time of the CS a survey of UK AM patients and carers was ongoing. This survey completed in January 2018; therefore, Chiesi has provided the methods and results to NICE, as part of this ERG clarification response, as they contain information relevant to the ongoing submission [ID800]. Full details of the survey are provided in **Appendix A** and associated DOF (9, 52). The UK AM patient and carer survey was convened:

- To collect qualitative reports of the impact of AM from patients and/or their carers
- To collect quantitative reports of QoL using widely adopted QoL tools from AM patients and/or their carers

Chiesi Limited commissioned MPS Commercial (a wholly owned, not for profit subsidiary of the UK MPS Society) to design the survey questionnaires and to conduct the survey. Chiesi Limited commissioned an external organisation ([redacted]) to perform qualitative and quantitative analysis of the anonymised survey responses.

Understanding the walking ability of each patient survey respondent was important for purposes of data analysis and for the potential stratification of survey respondents along the AM functional impairment axis from 'walking unassisted' to a 'severe immobility' state. As per the definitions used in the submitted cost-utility analysis model, the following definitions were used when asking patients and/or their carers about the walking ability of patients with AM in the UK MPS Society Survey (Table 7).

Table 7: Definition of the ambulatory health states

State	Description
Walking unassisted	• Patient is able to walk and go upstairs unassisted
Walking with assistance	• The patient requires any form of assistance to walk (e.g. help from another person, footwear to support stability, a walking cane, wheelchair for long distances, hand rails etc.)
Wheelchair dependent	• The patient is wheelchair-bound, but can still operate walking aids/use assistance to traverse short distances. The patient can still transfer themselves without carer support (e.g. the patient can transfer from the wheelchair into bed independently)
Severe immobility	• Patient requires a wheelchair/mobility device continuously and cannot transfer independently (i.e. requires hoists and other assistive equipment)

[redacted]

Please consult **Appendix A** for the full methods and results of the UK MPS Society Survey, which includes:

- Objectives
- Methods (funding, participants, outcome measures, statistical methods)
- Results
    - Participants
    - A summary of results (qualitative and quantitative)
    - Qualitative analysis – individual patient case studies
    - Quantitative analysis – patient and carer utility
        - Patient-level results
        - Health-state level results
- Discussion

Table 8: Summary of UK MPS Society Survey respondents

Survey phases completed by			Patient code	Current age (years)†	Age at diagnosis (years, months)‡	Weight (kg)‡	Walking ability‡	Received specific treatment for AM
1	2	3						
[redacted]								

[redacted]

A28. Please clarify if the 3-MSCT and 6-MWT are adjusted for age and height, or have predicted values for age and height. This is not described in summaries of the studies (e.g. Table 7, p87, p105-106 or in the results for rhLAMAN-05), although the results for rhLAMAN-10 refer to % of predicted (p142, p143). If available, please provide both distance and % of predicted data for rhLAMAN-05 and rhLAMAN-10 for all analyses. If % predicted data are not available, please indicate the likely impact of age and height on these scores, and of normal growth, especially in paediatric patients.

The 3-MSCT does not have reference normative values by age and/ or gender available, thus it was not adjusted in any analysis across the velmanase alfa development. As highlighted in answer to question A23, amongst the various reasons why the 3-MSCT was chosen as primary endpoint, the test is less influenced by differences in height than the 6-MWT; leg length appears to be a relevant contributor to step length, which can influence walking distance but has less of an impact on stair climbing. This greater independence from height makes the test also suitable to test endurance across a relatively large age group with less influence due to age and therefore less dependence from normative age- and gender-adjusted data.

The 6-MWT is not a normative test in its self (i.e. a test that is usually interpreted in reference to normative data), although standard distances by age, height and gender are available. In the Phase I/II and III studies, rhLAMAN-02, -03, -04, and -05, 6-MWT data were analysed and presented only as raw values in meters or as percent of change from baseline. As part of the integrated analysis of rhLAMAN-10, exploratory analysis of percent of predicted values of 6-MWT were performed after adjustment for age, height and gender.

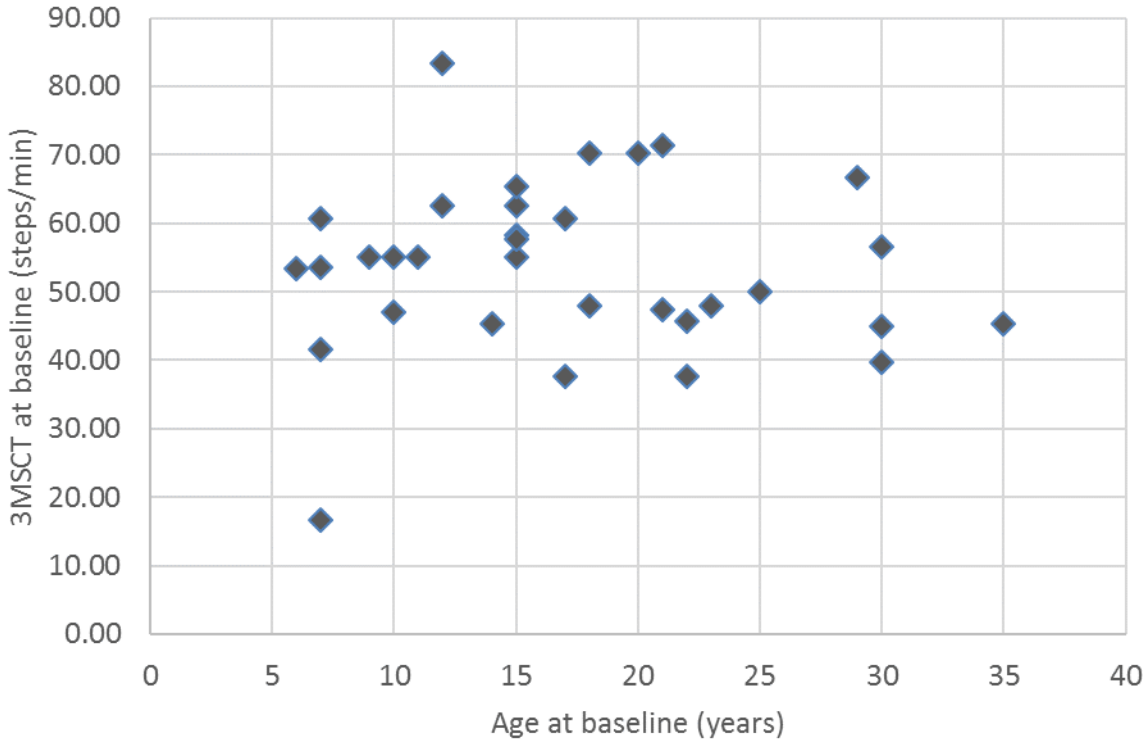
Mean 6-MWT as a percentage of predicted was relatively high at baseline, and showed a small increase from baseline to last observation in patients overall (from 69.04 to 70.20% predicted) and in those aged <18 years (from 69.34 to 71.20% predicted), but showed no change in patients aged ≥18 years. None of the observed changes were statistically significant. Table 9 and Table 10 show the corresponding data extracted from the rhLAMAN-10 clinical study report (CSR).

In terms of estimating the potential impact of age and growth on 3-MSCT and 6-MWT performance, it is of general understanding that the 3-MSCT is less impacted by growth in the scholar age and by the adolescence height burst given that leg length is not a major contributor to staircase climbing performance. Conversely, growth (especially in the adolescent phase) is expected to have a larger impact on the 6-MWT.

In the specific case of AM, some indirect data on the impact of growth on motor performance can be derived from the rhLAMAN-10 integrated analysis baseline data, as the enrolled patients ranged from 6 to 35 years of age at study start. As shown in Table 11, the baseline values for both the 3-MSCT and 6-MWT were not remarkably different between paediatric and adult patients, supporting the hypothesis that growth has a limited influence on these tests in AM patients. One potential explanation for the absence of differences between the two age groups can be related to the absence of the typical height burst associated with adolescence observed in AM patients, which also affects the final adult height.

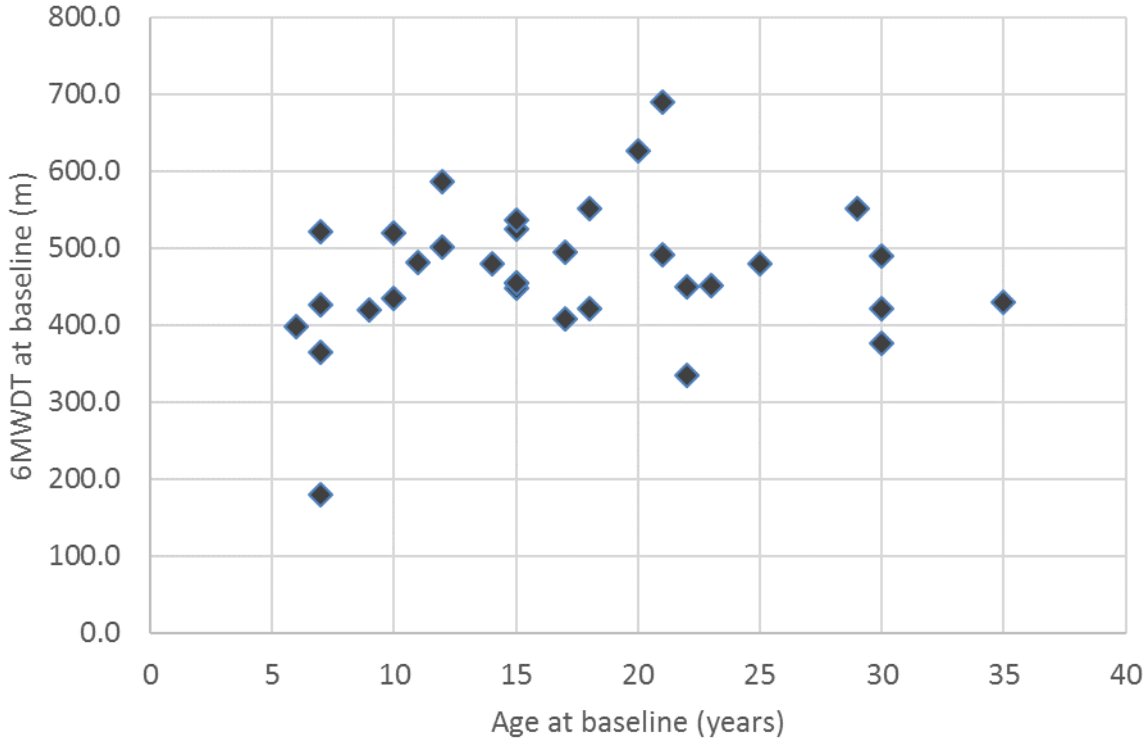
In Figure 3 and Figure 4, the baseline values of the 3-MSCT and 6-MWT have been plotted against the age of patients. Overall, no correlation between age and performance was present in these patients across any age group.

Figure 3: Scatterplot of individual 3-MSCT (Steps/min) and age (years) in rhLAMAN-10 at baseline



Source: rhLAMAN-10 listings

Figure 4: Scatterplot of individual 6-MWT (m) and age (years) in rhLAMAN-10 at baseline



Source: rhLAMAN-10 listings

Table 9: Summary of normalised 6-MWT (% of predicted) in rhLAMAN-10 by timepoint

Parameter Timepoint	Actual value	Absolute change from baseline	% Change from baseline	t-Test results Change from baseline	t-value (df)	p-value	95% CI
normalised 6MWT (%)							
Baseline							
n	33						
Mean (SD)	69.04(11.65)						
Median	67.96						
Min; Max	31.16;90.86						
Month 12							
n	31	31	31	Absolute change	1.323 (30)	0.196	(-1.29,6.032)
Mean (SD)	71.85(10.26)	2.372(9.980)	5.872(22.16)				
Median	69.99	2.754	3.457	% Change	1.476 (30)	0.150	(-2.26,14.00)
Min; Max	55.93;98.86	-17.9;33.41	-22.4;107.2				
Last Observation							
n	33	33	33	Absolute change	0.719 (32)	0.478	(-2.13,4.457)
Mean (SD)	70.20(10.50)	1.162(9.293)	3.552(18.30)				
Median	70.76	2.399	3.457	% Change	1.115 (32)	0.273	(-2.94,10.04)
Min; Max	50.37;93.45	-12.0;24.61	-19.2;78.99				

Source: rhLAMAN-10 CSR, Table 14.2.4.1
Note 1: FAS=Full Analysis Set. n=Number of subjects with data.
Note 2: Normalised 6MWT is given as percent of predicted value (normalised for age, height and gender).

Table 10: Summary of normalised 6MWT (% of predicted) in rhLAMAN-10 by timepoint and age group

Parameter / Visit	< 18 years (N=19) Actual value	< 18 years (N=19) Change from baseline	< 18 years (N=19) % Change from baseline	>= 18 years (N=14) Actual value	>= 18 years (N=14) Change from baseline	>= 18 years (N=14) % Change from baseline	Overall (N=33) Actual value	Overall (N=33) Change from baseline	Overall (N=33) % Change from baseline
Total distance walked relative to normal (%)									
Baseline									
n	19			14			33		
Mean (SD)	69.34 (12.39)			68.64 (11.01)			69.04 (11.65)		
Median	67.96			67.09			67.96		
Min; Max	31.16;90.86			48.72;89.57			31.16;90.86		
Month 12									
n	18	18	18	13	13	13	31	31	31
Mean (SD)	73.33 (10.82)	3.473 (11.94)	8.578 (27.83)	69.81 (9.459)	0.847 (6.524)	2.126 (10.20)	71.85 (10.26)	2.372 (9.980)	5.872 (22.16)
Median	71.49	2.247	3.351	69.41	2.754	3.457	69.99	2.754	3.457
Min; Max	59.43;98.86	-17.9;33.41	-22.4;107.2	55.93;84.54	-9.64;10.75	-11.2;22.05	55.93;98.86	-17.9;33.41	-22.4;107.2
Last Observation									
n	19	19	19	14	14	14	33	33	33
Mean (SD)	71.20 (10.78)	1.865 (10.56)	5.368 (22.04)	68.85 (10.34)	0.209 (7.509)	1.088 (11.86)	70.20 (10.50)	1.162 (9.293)	3.552 (18.30)
Median	70.89	2.399	3.598	65.62	0.817	0.861	70.76	2.399	3.457
Min; Max	52.49;93.45	-11.2;24.61	-12.9;78.99	50.37;84.54	-12.0;10.75	-19.2;22.05	50.37;93.45	-12.0;24.61	-19.2;78.99

Source: rhLAMAN-10 CSR, Table 14.2.4.2
Note 1: FAS=Full Analysis Set. N=Number of FAS subjects. n=Number of subjects with data.
Note 2: Normalised 6MWT is given as percent of predicted value (normalised for age, height and gender).

Table 11: Summary of 3-MSCT (Steps/min), 6-MWT (m), and normalised 6-MWT (% of predicted) in rhLAMAN-10 at baseline, by age group

Parameter Visit	< 18 years (N=19) Actual value	 Change from baseline	 % Change from baseline	>= 18 years (N=14) Actual value	 Change from baseline	 % Change from baseline	Overall (N=33) Actual value	 Change from baseline	 % Change from baseline
3MSCT (Steps/min)									
Baseline									
n	19			14			33		
Mean (SD)	54.04 (13.34)			53.00 (11.82)			53.60 (12.53)		
Median	55.00			48.00			55.00		
Min; Max	16.67;83.33			37.67;71.33			16.67;83.33		
6MWT (m)									
Baseline									
n	19			14			33		
Mean (SD)	454.2 (86.3)			483.4 (95.6)			466.6 (90.1)		
Median	454.0			466.0			454.0		
Min; Max	180; 586			335; 690			180; 690		
Total distance walked relative to normal (%)									
Baseline									
n	19			14			33		
Mean (SD)	69.34 (12.39)			68.64 (11.01)			69.04 (11.65)		
Median	67.96			67.09			67.96		
Min; Max	31.16;90.86			48.72;89.57			31.16;90.86		

Source: rhLAMAN-10 CSR, Tables: 14.2.2.2, 14.2.3.2, and 14.2.4.2.
Note 1: FAS=Full Analysis Set. N=Number of FAS subjects. n=Number of subjects with data.
Note 2: Normalised 6MWT is given as percent of predicted value (normalised for age, height and gender).

A29. Please confirm whether the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines define which reference values for lung function should be used, and if these were used (p88).

Spirometry were conducted and interpreted in accordance with the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (53), including determination of reference values. The reference values for growing lungs (54) were used given the inclusion of paediatric patients in the analysis.

The parameters measured were FVC and forced expiratory volume in 1 second (FEV_1; both as a percentage of predicted and in litres) and peak expiratory flow rate (PEF, L/s). The best result of three tests was used. All spirometry curves were reviewed blindly by a Chiesi pulmonologist to evaluate the quality of the manoeuvre. PFT values judged as not reliable owing to the poor quality of the manoeuvre were not used in the analysis.

A30. Please clarify why the strength subtest was not collected? Please also clarify what evidence there is to support this approach, and the likely effect on the scores collected? (p89)

The BOT-2 is a comprehensive and widely used motor proficiency test (Table 12). The complete assessment is composed by multiple domains and tests and requires more than one hour to be satisfactorily completed. The test can be interpreted at the level of each single domain or collectively with an overall score (55).

Table 12: BOT-2

Test domains	Number of tests/ items to be executed per-domain	Execution time
Fine Motor Precision	7 items	Approximately 60 minutes (without considering the impact of cognitive impairment in learning how to conduct the individual tests)
Fine Motor Integration	8 items	
Manual Dexterity	5 items	
Bilateral Coordination	7 items	
Balance	9 items	
Running Speed and Agility	5 items	
Upper-Limb Coordination	7 items	
Strength	5 items	

Based on their experience with execution of such tests on AM patients in clinical practice, the Copenhagen investigators responsible for performing the assessment in all patients judged that executing the assessment in full in addition to all other tests planned for the day was too cumbersome for most of the patients. The strength component includes physically demanding exercises such as jumps and sit-ups, with a focus on muscle resistance and strength. Based on their knowledge of the disease, the strength component of the test was considered the least relevant for AM. Conversely, domains related to balance, agility, speed, and fine/gross motor function were considered highly relevant for assessing disease severity and response to treatment. These domains also include items similar to some of the strength domain, but more oriented to agility (i.e. jumping jacks in the bilateral coordination domain).

Based on this feasibility consideration, it was therefore decided in agreement with the sponsor (Zymenex A/S, at the time) to perform the BOT-2 test without the strength component.

The BOT-2 Complete Form (i.e. including all items and domains) is considered the most reliable measure of motor proficiency when compared to only administering select composites, select subtests, or the short form. However, due to its lengthy administration time, the BOT-2 Complete Form may not be the most time efficient assessment tool to measure a child's motor function. Amongst the sub-scores, the strength component is considered to be poorly associated with the total test score (56).

In conclusion, the decision not to administer the strength domain tests of the BOT-2 was taken by the investigators in agreement with the study sponsor based on feasibility considerations (length of the overall tests within the context of the other efficacy assessments). The decision to specifically de-prioritise strength was based on the experience of the investigators and the expected (limited) relevance for the disease and the response to treatment. In the rhLAMAN studies, the other BOT-2 domains were analysed separately by domain in order.

A31. Please clarify exactly how *'impairment categories*' have been determined (e.g. literature to support thresholds) and whether they were pre-planned or post-hoc (section 9.4.4.2 p116)

In rhLAMAN-10, levels of impairment were used to assess the degree of disablement across multiple endpoints assessed during the rhLAMAN studies. The thresholds used to define the impairment levels were determined pre-hoc and included in the planned statistical analyses for the study.

A data-driven or literature-based approach was followed for each variable based on the availability of published data. A recap of the rationale for determining each threshold is herein provided.

Serum oligosaccharides

Published data on the level of oligosaccharides in serum and liquor are missing in the healthy population. The thresholds adopted for defining the impairment categories were generated on the basis of the distribution of baseline values observed in the AM patients enrolled into the rhLAMAN studies.

Lung function

For FEV_1 % of predicted, the severity of affliction was defined using the thresholds commonly applied to delineate the severity stages of COPD by spirometry (see http://advantage.ok.gov/CHCC/Publications/Spirometric%20Classifications%20of%20COPD.pdf) and the normal values were assumed as per Pakhale et al, 2009 (57). The same cut-off levels (50% and 80% of predicted by age and gender) were also applied to the FVC % of predicted

Endurance tests

The same cut-off levels (50% and 80% of predicted by age and gender) were also applied to the 6-MWT % of predicted, given the lack of commonly accepted thresholds. Due to the

absence of any normative data in the literature, the imputation of categorical status of the 3-MSCT was data driven. In particular, 55 steps/minute was the median value of the 3-MSCT at baseline in rhLAMAN-10 database. A reduction <20% and >20% from the median value was the cut-off used for classifying a moderate and a severe impairment in the test. This cut-off was chosen arbitrarily by Chiesi on the basis of the distribution of patient's values.

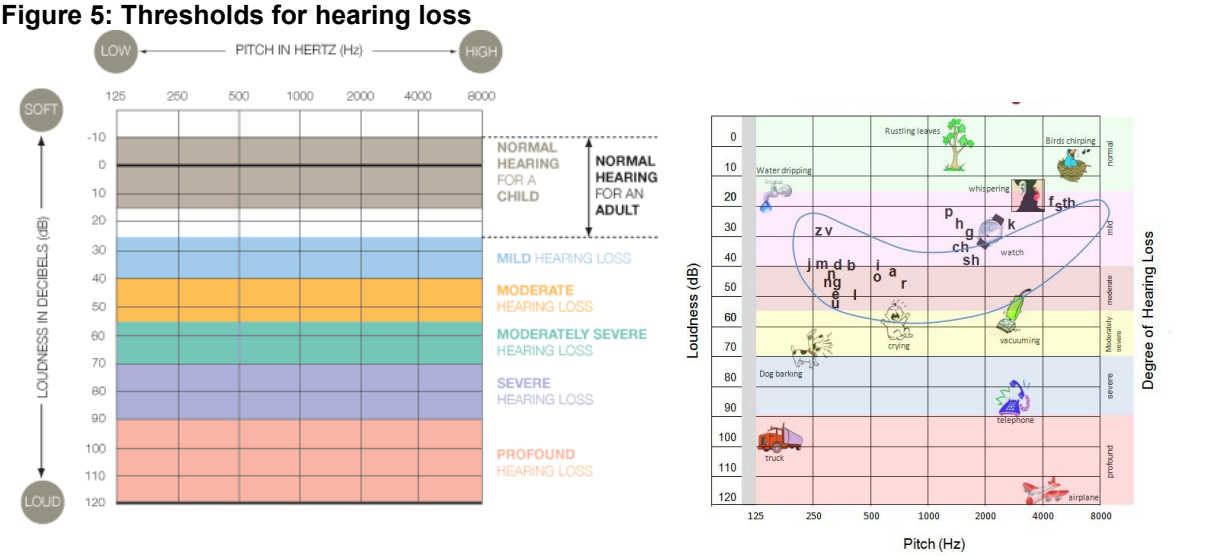
Quality of life

The CHAQ was selected to measure disability and pain because it is broadly applicable to AM and is a widely studied and validated scale for patients with musculoskeletal disorders and multiple sclerosis. The CHAQ consists of two components: disability and discomfort. Both domains are assessed by questions rated on a 4-point scale: without any difficulty (0), with some difficulty (1), with much difficulty (2) and unable to do (3). The maximum response of any of the pertinent questions is the domain score. A disability index is then calculated as the mean of the domain scores. Disability Index scores range from 0 to 3 with higher scores indicating greater disability. For the pre-hoc analysis, Chiesi selected the cut-off levels for CHAQ scores that represent no-mild (0–1), moderate (>1–2), and severe disability (>2–3), reflecting the possible responses to each component question proposed (according to Dempster et al, 2001 (32)). The same categorical approach was adopted for the assessment of VAS pain. Using a metric rule, the number in cm based on the location of the respondent's mark on the VAS is converted into the appropriate score ranging from 0 to 3, in adherence to the questionnaire-specific instructions (which can be retrieved here: https://www.niehs.nih.gov/research/resources/assets/docs/chaq_instructions_508.pdf).

Hearing

The gold standard hearing test used to determine hearing thresholds in an individual is pure tone audiometry (PTA). PTA uses both air conduction audiometry (quantifies hearing threshold of sound conducted through the entire auditory system; the external, middle and inner ear and the auditory nervous system) and bone conduction audiometry (quantifies hearing threshold of sound conducted through the inner ear and auditory nervous system). Pre-defined thresholds for impairment categories were adopted based on the guidelines from the American Medical Association and the American Academy of Otolaryngology, in which hearing loss is classified as mild to moderate (>26–55 dB), moderately severe to severe or profound (>56 dB) in degree according to the lowest intensity at which a signal measured in decibels is just audible to a person. Normal hearing is compatible with value <25 dB (Figure 5).

Figure 5: Thresholds for hearing loss



Source (image on left): The American Medical Association (AMA) and the American Academy of Otolaryngology (AAO)
Source (image on right): Adapted from American Academy of Audiology, and Northern and Downs, 2002 [Northern JL, Downs MP. Hearing in children. Lippincott Williams & Wilkins; 2002].

Immunoglobulins

Impairment categories for serum IgG were based on comparison with the normal range by age and gender according to Cassidy et al, 1974 (58). Deficiency or severe deficient status were assigned for values deflecting for one or two standard deviation from the lower value expected by age and gender.

Adverse events

A32. Priority Question: Please clarify what the protocols were for recording adverse events in all trials?

Information regarding the recording and reporting of adverse events (AEs) and serious adverse events (SAEs) is reported for each study below:

Recording of AEs

In rhLAMAN-02, -03, -04 and -05, the investigator monitored the condition of the patient throughout the study from the time of first dosing visit / informed consent until the end-of-study visit. For rhLAMAN-03, AEs reported in the continuation phase from Visits 32–52 were reported separately.

The investigator recorded all AEs on the AE page in the case report form with information about:

- Diagnosis
- Date and time of onset (only if on an infusion day)
- Causal relation to IMP
- Outcome

- Intensity
- Action taken to IMP and date and time of outcome

In rhLAMAN-10, disease signs, symptoms, and/or laboratory abnormalities present at the screening visit were recorded as medical history/concomitant illness. If a pre-existing condition recovered and later reoccurred, or if it, in the opinion of the investigator, represented a clinically significant exacerbation in intensity or frequency, it was recorded as an AE. Exacerbation in disease signs, symptoms, and/or laboratory abnormalities, which in the opinion of the investigator were caused by progression of AM, were not recorded as AEs.

Reporting of AEs

In rhLAMAN-02, -03, -04 and -05, the necessity and time requirements for reporting of AEs to Zymenex, the original developer of velmanase alfa prior to acquisition by Chiesi, or their designee and/or regulatory agencies are evaluated based on the investigators brochure.

All SAEs and IRRs, non-serious and serious, were reported to Zymenex or their designee within 24 hours of the investigators first knowledge of the event, even if the experience did not appear to be related to the IMP (rhLAMAN-02, -03, and -04) or velmanase alfa/Placebo (rhLAMAN-05). Such communications were directed to the person responsible for safety at Larix (rhLAMAN-02, -03, and -04); Larix was the CRO charge of statistics, data management, and pharmacovigilance for all velmanase alfa studies.

All SAEs had to include a detailed written description of the event using SAE CRF pages and following procedures as described in the applicable standard operating procedure and safety agreement. Copies of relevant patient records, autopsy reports, and other documents may be requested by and were to be sent to Zymenex or their designee. This additional information was sent to Zymenex or their designee within 5 days upon request.

All suspected, unexpected, serious adverse drug reactions (SUSAR) were reported by Zymenex or their designee to appropriate regulatory agencies. Fatal or life-threatening SUSARs were reported within 7 days, and non-fatal, non-life threatening SUSARs were reported within 15 days after first knowledge of the event was obtained by Zymenex.

In rhLAMAN-10, for each AE severity (mild, moderate, or severe), relationship to IMP (not related, possible, probable or definitely) and the AE outcome (recovered, recovered with sequelae, not recovered, fatal, or unknown) were reported. SAEs were reported from the time of signing of the informed consent until completion of the trial. Adverse drug reactions (ADRs) were all AEs assessed to be related to trial drug, i.e. the relationship was assessed as possible, probable or definitely related to IMP. Infusion related reactions were defined as those ADRs which occurred during or up to two hours after the infusion of velmanase alfa (the IMP) and that were assessed by the Investigator as being infusion related.

A33. Please clarify why the patient mentioned on page 146 required an amputation. Was this due to AM?

AM is characterised by an insidious progression of neuromuscular and skeletal deterioration over several decades, making a large portion of patients partially or completely wheelchair dependent in adulthood (1). Musculoskeletal abnormalities have been described in the majority of patients with AM (59). Furthermore, clinical or radiographic evidence of

musculoskeletal abnormalities were reported in 92% for patients above age 18 years, and for 62% for patients younger than age 18 years (21).

The event of interest was the amputation of the left ankle due to an infection and occurred during the compassionate use period, when no formal collection of data was performed. The event was spontaneously reported and detailed information is not available.

Given the musculoskeletal component of the disease and the frequency of infections due to immunodeficiency, it is not possible to exclude that the event of amputation could be linked to AM.

A34. Please clarify where infusion-related reaction (IRR) appears in the adverse event tables and whether it was established why the small number of patients with IRRs experience multiple events (p158).

IRRs were defined as those ADRs, which occurred during or up to two hours after the infusion of velmanase alfa and that were assessed by the investigator as being infusion related. The IRR encountered during clinical development concern three paediatric patients with the majority of events experienced by one patient (patient 403/520 experienced 14 out of 19 IRR events).

Most of the IRRs across the three paediatric patients (11/19 events) involved disturbances of temperature homeostasis. The IRR did not involve any of the body systems leading to concerns regarding anaphylaxis. There were no respiratory symptoms, and no rashes associated with IRRs. The IRRs with velmanase alfa were never classified as severe or serious, and were managed by slowing of the infusion or, in certain cases, administration of pre-medication. Listing 16.2.20.2 provides the complete list of events per patient, with statement if the event was classified as an IRR or not; a summary of what can be found in terms of IRRs in the listing is shown in Table 13.

Table 13: Summary of IRRs in the three paediatric patients

	403/520		404		408		All	
System Organ Class Preferred Term	**n**	**E**	**n**	**E**	**n**	**E**	**n**	**E**
Any IRR	**1**	**14**	**1**	**4**	**1**	**1**	**3**	**19**
IMMUNE SYSTEM DISORDERS	**1**	**3**	**1**	**2**			**2**	**5**
Anaphylactoid Reaction	1	3					1	3
Hypersensitivity			1	2			1	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**8**	**1**	**2**	**1**	**1**	**3**	**11**
Chills	1	7	1	1			2	8
Feeling hot			1	1			1	1
Pyrexia	1	1			1	1	2	2
GASTROINTESTINAL DISORDERS	**1**	**2**					**1**	**2**
Nausea	1	1					1	1
Vomiting	1	1					1	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**1**	**1**					**1**	**1**
Hyperhidrosis	1	1					1	1

Source: CSR rhLAMAN-10 Listing 16.2.20.2

E=number of events, n=number of patients, SOC=system organ class, PT=preferred term, SAS=safety analysis set, TEAE=treatment emergent adverse event

Amongst the three patients who had an IRR reported, one was ADA negative throughout the study (408), and experienced an IRR of mild pyrexia during the first infusion (100 U/kg) only. The other two patients had IRR with a consistent pattern of onset:

- onset – more than 1 month after initiation of treatment
- seroconversion - neither were ADA+ prior to first velmanase alfa treatment
- increased ADA titres (above 80 U/mL)
- management by premedication and reductions in infusion speed
- with appropriate premedication, ADA titres reduced with time and, in the longer term, management measures could be reduced or stopped

The three patients with IRRs were all paediatric patients initially treated in the dose-ranging studies. In the 14 treatment-naïve patients who received velmanase alfa during rhLAMAN-05 no IRRs were observed during the course of the study. No IRRs were reported in any of the 10 patients originally under placebo treatment who received their first infusion of velmanase alfa during studies rhLAMAN-07, or -09, or during the compassionate use programme.

The majority of the events of IRRs were experienced by patient 403/520 (14 out of 19 events), who participated initially to study rhLAMAN-02 and rhLAMAN-03 but then discontinued from the study due to the anaphylactoid reaction. The patient subsequently participated to study rhLAMAN-05, with a total time off treatment of 21 months. In rhLAMAN-05, the patient continued to experience IRRs that were managed by slowing the infusion rate and pre-medications. The patient continued receiving treatment in the rhLAMAN-07 study and continues receiving treatment as of today. This patient is also the one with the highest ADA recorded.

Patient 404 experienced four events of IRRs that were managed with reduction of infusion speed and administration of pre-medications. The last patient, ID 408, experienced one single event of IRR (mild pyrexia). The patient continued though study rhLAMAN-03, rhLAMAN-04 and rh-LAMAN10 with no further infusion reactions and no positive ADA titres.

Overall, there were 2,006 infusions in paediatric patients in the velmanase alfa development programme, with 1 in 105 infusions in children leading to IRRs.

Results

A35. <u>Priority Question</u>: Please clarify how many patients have discontinued the use of VA and for what reasons. Please relate this to the numbers at each time point given in Table 14, p103.

There are three instances of patients discontinuing treatment with velmanase alfa:

- One patient withdrew in rhLAMAN-03 (patient 403) due to IRR symptoms and re-joined in rhLAMAN-05 (as patient 520) where the patient continued to experience IRRs which were managed by slowing the infusion rate and use of pre-medication. Accordingly, the rhLAMAN-03 period for this patient is excluded from the integrated analysis

- In rhLAMAN-03, during the infusion at Visit 10, the patient (403) experienced an IRR – an anaphylactoid reaction of mild intensity. The investigator decided to stop the infusion hence the infused volume was reduced and only 63.5% of the planned infusion was infused. The patient refused to receive any treatment for the IRR. For the next infusion, pre-medication and reduced infusion rate was planned; however, the patient did not receive further treatments. The patient discontinued the trial and was withdrawn on the 24-Oct-11 due to IRR symptoms

- One patient (502) discontinued treatment shortly after initiating velmanase alfa in the compassionate use programme. This patient had no velmanase alfa data to contribute to the integrated analysis. The reason for withdrawal is unknown.
- One patient (501) did not enrol in rhLAMAN-10 clinical evaluation visit (CEV) but did have previous velmanase alfa data (12 months) that were included in the integrated analysis. The reason for non-enrolment to rhLAMAN-10 is unknown and the patient continues to receive velmanase alfa as part of the compassionate use programme.

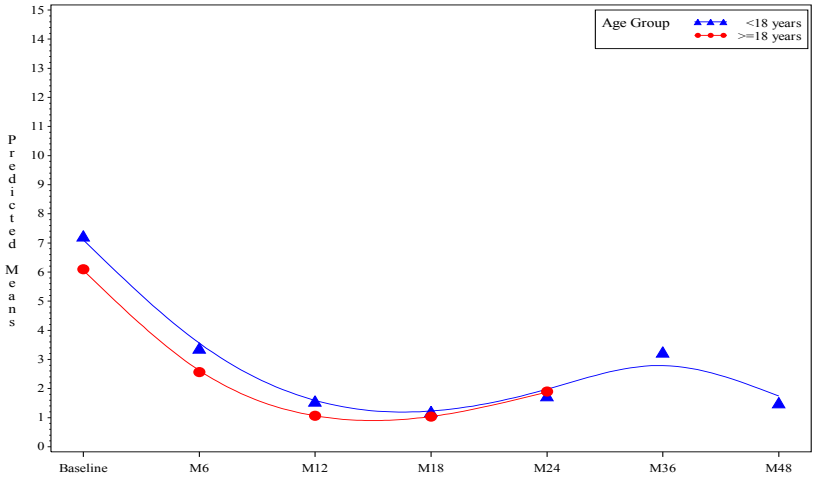
A36. <u>Priority Question</u>: Please clarify whether interaction tests have been performed to ascertain if there are different effects between subgroups. For example, in the ANCOVA and between results observed for those aged under 18 years and those aged 18 years and over. (e.g. Table 25, Figures 18-24). Provide similar tests for the post-hoc analyses undertaken when categorising three age groups, for instance with the data contained in Table 27.

In rhLAMAN-05, changes from baseline in the primary and prioritised secondary efficacy endpoints were compared between the two treatment groups using an ANCOVA model with treatment as a fixed factor, and baseline values and age as continuous covariates. The adjusted means in each treatment group, the adjusted mean difference between groups, their 95% CIs and associated p-values were estimated by the model taking into account the baseline value and subject age. Although no subgroup analysis was pre-specified in the SAP, primary and prioritised secondary efficacy endpoints were also presented in a post-hoc analysis by age subgroups (<18 years; ≥18 years). As this was only for descriptive purposes, interaction was not tested. The trial consisted of a very small sample size (25 subjects) and therefore adding additional terms in the ANCOVA model might have produced over-parameterisation issues.

In the integrated rhLAMAN-10 analysis, results for the primary endpoints (serum oligosaccharides and 3-MSCT) showed a statistically significant change compared with baseline. In order to further explore the pattern of the change over time and the possibility of a different effect between younger and older patients, an additional post-hoc longitudinal model was performed (and presented to EMA in eCTD sections 2.5 and 2.7.3). Change over time in serum oligosaccharides and 3-MSCT were analysed using a longitudinal model including age (< 18 years; >= 18 years), time and age x time interaction.

Explorative post-hoc longitudinal modelling of serum oligosaccharides using age (<18 years; ≥18 years), time and age by time interactions showed significance for age and time effects alone but not for age by time interactions, confirming that serum oligosaccharides change over time but this change was not different between the two age groups (Figure 6).

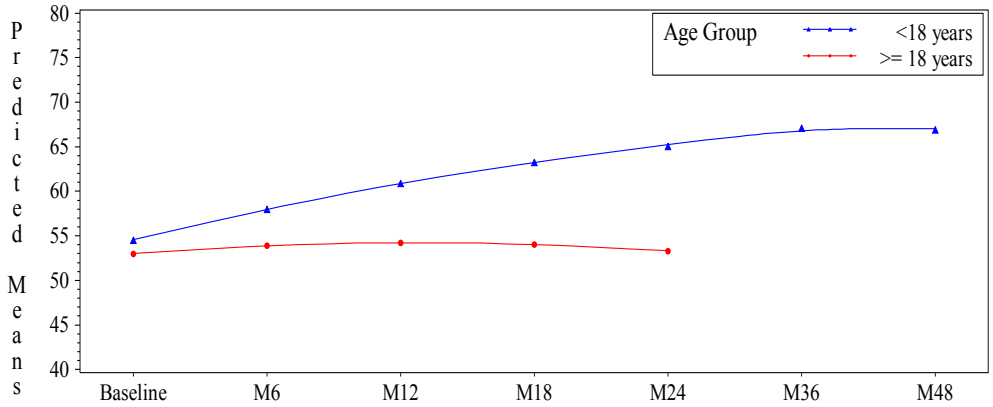
Figure 6 Post-hoc Longitudinal Model: Predicted Means Serum Oligosaccharide



Source: eCDT Section 2.5

Explorative post-hoc longitudinal modelling of 3-MSCT using age (<18 years; ≥18 years) time and age by time interactions showed significance for time and age by time interactions, indicating that 3-MSCT changes over time and this change is different between the two age groups. This confirms the presence of a trend for a greater improvement within the paediatric patients (Figure 7).

Figure 7 Post-hoc Longitudinal Model: Predicted Means 3MSCT (step/min) Over Time



Source: eCDT Section 2.5

The analysis was not performed when categorising three age groups, because of the very limited size of the subgroups.

A37. Please clarify how missing data were accounted for in the intention-to-treat analysis in rhLAMAN-10.

In the rhLAMAN-05 double-blind placebo-controlled trial, no missing data have been observed for the two primary endpoints (serum oligosaccharides and 3-MSCT) and one of the two prioritised secondary endpoint (6-MWT). Missing values were observed for the prioritised secondary endpoint, FVC (%). In this case, under the assumption of missing at random (MAR), a multiple imputation method was applied before performing the ANCOVA model. Imputation was performed by proc multiple imputation (MI) using the Markov Chain

Monte Carlo (MCMC) approach by treatment. Each record included baseline, 26 weeks and 52 weeks and the baseline age. 1000 imputations were created. The imputed data sets are then analysed with PROC MIANALYSE.

The rhLAMAN programme consists of the following studies: rhLAMAN-02 (Phase I), rhLAMAN-03 (Phase IIa), rhLAMAN-04 (Phase IIb), rhLAMAN-05 (Phase III), rhLAMAN-07 (long-term Phase IIIb), rhLAMAN-09 (long-term Phase IIIb), rhLAMAN-10 (long-term Phase IIIa) and one compassionate AfterCare programme. An integrated database has been created by pooling all data collected from rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-07, rhLAMAN-09 and rhLAMAN-10. In the integrated rhLAMAN-10 analysis, all efficacy endpoints were presented by timepoints and last observation. As the visit schedule was different among trials, windowing was applied. The date of assessment and the date of the first velmanase alfa dose have been used to calculate the study day. Windowing was then performed using this study day and a window that was built around a target day for each visit. Based on the calculated study day, each assessment has been assigned to a timepoint: Baseline, M6, M12, M18, M24, M36, M48, and last observation. The last observation values were defined as the last available value at end of rhLAMAN trials (derived from the last trial the subject participated in). Missing data therefore were not imputed and/or replaced. Any missing data was reviewed and discussed during the Data Review Meeting and fully documented in the Data Review Report.

A38. Please provide ranges, as well as mean and standard deviation, for rhLAMAN-05 for the following measures (where missing): 3-MSCT, 6-MWT, FVC and serum oligosaccharides (Table 16 p110). Also, there appears to be a typo in the placebo column of this table (6-MWT placebo ≥500m). Please clarify this data.

The requested values have been added and highlighted (green) in Table 14. The typo has also been corrected.

Table 14 (CS Table 16): Baseline characteristics of rhLAMAN-05

Characteristic	VA (N=15)	Placebo (N=10)
Age, n (%)		
<12	4 (26.7)	2 (20.0)
12–<18	3 (20.0)	3 (30.0)
≥18	8 (53.3)	5 (50.0)
Female, n (%)	6 (40.0)	5 (50.0)
Male, n (%)	9 (60.0)	5 (50.0)
Race (white)	15 (100.0)	10 (100.0)
Weight, kg		
Mean (SD)	60.2 (21.5)	64.2 (12.2)
Height, metres		
Mean (SD)	1.51 (0.19)	1.61 (0.14)
BMI, kg/m^2		
Mean (SD)	25.1 (4.9)	24.7 (2.7)
3-MSCT, steps/min		
Mean (SD)	52.9 (11.2)	55.5 (16.0)
Range	37.7–83.3	32.0–78.0

Characteristic	VA (N=15)	Placebo (N=10)
35–45, n (%)	1 (6.7)	3 (30.0)
45–55, n (%)	9 (60.0)	2 (20.0)
55–65, n (%)	3 (20.0)	1 (10.0)
≥65, n (%)	2 (13.3)	4 (40.0)
6-MWT, metres		
Mean (SD)	460 (72.3)	466 (140)
Range	335–627	219–696
200–400, n (%)	2 (13.3)	3 (30.0)
400–500, n (%)	11 (73.3)	3 (30.0)
≥500, n (%)	2 (13.3)	4 (40.0)
FVC		
% of predicted, mean (SD)	81.7 (20.7)	90.4 (10.4)
% of predicted, range	50.0–119	72.0–109
L, mean (SD)	2.5 (1.1)	3.3 (0.9)
L, range	0.9–4.6	2.6–5.3
FEV_1		
% of predicted, mean (SD)	80.3 (19.6)	85.9 (18.2)
L, mean (SD)	2.3 (1.0)	2.9 (0.9)
PEF, L/s		
Mean (SD)	4.6 (2.2)	5.7 (1.6)
Leiter-R, years		
TEA-AME mean (SD)	6.3 (2.6)	6.6 (1.8)
TEA-VR mean (SD)	5.7 (1.7)	6.1 (1.6)
Serum oligosaccharides, µmol/L		
Mean (SD)	6.8 (1.2)	6.6 (1.9)
Range	4.9–8.7	4.4–10.2
CSF oligosaccharides, µmol/L		
Mean (SD)	11.4 (3.0)	10.3 (2.9)
BOT-2 Total Score, points		
Mean (SD)	94.93 (41.68)	109.2 (51.84)
CHAQ disability index, score		
Mean (SD)	1.37 (0.82)	1.59 (0.64)
EQ-5D index, score		
Mean (SD)	0.61 (0.19)	0.61 (0.18)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation; TEA-AME, total equivalence age for attention and memory; TEA-VR, total equivalence age for visualisation and reasoning; VA, velmanase alfa.

A39. Please provide absolute values at baseline and at each assessment for all outcomes, particularly for CHAQ and EQ-5D, in both rhLAMAN-05 and rhLAMAN-10.

Please consult Table 15 and the provided 'DOF: Response to ERG clarification question A39 (60) for the requested data.

Table 15: Location of absolute values at baseline and at each assessment for all outcomes reported in DOF: Response to ERG clarification question A39 (60)

Outcome	rhLAMAN-05		rhLAMAN-10	
	Page in DOF	Table	Page in DOF	Table
Serum oligosaccharides	3	11-2	29	10
3-MSCT	4	11-6	30	16
6-MWT	5	11-10	31	21
FVC, % of predicted	6	11-14	32–33	14.2.5.1
FVC, L	7	14.2.1.27	34–35	14.2.6.1
FEV_1 % of predicted	8	14.2.1.27	36–37	14.2.6.1
FEV_1, L	9	14.2.1.27	38–39	14.2.6.1
PEF, L/s	10	14.2.1.27	40–41	14.2.6.1
CHAQ disability index	11	14.2.1.41	42	49
CHAQ pain VAS	12	14.2.1.41	43–44	14.2.16.1
EQ-5D index	13	14.2.1.42	45–46	14.2.18.1
EQ-5D VAS	14	14.2.1.42	47–48	14.2.19.1
BOT-2 outcomes	15–19	14.2.1.13	49 and 50–57 and 58–71	34 and 14.2.7.1 and 14.2.7.6
Leiter R	20–21	14.2.1.24	72–73 and 74–75	14.2.8.1 and 14.2.8.4
PTA outcomes	22–24	14.2.1.36	76–81	14.2.9.1
Serum IgG	25–27	14.3.4.7	82–83	14.2.14.1

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; DOF, data on file; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; PTA, pure tone audiometry.

A40. Please provide N for all outcomes reported in rhLAMAN-05 and rhLAMAN-10.

Please see the response to Question **A39**.

A41. Please clarify the changes in EQ-5D values, classified by multi-domain response, for patients receiving VA and placebo in rhLAMAN-5.

To address this question, Chiesi stratified the change from baseline in the EQ-5D-5L overall Index score according to the number of domains with a relevant improvement from baseline to 12 months of follow-up (i.e. at least one variable with a change from baseline beyond the MCID for the variable).

Overall, no clear path of relationship between the two measures emerges from this analysis for either group (Table 16).

Table 16: Change from baseline to Month 12 in the EQ-5D-5L index in patients treated with velmanase alfa or placebo from rhLAMAN-05 study, stratified according to global treatment response as number of domains with improvement.

Change from baseline	EQ-5D-5L change from baseline stratified by treatment response									
	Placebo					Velmanase alfa				
	Number of improved domains				All	Number of improved domains				All
	0	1	2	3		0	1	2	3	
N	4	2	2	0	8	0	2	10	2	14
Mean	0.010	-0.083	0.170	-	0.027	-	-0.001	0.057	-0.019	0.038
SD	0.121	0.257	0.117	-	0.164	-	0.042	0.094	0.016	0.085
Median	-0.018	-0.083	0.170	-	0.043	-	-0.001	0.004	-0.019	0.000
Min	-0.102	-0.264	0.087	-	-0.264	-	-0.030	-0.036	-0.031	-0.036
Max	0.180	0.099	0.252	-	0.252	-	0.029	0.237	-0.008	0.237

Abbreviations: SD, standard deviation.

To further investigate whether the observed results might have been influenced by differences at baseline, Chiesi also evaluated the absolute EQ-5D-5L Index values in the two groups both at baseline and at 12 months of follow-up. Results are reported in Table 17.

As a general remark, both groups start at baseline with similar average index scores. The only sub-group where there is a potential difference at baseline between the two arms is the sub-group of 'one domain responders' (noting that there are only two patients in this sub-group for both the placebo and velmanase alfa arms). The baseline index score is numerically higher in the placebo arm (0.824) compared to the velmanase alfa arm (0.564).

At 12 months' follow-up, a greater response to "treatment" is associated with a higher final EQ-5D-5L score and this trend is visible in both groups; however, the within-group variability appears to be significantly larger than the between-group differences.

In conclusion, no clear evidence of a correlation between response to treatment and change in EQ-5D-5L can be drawn, as well as no hypothesis on the reciprocal influence between the two variables. A possible statistical explanation for this absence of correlation can be found in the extremely small numbers of patients in each of the stratified groups, with 6 out of 8 sub-groups being constituted by ≤2 patients.

Table 17: Baseline and 12-month values of EQ-5D-5L index in patients treated with velmanase alfa or placebo from rhLAMAN-05 study, stratified according to global treatment response as number of domains with improvement.

Time point	EQ-5D-5L change from baseline stratified by treatment response	
	Placebo	Velmanase alfa

		Number of improved domains				All	Number of improved domains				All
		0	1	2	3		0	1	2	3	
Baseline	N	4	2	2	0	8	0	2	11	2	15
	Mean	0.513	0.824	0.601	-	0.613	-	0.564	0.606	0.684	0.610
	SD	0.102	0.249	0.075	-	0.181	-	0.069	0.206	0.202	0.186
	Median	0.492	0.824	0.601	-	0.598	-	0.564	0.575	0.684	0.575
	Min	0.421	0.648	0.548	-	0.421	-	0.515	0.268	0.541	0.268
	Max	0.648	1.000	0.654	-	1.000	-	0.612	1.000	0.827	1.000
12-month follow-up	N	4	3	3	0	10	0	2	10	2	14
	Mean	0.524	0.641	0.727	-	0.620	-	0.563	0.650	0.665	0.640
	SD	0.096	0.175	0.155	-	0.153	-	0.110	0.206	0.186	0.185
	Median	0.525	0.736	0.641	-	0.624	-	0.563	0.645	0.665	0.627
	Min	0.434	0.439	0.635	-	0.434	-	0.485	0.275	0.533	0.275
	Max	0.612	0.747	0.906	-	0.906	-	0.641	1.000	0.796	1.000

Abbreviations: SD, standard deviation.

A42. Please clarify if there is evidence for whether or not the efficacy of VA will be maintained as treatment duration increases considerably?

The long-term efficacy of velmanase alfa has been reported in four key sources (9, 17, 49, 61). The UK expert elicitation panel reported that rhLAMAN trial data (12 month RCT [rhLAMAN-05] and 48-month observational data [rhLAMAN-10]) were sufficient to demonstrate the treatment effect of velmanase alfa in the long-term. Data from rhLAMAN-10 showed that efficacy results for velmanase alfa persisted for up to 48 months; 88% of patients achieved a response (according to the multi-domain responder criteria) at last observation (17). The higher proportion of three-domain responders at last observation in rhLAMAN-10 compared with rhLAMAN-05 (46% vs 13%) may also be indicative of benefit received from long-term treatment with velmanase alfa (17). Similarly, clinical trial KOL interviews confirmed that the treatment effect of velmanase alfa persisted into the long term (49), as did a [redacted] (9).

A43. Please clarify what the impact on the clinical effectiveness evidence would be if the MCID thresholds for each response criteria were varied by ±10%.

To address the question, Chiesi performed two additional sensitivity analyses for the rhLAMAN-05 trial at 12 months and for the rhLAMAN-10 trial at last observation changing the MCID thresholds for all variables considered in the multi-domain analysis. In particular, three scenarios were generated:

- Original: in this scenario the original MCID thresholds used in the EMA submission and response were applied.

- More challenging: in this scenario an MCID threshold 10% higher or lower than the original one in order to make response more difficult to achieve was used for each of the variables included in the model. For example, a threshold of <3.6 µmol/L instead of <4 µmol/L was used to determine response in the oligosaccharides.
- Less challenging: in this scenario an MCID threshold 10% lower or higher than the original one in order to make response less difficult to achieve was used for each of the variables included in the model. For example, a threshold of <4.4 µmol/L instead of <4 µmol/L was used to determine response in the oligosaccharides.

The thresholds used in the analysis for the three scenarios are reported in Table 18.

Table 18: MCID thresholds applied in the sensitivity analysis

Variable	MCID Thresholds		
	More challenging	Original	Less challenging
Serum Oligosaccharides (umol/L)	<3.6	<4	<4.4
Change in 3-MSCT vs baseline (steps/ min)	≥7.7	≥7	≥6.3
Change in 6-MWT vs baseline (m)	≥33	≥30	≥27
Change in FVC % predicted vs baseline	≥11	≥10	≥9
Change in CHAQ-DI vs baseline	≤-0.143	≤-0.130	≤-0.117
Change in CHAQ-VAS PAIN vs baseline	≤-0.2706	≤-0.2460	≤-0.2214

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; CHAQ, childhood health assessment questionnaire; FVC, forced vital capacity; MCID, minimal clinically important difference.

Table 19 displays the number of domains with a significant response to treatment in the velmanase alfa and placebo arms of rhLAMAN-05 on the basis of the three scenarios of MCID thresholds used in the analysis. Applying the original thresholds for determining the MCID of the clinical and biochemical variables used in the multi-domain model, patients treated with velmanase alfa appear to respond to treatment 2.9 times more the placebo (i.e. 86.7% vs 30.0% respectively). When the sensitivity thresholds are applied, the difference between the two groups appears to be fully maintained and even larger when more challenging thresholds are applied. In fact, the velmanase alfa patients respond to treatment 2.3 times more than placebo patients when the less challenging thresholds are applied and 3.7 times when more challenging MCIDs are used. This analysis further supports the robustness of the observed difference between the two experimental groups in the rhLAMAN-05 trial.

Table 19: Global response and number of domains with a significant response according to the three MCID sensitivity thresholds in the two groups of rhLAMAN-05 study at Month 12

		More challenging		Original thresholds		Less challenging	
		Placebo N (%)	VA N (%)	Placebo N (%)	VA N (%)	Placebo N (%)	VA N (%)
N of patients		10	15	10	15	10	15
Domains with a significant response	0	4 (40.0)	0 (0.0)	4 (40.0)	0 (0.0)	4 (40.0)	0 (0.0)
	1	4 (40.0)	4 (26.7)	3 (30.0)	2 (13.3)	2 (20.0)	1 (6.7)
	2	2 (20.0)	10 (66.7)	3 (30.0)	11 (73.3)	4 (40.0)	9 (60.0)
	3	0 (0.0)	1 (6.7)	0 (0.0)	2 (13.3)	0 (0.0)	5 (33.3)
Global responders		2 (20.0)	11 (73.7)	3 (30.0)	13 (86.7)	4 (40.0)	14 (93.3)

Abbreviations: MCID, minimal clinically important difference; VA, velmanase alfa.

A similar exercise was also run using the long-term data collected as part of the rhLAMAN-10 study. The three proposed scenarios were applied to data observed at last observation (vs baseline whenever relevant) and the results are shown in Table 20. This analysis also provides a picture of the robustness of the results, as the three scenarios provide remarkably similar results.

Table 20: Global response and number of domains with a significant response according to the three MCID sensitivity thresholds at the last observation of the long-term rhLAMAN-10 study at last observation.

		More challenging N (%)	Original thresholds N (%)	Less challenging N (%)
N of patients		33	33	33
Domains with a significant response	0	1 (3.0)	1 (3.0)	0 (0.0)
	1	3 (9.1)	3 (9.1)	3 (9.1)
	2	16 (48.5)	14 (42.4)	15 (45.4)
	3	13 (39.4)	15 (45.4)	15 (45.4)
Global responders		29 (87.9)	29 (87.9)	30 (90.8)

Abbreviations: MCID, minimal clinically important difference.

In conclusion, the sensitivity analysis conducted generating a less challenging MCID scenario (by loosening MCID thresholds by 10% compared to the original exercise) and a

more challenging one (by tightening MCID thresholds by 10%) provides evidence of the robustness of the estimated therapeutic effect both in terms of comparison vs placebo (rhLAMAN-05) and in the long-term estimation of treatment response (rhLAMAN-10).

A44. Please clarify what proportions of patients receiving VA and placebo in rhLAMAN-05 transitioned between the health states that are used in the economic model (that is the health states based on ambulatory status – walking unassisted, walking with assistance, wheelchair dependent, and severe immobility)

The aides and devices assessed in the 'Helps and Aids' questions of the CHAQ questionnaire are as follows:

- Dressing and Grooming: Devices used for dressing (button hook, zipper pull, shoe horn, etc.)
- Arising: Special or built up chair
- Eating: Built up or special utensils
- Walking: Cane, Walker, Crutches, Wheelchair
    - In addition, a category exists for walking that requires assistance from another person

Patients' ambulatory status in rhLAMAN-05 were assessed at baseline and Month 12 according to the CHAQ 'Helps and Aids' questions relating to 'walking'. There are two key differences in the definitions used to assess patients' ambulatory status based on the CHAQ classification system in rhLAMAN-05 and the health state definitions used in cost utility analysis model (Table 21). Firstly, the health state definition for the 'walking with assistance' is slightly broader in the cost utility analysis – for example, footwear for stability and/or hand rails were included as potential assistive means for walking as per advice gained from UK KOLs during model development. Conversely, in the CHAQ 'Helps and Aids' assistive means for walking are confined to only the use of a cane, walker, crutches, wheelchair or help from another person. Although wheelchair use is recorded using the CHAQ 'Helps and Aids', patients were not strictly wheelchair bound/dependent at baseline (as per the eligibility criteria of the rhLAMAN clinical trials) as patients were required to complete endurance/walking tests. Conversely, the 'wheelchair-dependent' health state definition for the cost utility analysis is stricter, with patients classed as wheelchair-dependent if they are only able to traverse short distances by themselves.

Table 21: Health state definitions from the rhLAMAN-05 trial (CHAQ) and the cost utility analysis

Classification system	Walking with assistance	Wheelchair-dependent
CHAQ 'Helps and Aids'	The CHAQ defines the use of aids/devices to support walking as any one of the following: cane, walker, crutches, wheelchair or help from another person	Although wheelchair use is recorded using the CHAQ, patients were not strictly wheelchair bound/dependent at baseline (as per the eligibility criteria of the rhLAMAN trials) as patients were required to complete endurance/walking tests
Cost utility analysis	The patient requires any form of assistance to walk: e.g. help from another person, footwear to support stability, a walking cane, wheelchair for long distances, hand rails etc.	The patient is wheelchair-bound, but can still operate walking aids/use assistance to traverse short distances. The patient can still transfer themselves without carer support (e.g. the patient can transfer from the wheelchair into bed independently)

Patient-level transitions from baseline to Month 12 in rhLAMAN-05 for the velmanase alfa arm and the placebo arm are described in Table 22, using the CHAQ 'Helps and Aids' classification system. If wheelchair users are combined with those requiring walking aids/assistance (cane, walker, crutches, help from another person) at baseline to create a 'walking with assistance' definition more closely aligned to the definition employed in the cost utility analysis, the following observations can be made:

- Velmanase alfa arm (n=15):
    - Overall, there were five patients 'walking with assistance' (i.e. required help from a person, walking aids [cane, walker, crutches], or a wheelchair) at baseline
        - Of these five patients, two (40%) became device- or third party-independent at Month 12 – i.e. transitioned to a 'walking unassisted' state
    - Overall, there were 10 patients 'walking unassisted' (i.e. did not require help from a person, walking aids, or a wheelchair) at baseline
        - Of these 10 patients, two (20%) became dependent on device- or third party assistance at Month 12 – i.e. transitioned to a 'walking with assistance' state
- Placebo arm (n=10):
    - Overall, there were five patients 'walking with assistance' (i.e. required help from a person, walking aids [cane, walker, crutches], or a wheelchair) at baseline
        - Of these five patients, two (40%) became device- or third party-independent at Month 12 – i.e. transitioned to a 'walking unassisted' state
    - Overall, there were five patients 'walking unassisted' (i.e. did not require help from a person, walking aids, or a wheelchair) at baseline

- Of these five patients, two (40%) became dependent on device- or third party assistance at Month 12 – i.e. transitioned to a 'walking with assistance' state

It is only in the velmanase alfa arm that a net effect (20%) was observed for an improvement in walking ability after 12 months of treatment, i.e. a higher proportion of patients treated with velmanase alfa transitioned to an improved walking ability state (40%) compared to the proportion of patients treated with velmanase alfa that transitioned to a worse walking ability state (20%).

It should be noted that longer-term data (up to 48 months of treatment) are available from the rhLAMAN-10 trial. Overall, ten patients required help from a person, walking aids (cane, walker, crutches), or a wheelchair at baseline[b] according to the CHAQ 'Helps and Aids' responses. Of the ten patients, seven (70%) became device- or third party-independent at last observation: 4/5 (80%) paediatric patients and 3/5 (60%) adults. In particular, two paediatric patients and one adult forced to adopt the wheelchair for long distance mobility/functional capacity at baseline discontinued use at last observation. Overall, three patients out of the 23 (13%) who did not require help from a person, walking aids, or a wheelchair at baseline, did so at last observation (one adult and two paediatric patients).

[b] For patients receiving placebo in rhLAMAN-05, their baseline in rhLAMAN-10 is their condition at Month 12 of rhLAMAN-05.

Table 22: Health state definitions from the rhLAMAN-05 trial (CHAQ) and the cost utility analysis

Patient ID	Arm	Age†	Baseline (N=25)		12 months (N=25)	
			Walking unassisted	Walking with assistance‡	Walking unassisted	Walking with assistance‡
501	VA	35	Yes		Yes	
503	VA	30		Yes		Yes
504	VA	29		Yes		Yes
507	VA	25		Yes	Yes	
508	VA	23	Yes		Yes	
509	VA	22	Yes		Yes	
511	VA	20	Yes			Yes
513	VA	20	Yes		Yes	
514	VA	17	Yes		Yes	
518	VA	14	Yes		Yes	
519	VA	12	Yes		Yes	
403/520	VA	10	Yes			Yes
521	VA	8		Yes		Yes
523	VA	7		Yes	Yes	
525	VA	6	Yes		Yes	
502	Placebo	35		Yes		Yes
505	Placebo	29		Yes		Yes
506	Placebo	28	Yes		Yes	
510	Placebo	21	Yes			Yes
512	Placebo	20	Yes		Yes	
515	Placebo	17	Yes		Yes	
516	Placebo	16	Yes			Yes
517	Placebo	14		Yes		Yes
522	Placebo	11		Yes	Yes	
524	Placebo	6		Yes	Yes	

Abbreviations: CHAQ, childhood health assessment questionnaire; DI, disability index; ID, identification; VA, velmanase alfa
†At rhLAMAN-05 baseline. ‡Patients are classed as 'Walking with assistance' if they required help from a person and/or frame and/or stick and/or wheelchair use according to the CHAQ 'Helps and Aids' classification system.

A45. Please clarify how the adjusted mean difference in the change from baseline in serum oligosaccharides has been generated for each treatment in rhLAMAN-05 and explain the discrepancy in the point estimate for the treatment effect in the following (Table 24 p126):

- **VA** **-77.60% (95% CI: -81.58, -72.76)**
- **Placebo** **-24.14% (95% CI: -40.31, -3.59)**
- **Difference** **-70.47% (95% CI: -78.35, -59.72)**

The relative change from baseline is based on the ANCOVA model after log-transform of the endpoint and baseline. Data were log-transformed and then submitted to an analysis of covariance (ANCOVA) with treatment as fixed factor, corresponding baseline values and age as continuous covariates. The LS Mean estimates from the model were then back-transformed. The relative change is found as (exp(estimate) - 1)*100, where estimate is from the log-transformed analysis. The LS Mean estimates and estimated difference comes from the analysis on the log-scale. As the calculation is on the log-scale and then back-transformed, it corresponds to (1-0.776) – (1-0.241))/(1-0.241) = -0.705. Therefore, the difference in change since baseline is expressed as a fraction of change from baseline for the denominator.

A47. For the post hoc analysis of serum IgG, please clarify if the 10 patients who had normal IgG at baseline in the VA group maintained a normal value at month 12 (p135)?

In the rhLAMN-05 trial laboratory values have been classified as low, normal or high according to their normal ranges and shift from baseline to each visit have been presented. With regard to serum IgG, the shifts from baseline to Month 12 are shown in Table 23.

Table 23: Change in serum IgG

	Lamazym (N=15) n (%)	Placebo (N=10) n (%)
Immunoglobulin G (g/L)		
n	15	10
High -> High	2 (13.3%)	
High -> Low	0 (0.0%)	0 (0.0%)
High -> Normal	0 (0.0%)	0 (0.0%)
Low -> High	0 (0.0%)	0 (0.0%)
Low -> Low	2 (13.3%)	2 (20.0%)
Low -> Normal	3 (20.0%)	1 (10.0%)
Normal -> High	2 (13.3%)	0 (0.0%)
Normal -> Low	0 (0.0%)	1 (10.0%)
Normal -> Normal	6 (40.0%)	6 (60.0%)

Source: Table 14.3.4.9 Incidence of shift in chemistry baseline to week 52

At baseline, eight patients in the velmanase alfa group presented a normal value, five with low, and two with high. Out of the eight subjects with normal IgG, six (75%) maintained a normal value at month 12.

Section B: Clarification on cost-effectiveness data

- In response to the ERG clarification questions, Chiesi has updated the cost utility analysis to provide a revised set of results (CUA2, see **Appendix B** and **Appendix C**).
- Full details of the implementation amends, and change to the base case patient utility values of the updated cost utility analysis are described in Table A of the **Appendix B**.
- The updated base case ICERs (list price) for velmanase alfa vs BSC using CUA2 are:
  - £[redacted] in the paediatric (≥6–11) cohort
  - £[redacted] in the adolescent (12–17) cohort
  - £[redacted] in the adult (≥18) cohort
- The PAS template ([redacted]) and associated PAS price model ([redacted]) using the updated cost utility analysis are also provided as part of this response.
- The updated base case ICERs (PAS price) for velmanase alfa vs BSC are:
  - [redacted] in the paediatric (≥6-11) cohort
  - [redacted] in the adolescent (12-17) cohort
  - [redacted] in the adult (≥18) cohort

Model Conceptualisation

B1. <u>Priority Question</u>: Please clarify whether patients in the following states are intended to be treated with VA and if so, clarify whether the time on treatment was as intended.

a. The Severe Immobility (SI) state

b. The Short End state

In the SI state patients who are treated apparently receive treatment for exactly one year. In the short end state, patients will apparently receive treatment for one year despite dying after 4 weeks (see Appendix B1)

Regarding the severe immobility state, patients spend a cycle in the model where they discontinue (move from 'on treatment severe immobility' to 'off treatment severe immobility'). This is to reflect that once a person moves into the severe immobility state, there will be a period where their health status in confirmed by their specialist consultant, and the decision is made in collaboration with the patient and their carer to withdraw active treatment.

Regarding the short end stage state, the ERG are correct that velmanase alfa treatment has been incorrectly costed for one year while the state is designed to reflect a 4-week period at the end of life. This error has been corrected in the new version of the model (**Appendix C** [CUA2]), and the correction is included in the updated cost utility analysis results provided in **Appendix B**.

B2. <u>Priority Question</u>: If patients treated with VA are intended to be treated in the SI state, please clarify whether patients receiving VA in the SI state can have severe infections and how this is implemented in the model. It appears as though patients are not at risk of severe infection in the year that they are in the SI on treatment health state (see Appendix B2)

Patients are intended to be treated with velmanase alfa for one cycle only in the 'severe immobility' health state. As stated in response to **B1** this is to reflect that once a person moves into the 'severe immobility' state, there will be a period of time where their health status in confirmed by their specialist consultant, and the decision is made in collaboration with the patient and their carer to withdraw active treatment. During this 'discontinuation' cycle the patient can only move from an 'on treatment severe immobility' state to an equivalent 'off-treatment severe immobility' health state.

B3. <u>Priority Question</u>: Please clarify the likely impact of the simplification of not allowing backward transitions in the placebo arm. It is not the case that the incremental costs and QALYs remain constant when a fixed value is removed from both interventions and added to the transitions to other health states. Ideally, please include the possibility for improvement on standard of care within the model.

Disease improvements to the ambulatory status of patients based on treatment intervention are captured by backward transitions along the functional impairment axis. Whilst improvements to patients' ambulation are clinically plausible with BSC (for example, a successful hip replacement allowing a patient to move out of a 'wheelchair dependent' state to 'walking with assistance'), the model excludes backward transitions for the patient cohort on BSC alone. This is a simplifying assumption, as the probability of backward transitions due to BSC are assumed to be equivalent in both the intervention (velmanase alfa + BSC) and comparator (BSC) arms, and are therefore not formally modelled. Instead, the model allows backward transitions for patients treated with velmanase alfa + BSC only; this is to account for the ability of velmanase alfa (over and above BSC) to achieve disease improvements in the ambulatory status of patients. Please see question **A44** for rhLAMAN-05 trial data regarding the improvement/deterioration in walking ability in the velmanase alfa and placebo arms after 12 months of treatment.

Expert clinical opinion derived from UK KOL interviews agreed that disease improvement (backward transitions) as a result of treatment with velmanase alfa (over and above BSC) were clinically plausible and improvement in the ambulatory status of patients was also observed in the velmanase alfa clinical trial programme, particularly after longer-term treatment (in rhLAMAN-10, of the ten patients requiring assistance at baseline [prior to treatment with velmanase alfa], seven [70%] became device- or third party-independent at last observation). Based on these observations, backwards transitions are not modelled in the BSC arm.

B4. <u>Priority Question</u>: Please provide the incremental cost-effectiveness ratio (ICER) of VA vs best supportive care (BSC) if all the patients were assumed to reside in a chosen health state at a time at the start of the model (e.g. 100% of patients reside in the Walking Unassisted health state, 100% of patients reside in the Walking with assistance health state…).

This scenario analysis is provided in Table 24 using the updated cost utility analysis model (CUA2, please see **Appendix B** and **Appendix C** for further details).

Table 24: Scenario analysis of alternative health state cohorts at start of model

Scenario	VA ICER (vs BSC)		
	Paediatric	Adolescent	Adult
Base case (CUA2)	[redacted]	[redacted]	[redacted]
100% WU	[redacted]	[redacted]	[redacted]
100% WWA	[redacted]	[redacted]	[redacted]
100% WC	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; VA, velmanase alfa; WC, wheelchair; WU, walking unassisted; WWA, walking with assistance.

B5. Please clarify why no relationship was assumed within the model between the level of formal carer costs and the utility loss and productivity loss assumed for individual carers. Please clarify whether you consider the present method would lead to double counting.

Due to limited data identified to model carer costs, carer utility loss, and productivity loss in patients with AM, it was not possible to account for any perceived relationship between these elements of carer and societal impact. The effect of including/excluding these elements within the model has been extensively tested in a set of scenario analyses (**Appendix B,** Section 12.5.16**)**.

B6. Please clarify the potential level of double-counting that could occur when using three independent sources for disutility as detailed in Table 43 p316. For instance, having hearing difficulties may be correlated with cognitive limitations and if so applying both disutilities in full would be invalid.

Health related quality of life data (HRQoL) is limited for patients with AM. Therefore, the original cost utility analysis incorporated three sources for patient health state utility values (HSUVs):

1. AM data – KOL AM patient audit
2. AM data – rhLAMAN-10 data ('Walking Unassisted' and 'Walking with Assistance' health states only)
3. Multi-morbid utility calculation using independent sources of disutility

As the multi-morbid utility calculation is likely to be less robust that using direct AM utility data, it has only been included as a scenario analysis within the company's submission.

New UK, AM-specific patient utility data have become available since the original CS as a result of the UK MPS Society Survey. Chiesi proposes that the UK MPS Society Survey EQ-5D data are most relevant to the decision problem, and therefore become the base case patient HSUVs for the updated cost utility analysis (CUA2, please see **Appendix B** and **Appendix C**). Therefore, we would also refer the ERG to consider our responses to questions **A27, B47** and **Appendix A** where the UK MPS Society Survey data are reported in detail.

B7. Please clarify why the model does not adjust the utilities for age and comment on the likely impact of this on the ICERs.

As the direct AM data used in the model (KOL AM patient audit data, rhLAMAN-10 data, and UK MPS Society Survey data) are classified by health state, these values will indirectly account for any change in utility related to age at a health state level. Also, adjusting utility for age is not viewed as appropriate because patients with AM are typically diagnosed in childhood and unlikely to have a trajectory of HRQoL over their lifetime like that observed on average in the general population.

Potential Model Implementation Errors

B8. <u>Priority Question</u>: It is believed that there are errors relating to the life years, and costs associated with the Short End state: please see appendix B8. Please clarify if this is correct. Most notable, it appears that patients are treated with VA for 52 weeks despite dying within 4 weeks (see question B1).

Please see our response to question **B1**. This error has been corrected and has a negligible impact on the incremental cost-effectiveness ratio (ICER; lower by approximately [redacted] per quality adjusted life year [QALY]). Please see **Appendix B** for a revised set of results using an updated version of the cost utility analysis.

B9. Please clarify whether there is an inconsistency between treatment discontinuation and surgical-related mortality as applied for VA and as applied for BSC (see Appendix B9).

Yes, this is an implementation error and has been corrected. This has a negligible impact on the ICER (higher by approximately [redacted] per QALY). Please see **Appendix B** for a revised set of results using a corrected version of the cost utility analysis.

B10. Please clarify whether there is an inconsistency within the VA arm relating to on treatment discontinuation (see Appendix B10).

Yes, this is an implementation error and has been corrected. This has a negligible impact on the ICER (higher by approximately [redacted] per QALY). Please see **Appendix B** for a revised set of results using a corrected version of the cost utility analysis.

B11. Please clarify why costs for first attendance at each consultation are included in each year for health state costs, rather than only for the first attendance as an adult or child (see Appendix B11).

Yes, this is an implementation error and has been corrected. This has a negligible impact on the ICER (lower by approximately [redacted] per QALY). Please see **Appendix B** for a revised set of results using a corrected version of the cost utility analysis.

B12. Please clarify the source of paediatric ophthalmology visit costs, as these appear to be the same as adults. Paediatric costs are available in NHS reference costs (see Appendix B12).

Yes, this is an implementation error and has been corrected. The updated values and sources in the model for ophthalmology visits are provided in Table 25. Correcting this has a negligible impact on the ICER (lower by approximately [redacted] per QALY). Please see **Appendix B** for a revised set of results using a corrected version of the cost utility analysis.

Table 25: The NHS reference costs for ophthalmology visits used in the model

Ophthalmology consultation	First visit	Follow-up
Paediatric	£119.00	£115.00
Adult	£110.48	£87.00

NHS reference costs 2015–16 Consultant led non-admitted face-to-face attendance

B13. Please clarify why the year 1 administration costs are applied in the model for all years of treatment. It is anticipated that these will reduce after the initial hospitalisation visits within year 1 (see Appendix B13).

Yes, this is an implementation error and has been corrected. This has a negligible impact on the ICER (lower by approximately [redacted] per QALY). Please see **Appendix B** for a revised set of results using a corrected version of the cost utility analysis.

B14. Please clarify whether cell E20 of the 'Treatment' sheet in the Excel model was deliberately left blank. This cell is used in numerous calculations, for example in K15 of the 'Matrices' sheet.

Yes, this cell is deliberately blank and can be ignored.

Model Parameterisation - Utility

B15. <u>Priority Question</u>: Please clarify how the VA utility increment of 0.1 was derived.

A cohort model, by design, cannot fully account for the heterogeneity and complexity of AM. However, this modelling approach was chosen due to the paucity of data that would be required to populate a 'patient-level' model. Thus, a pragmatic approach to modelling had to be taken, in which only the key elements of how a 'typical' AM patient cohort progresses are accounted for. As a result of this pragmatic approach to modelling, numerous aspects of AM are incompletely captured in the model structure including:

- Costs and disutility associated with minor infections (infections treated in primary care)
- Costs and disutility associated with psychiatric problems, such as acute psychosis, sleep disorder and anxiety

- Disutility associated with minor surgeries (tonsillectomy/adenoidectomy, grommet surgery, inguinal hernia repair, carpal tunnel release surgery, feeding tube insertion)
- Mortality risk associated with other key causes of death in AM patients including cardiorespiratory failure (due to causes other than severe infection), cardiac arrhythmia and cardiac failure
- Disutility associated with ventilator-dependency (nocturnal and/or 24-hour)
- 'Intra-ambulatory health state' improvements/progression; for example, the model does not formally account for the cost or utility changes that a patient may experience when moving from requiring one aid for walking (e.g. footwear for stability) to requiring multiple aids/assistance for walking
- Utility benefit associated with homecare

Expert advice, provided during the UK KOL interviews (49) and the rhLAMAN clinical trial KOL interviews (62), indicated that treatment with velmanase alfa may impact (improve) on several of these, incompletely accounted for, aspects of AM by:

- Reducing rates of minor infections
- Reducing rates of psychiatric problems
    - Whilst it should be noted that velmanase alfa is indicated for the treatment of the non-neurological manifestations of AM, clinical trial KOL investigators noted that in [redacted]
- Reducing ventilator-dependency
- Providing 'intra-ambulatory health state' improvements; for example, moving from multiple aids/assistance for walking to only requiring one minimal aid for walking (e.g. footwear for stability)
- Providing a structured homecare visit programme, with regular (weekly) nurse visits [redacted]

All UK KOLs (n=4) in the stage 3 interviews confirmed that applying an 'on-treatment utility increment' was appropriate, to account for these additional benefits that treatment with velmanase alfa may incur, which are not formally accounted for in the model by other existing parameters. A value of 0.1 was deemed appropriate based on the available data anchors of:

- Velmanase alfa is associated with a utility improvement of 0.05 and 0.058 in the 'walking unassisted' and 'walking with assistance' states, respectively, based on analysis of EQ-5D data from the rhLAMAN-10 trial (see Section 10.1.3 of the CS).
    - UK KOL feedback suggested that the 'on-treatment utility' increment may differ from this reported '0.05' and '0.058' on the grounds of:

        - There is a chance the rhLAMAN-10 trial underestimated the utility benefit of velmanase alfa as some effects will only be apparent after a number of years of treatment

- [redacted]
    - These data points show the potential 'intra-health state' range of patient utilities, potentially as a result of velmanase alfa treatment. An 'on-treatment' utility incremented value of 0.1 falls within this range.

B16. <u>Priority Question</u>: The submission states that the utilities produced by the 'minimum' method are aligned to those published in the literature from proxy diseases (p179). Please provide details of the published studies to support this statement, including the diseases on which they are based and the utility values they report.

Two studies (Hendriksz et al, 2014 (50) and Kanters et al, 2015 (51)) were identified that provided KOL-validated proxy disutility scores for each of the primary health states. Both were studies of LSDs (MPS IVA and Pompe disease, respectively) and included EQ-5D utility values stratified by ambulatory status. These values were compared with the multi-morbid utility values and the minimum method was found to align most closely to these proxy conditions (Table 26). It should be noted that AM does not have a close proxy condition and MPS IVA and Pompe disease broadly compare in terms of functional and ambulatory impact of the condition only.

Table 26: Comparison of EQ-5D utility values stratified by ambulatory status with multi-morbid utility values

Source	Method of comparison	Primary health states			
		Walking unassisted	Walking with assistance	Wheelchair	Severe immobility
Multi-morbid utility method (Hendriksz 2014 (50) functional disutility)‡	Additive	0.146	-0.201	-0.847	-0.932
	Multiplicative	0.342	0.203	0.017	0.015
	Minimum	0.574	0.506	0.059	0.059
Hendriksz 2014 (50)	MPS IVA proxy	0.846	0.582	0.057	0.057
Kanters 2015 (51)	Pompe disease proxy	0.729	0.631†	0.533	0.533

†Average of 'no wheelchair' and 'wheelchair' utilities in study.
‡Based on a patient aged 20 years.

B17. Priority Question: Please clarify why the proxy-reported EQ-5D values for 'Walking Unassisted' and 'Walking with Assistance' from rhLAMAN-10 were not used in base case economic analyses.

Due to the study inclusion/exclusion criteria, the rhLAMAN-10 study only provides EQ-5D values that can be used in the 'Walking Unassisted' and 'Walking with Assistance' health states, leaving the 'Wheelchair' and 'Severe Immobility' states unpopulated. We therefore used one consistent data source, the KOL audit data, in the base case analysis because it can populate all four primary health states. However, for completion scenario analysis has been conducted using the rhLAMAN-10 EQ-5D data to populate the 'walking unassisted' and/or 'walking with assistance' health states (**Appendix B,** Section 12.5.16, Table 111). We would also refer the ERG to consider our response to questions **A27**, **B47** and **Appendix A** where the UK MPS Society Survey data are reported in detail, and **Appendix B** where the revised cost utility analysis includes the UK MPS Society Survey EQ-5D data in the base case analysis.

B18. Priority Question: Please clarify why the 'minimum' method (p179) has not been used in the base case analyses when it has been stated that 'Overall, using the 'minimum' method would appear to be the most appropriate/conservative approach, as this method produces utilities that are more aligned to those published in the literature (from proxy diseases) as well as the utilities derived from the EQ-5D data from the rhLAMAN trials.'

The response to question **B17** provides a justification for using the KOL audit data for the base case analysis. The decision to use the KOL audit data for the utility values instead of the minimum method multi-morbid utilities was a preference for using direct AM data, rather than a calculation of disutilities from proxy conditions. Chiesi proposes that the UK MPS Society Survey EQ-5D data are most relevant to the decision problem, and therefore become the base case patient HSUVs for the updated cost utility analysis (CUA2, please see **Appendix B** and **Appendix C**). Therefore, we would also refer the ERG to consider our responses to questions **A27, B47** and **Appendix A** where the UK MPS Society Survey data are reported in detail.

B19. Please clarify how the studies for the multi-morbid utility calculations were chosen and whether the approach taken was systematic.

As described in Section 10.1.9.2 of the CS, by identifying both functional and 'wider disease' disutilities related to AM, multi-morbid utilities can be generated to represent proxy AM HSUVs. These multi-morbid utilities were presented as a scenario analysis only. The most important 'wider disease' symptoms to affect patient QoL were identified as hearing impairment, cognitive impairment, and pain during UK KOL interviews. As the data identified from the HRQoL systematic literature review (described in Section 10.1.5 of the CS) were not sufficient for the analysis, a targeted literature search was performed to identify appropriate proxy data for:

- HRQoL due to functional impairment in related, proxy diseases (e.g. other progressive LSDs)
- HRQoL due to hearing impairment, cognitive impairment, and pain

Details of the search terms used during these targeted literature searches are presented in Appendix 6, Section 17.6.1 and 17.6.2 of the CS. Although the targeted literature searches were not systematic, the following approach was taken:

- An analyst screened all abstracts to identify potentially relevant studies (first pass)
- All first pass abstracts were reviewed by a second analyst to identify/confirm relevant studies (second pass), who subsequently extracted data into Excel. Categories of data extracted into Excel included study information; participant/patient demographics; disease/indication; stratification/health states (ambulatory categories for proxy functional impairment utilities; severity categories for proxy 'wider disease' impairment utilities); utility measure; utility values
- All extracted data were reviewed by a senior health economist before the most appropriate data were selected for inclusion in the cost-utility analysis (CUA)

The key criteria used to identify relevant data for inclusion into the model (scenario analysis only) were:

- For functional impairment utilities from proxy, related disorders:
    - Stratification of utilities by clearly defined ambulatory categories that aligned to the ambulatory health states of the cost utility analysis model
    - Provision of utilities in a proxy disease with similar functional impairment as observed in AM patients
    - EQ-5D instrument
    - UK population
- For 'wider disease' impairment utilities:
    - Stratification of utilities by clearly defined severity categories that aligned to the three levels of clinical severity (mild, moderate and severe) as reported by UK KOLs in interviews during model conceptualisation
    - EQ-5D instrument
    - UK population

Model Parameterisation – Resource Use

B20. <u>Priority Question</u>: The model appears to calculate the weight for males and females and takes the average then calculates the number of vials required, rather than calculating the number of vials required for males and females and taking the average. Please clarify why a more accurate approach of considering a distribution of patient weights within the population to estimate the number of vials required was not undertaken. Please provide an indication of the impact on the costs of VA were a distribution to be used (see Appendix B20).

Yes, this is an implementation error and has been corrected. This has a negligible impact on the ICER (lower by approximately [redacted] per QALY). Please see **Appendix B** for a revised set of results using a corrected version of the cost utility analysis. Clinical data were not available to derive a population distribution from which to estimate an expected number of vials.

B21. The ventilation costs assumed in the model are taken from Noyes et al (2006) and are total support costs, which include other hospital, community health, social services and education costs. Please clarify whether using these values introduces double counting? Please provide analyses using only these costs (excluding health state and carer costs) and provide analyses using the ventilation costs reported from MPS IVA as reported in http://www.gov.scot/Resource/Doc/293936/0090811.pdf.

The provision of ventilation was identified during UK KOLs interviews as an important and costly component of care in the 'wheelchair dependent' and 'severe immobility' health states. For patients in these health states, the care and support required for a patient who requires either overnight or 24-hour ventilation is likely to be considerably higher than for an equivalent patient who does not require ventilation, and this is in addition to the complex package of care and support each patient will need. For this reason, it was considered important to ensure that all potential care costs were incorporated. The Noyes et al, 2006 study (63) provides a range of costs for different ventilation settings and modalities enabling the benefit of velmanase alfa in terms of improved lung functioning and a potential reduction in ventilation to be accounted for. The assumptions and data sources used to model ventilation has been extensively tested in scenario analyses (**Appendix B,** Section 12.5.16, Table 111).

B22. Please provide the HRG code assumed to represent the administration cost of VA

The HRG code assumed to represent the administration cost of velmanase alfa is QZ14B, and is consistent with the source used for the Elosulfase alfa for the treatment of MPS type IVA NICE HST submission (64). The reference and value in the original model and CS was incorrect and should be amended to be the 2015–16 NHS national tariff, outpatient procedure (QZ14B) with a cost of £209. This has been corrected in the latest version of the cost utility analysis (CUA2, **Appendix B** and **Appendix C**).

B23. Please clarify how uncertainty distributions were derived for NHS reference costs. It appears that the Standard Error, calculating using the number of data submissions and the inter-quartile range, has not been used.

For consistency with other parameters, uncertainty distributions for NHS reference costs are derived using ± 25% of the point estimate.

B24. Please clarify why the values calculated for severe infection costs used in the model (which have been calculated using severe sepsis costs) are preferable to the cost that can be estimated from NHS Reference costs (using non-elective long stay codes WJ05A, WJ05AB, WJ06A, WJ06B, WJ06C, WJ06D, WJ06E,

WJ06F, WJ06G, WJ06H, WJ06J,). These are £2742 with an average length of stay of 6.39 days when weighted by the number of Finished Consultant Episodes.

The cost of care for a patient with a severe infection (sepsis) was micro-costed using the Levy et al, 2012 (65) and Paul et al, 2012 (66) studies and intensive care unit (ICU)/general care NHS reference costs. This approach was to enable paediatric and adult specific costs of care to be estimated, as well as the potential to vary the time spent in ICU/general care within sensitivity analysis.

B25. Please clarify the mean, maximum and minimum infusion times related to VA treatment.

The dosing regimen of velmanase alfa is an infusion of 1 mg/kg weekly. After reconstitution, 1 mL of the solution contains 2 mg of velmanase alfa. As detailed in the summary of product characteristics, the total volume of infusion is determined by the patient's weight and should be administrated over a minimum of 50 minutes. For patients weighing <18 kg (corresponding to a calculated infusion time <50 minutes) the infusion rate should be adjusted so that the length of infusion is ≥50 minutes. The maximum infusion rate is 25 mL/hour. The maximum infusion rate and minimum infusion time according to the patient cohort are shown in Table 27.

Table 27: Maximum and minimum rates of velmanase alfa infusion in different patient age groups

Patient cohort	Modelled patient weight (kg)†	Dose (mL)	Maximum infusion rate (mL/h)	Minimum infusion time (min)
Paediatric (age 6)	23	11.5	13.8	50
Adolescent (age 12)	45	22.5	25	54
Adult (age 18)	65	32.5	25	78

†rounded up to nearest kg.

B26. Please clarify why resource use is not varied in sensitivity analysis.

This is an implementation error and has been corrected. Please see **Appendix B** for a revised set of sensitivity analysis results using an updated version of the cost utility analysis.

Model Parameterisation – General

B27. <u>Priority Question</u>: Please justify the distributions used, including the use of +/- 25% as the 95% confidence interval in parameters that were not formally elicited.

Probabilities were assigned beta distributions so that sampled values were bound between zero and one. Time-to-event estimates and cost estimates were assigned gamma distributions so that sampled values were non-negative. Adding or subtracting 25% to the point estimate was used as a proxy for the 95% credible/CI where data on a parameter's uncertainty were not available.

B28. <u>Priority Question</u>: Please clarify what evidence exists to support the modelling assumption that values for the following parameters must be greater than 0:

- **the reduction in the rate of severe infections;**
- **the reduction in recovery period post severe infections;**
- **the reduction in mortality post-infection;**
- **the reduction in surgical-related mortality;**
- **the reduction in surgical-related complications;**
- **the reduction in recovery period post severe infections.**

We note that Table 32 p158 indicates that there were more infections and infestations in the VA arm than in the placebo arm.

Evidence to support each modelling assumption is provided below:

- **the reduction in the rate of severe infections**
  - UK KOL interviews
  - Clinical trial KOL interviews
  - rhLAMAN-05, serum IgG analysis
  - Response to question A20 in relation to serum IgG analysis and caregivers reporting reduced infection rates after treatment with velmanase alfa
- **the reduction in recovery period post severe infections**
  - UK KOL interviews
- **the reduction in mortality post-infection**
  - UK KOL interviews
- **the reduction in surgical-related mortality**
  - UK KOL interviews
- **the reduction in surgical-related complications**
  - UK KOL interviews
- **the reduction in recovery period post severe infections**
  - UK KOL interviews

In response to the statement: *We note that Table 32 p158 indicates that there were more infections and infestations in the VA arm than in the placebo arm* – The dataset available recapitulating the entire clinical programme with velmanase alfa cannot robustly demonstrate a positive effect of the treatment with velmanase alfa on infection rate, as the rate of infections was not systematically investigated as an efficacy endpoint or as an AESI. However, there are multiple indicators that point to the beneficial clinical effect experienced by patients treated with velmanase alfa as described in response to question **A20.**

B29. Priority Question: Please clarify why the number of additional years in 'Walking Unassisted' 'with VA (Table 73) is bounded at zero in sensitivity analysis when the lower bound from elicitation is negative.

This is an error and the number of additional years in 'Walking Unassisted' with VA should have a lower bound of –0.31. This error does not impact the base case analysis, only the sensitivity analysis. Please see **Appendix B** for a revised set of results using an updated version of the cost utility analysis.

B30. Please clarify, with reference to the NICE methods guide, why a discount rate of 1.5% was used.

NICE recommends that a discount rate of 1.5% can be used for costs and QALYs in treatments where patients would otherwise not survive, patients suffer from severely impaired life conditions or when the condition is sustained for over 30 years. As AM is a progressive, life-long, life-limiting condition, treatment with velmanase alfa may delay long-term disease progression, as well as reduce the risk of key drivers of mortality. Therefore, the base case adopts the 1.5% discount rate for costs and QALYs. The use of the 1.5% discount rate is consistent with the model for the elosulfase alfa for the treatment of MPS type IVA NICE HST submission (64). In the NICE HST appraisal final evaluation determination document (67), the ERG *"noted that the discounting rate of 1.5% per year might be considered reasonable, in the context of the NICE Guide to the methods of technology appraisal 2013 (which is considered to be relevant to the highly specialised technologies programme)."*

B31. Please clarify why the baseline age of paediatric, adolescent and adult patients was assumed to be the lowest age of each band, rather than the average age (which is an option in the model).

The lowest age of each band was selected to reflect UK KOLs comments that the earlier the intervention with an ERT (such as velmanase alfa), the more potential for a treatment benefit to be realised, and to reflect the reality that future patients with AM are likely to be diagnosed as an incident population in childhood, rather than the rhLAMAN clinical programme which identified patients from a prevalent cohort of patients with AM.

B32. Please clarify the source of the following parameters, and associated uncertainty, with details of questions asked and responses at the Expert Elicitation Panel or KOL interviews:

a. **Backward transitions / improvement for VA**

b. **10% annual VA discontinuation**

c. **Surgery-related mortality**

d. **Surgery-related complications**

e. **Minor surgery probabilities**

f. **Duration of short end-stage state**

g. Proportion of care provided by formal carer in each health state

h. Reduction in Severe infections due to VA

Please note this information has been provided in the following DOF references supplied with the CS:

- DOF. Chiesi – UK Expert Elicitation Panel.pdf (61)
    - DOF. Chiesi – UK Expert Elicitation Panel – Appendix C – Disaggregated results.xlsx
    - DOF. Chiesi – UK Expert Elicitation Panel – Answers to pre-meeting questionnaire (Appendix B of Evidence dossier).xlsx
- DOF. Chiesi – UK KOL interviews.pdf (49)

For completion and ease, we have tabulated where the ERG can locate each parameter in Table 28.

Table 28: Summary of parameters applied in the cost-utility model

Variable	Source	DOF	Questions/responses	Uncertainty/range†
Backward transitions / improvement for VA	UK KOL interviews (Stage 3)	Chiesi – UK KOL interviews.pdf	Located in DOF on pages: • p161/225 • p182/225 • p203/225 • p224/225	0.0%, 70.0% (year 1 and 2) 0.0%, 5.0% (year 3+)
10% annual VA discontinuation	UK KOL interviews (Stage 3)	Chiesi – UK KOL interviews.pdf	Located in DOF on pages: • p162/225 • p183/225 • p204/225 • p225/225	+/- 25%
Surgery-related mortality Surgery-related complications Minor surgery probabilities	UK KOL interviews (Stage 2 and Stage 3)	Chiesi – UK KOL interviews.pdf	Located in DOF on pages: • p152/225 • p174/225 • p195/225 • p216/225 • p77-78/225 • p102-103/225 • p125-126/225	+/- 25%
Duration of short end-stage state	UK KOL interviews (Stage 2)	Chiesi – UK KOL interviews.pdf	Located in DOF on pages:‡ • p85/225 • p108/225 • p133/225	+/- 25%
Proportion of care provided by formal carer in each health state	Assumption	N/A	N/A	+/- 25%
Reduction in Severe infections due to VA	UK KOL interviews (Stage 3)	Chiesi – UK KOL interviews.pdf	Located in DOF on pages: • P156/225 • P177/225 • P198/225 • P219/225	+/- 25%

Abbreviations: DOF, data on file; KOL, key opinion leader; VA, velmanase alfa.
†The -/+ 25% upper and lower bound is in line with other model parameters lacking a formal source of uncertainty. ‡Only one KOL provided a formal response to the question during the interviews, and responded with '1–3 weeks'. A time period of 4 weeks was chosen for modelling as an assumption.

B33. Please clarify whether the default distribution of all parameters (e.g. disease progression) matches that of patients currently with AM in England.

Please see Table 8 (Summary of UK MPS Society Survey respondents) for data on the ambulatory status and age of current AM patients in the UK. Please note that these data include patients with prior allogeneic HSCT, patients who are currently severely immobile, and the data do not provide the ambulatory status of a patient when they were originally diagnosed. Therefore, while the data are informative about the current distribution of UK patients by ambulatory status, the data cannot be used to completely validate the starting-state cohort distribution of the economic model. The rhLAMAN-10 data (see Table 21 – Health state definitions from the rhLAMAN trials (CHAQ) and the cost utility analysis) were used in the cost utility analysis to provide the starting state distribution, in the absence of any other data. This is to ensure the model informs the decision problem and estimates the expected cost-effectiveness of velmanase alfa within its licensed indication, and to ensure the model can inform guidance pertaining to a recently diagnosed patient with AM. Sensitivity analysis regarding the starting state distribution is provided in **Appendix B** in response to question **B4**. Please also see the response to question **B45** for the response to a related question regarding the starting state distribution of the model cohort.

B34. Please provide the parameter values for the distributions contained in Table 74 p245.

Full parameter values for each probabilistic sensitivity analysis (PSA) parameter distribution are available for review in the 'Data & References' tab of the economic model.

B35. Please comment on the apparent discrepancy between the carer time required for children in Morquio A syndrome (Figure 39 p301: little difference between patients who do and do not require wheelchair use), and the data provided in Table 68 p235 (Hendriksz: sharp increase in care-giving requirements when a patient enters the wheelchair state).

Table 68 (Personal social service caregiver costs by health state) in the CS (Section 12.3.9.1) reports the hours of care-giving/day from Hendriksz et al, 2014 (50) for each model health state. This corresponds to 1.3 hours in the 'walking unassisted' state, 3.9 hours in the 'walking with assistance' state, and 13.8 hours in the 'wheelchair dependent' and 'severe immobility' state. The data are from the weekdays average caregiving time for adults. The discrepancy apparently observed by the ERG is in respect to Figure 39 (Mean number of caregiving hours/days on weekdays and weekends for adults (A) and children (B) with Morquio A syndrome, according to wheelchair use/mobility level) of the CS. The top part of figure (A) reports the adult data, matches Table 68 and are the data used in the model. The bottom part of the figure (B) reports the child specific data where there is little difference in caregiver time between patients who do and do not require wheelchair use. We expect that this lack of difference is because children will require a greater amount of caregiver time and support, irrespective of their ambulatory status. A patient who becomes an adult and does not require a wheelchair is likely to see a reduction in their caregiver time as they gain independence.

B36. Please provide, as appropriate, the following with respect to Table 74 p245:

- **confirmation that the use of normal distributions gives effectively zero probability of negative values for uncertain values that are strictly positive**
- **a justification for the use of gamma distributions for relative estimates of treatment effects that could take negative values**

All probability distributions were tested to ensure that the probability distribution type selected did not result in the sampling of implausible values (e.g. negative costs, or negative time). The relative estimates of treatment effects were parameterised using the output of the SHELF elicitation package where the best fitting distribution was selected by the package.

Elicitation Exercise / KOL interviews

B37. <u>Priority Question</u>: Please comment on the face validity of the utility value for being wheelchair dependent, particularly in reference to the description of the health state provided in Table 47. Please comment on whether this value indicates that the values provided by the KOLs are not reliable.

The data from the UK KOL AM patient (n=7) audit suggests that a transition to wheelchair dependency is believed to be associated with the largest reduction in patients' QoL, as the 'wheelchair dependent' health state had the lowest level of utility of the four ambulatory states assessed. One rationale for this observation, as provided by the treating clinician, is because this is the stage of the disease when AM patients become self-aware of the severity of their situation in relation to their (lack of) mobility. For example, patients realise the loss of independence that occurs when transitioning to a state where their (lack of) mobility significantly hinders social integration and activities of daily living (for example, wheelchair access in public places is inconsistent and further adaptations to the home are often required). Another explanation is that if a patient's level of cognition declines further once they move into a 'severely immobile' state their anxiety/discomfort goes away as they are no longer aware, or less aware, of their disease state.

However, it was noted by the clinician providing the audit data that this QoL trend (where 'wheelchair dependency' is associated with the lowest level of utility) may not be replicated in all patients, as each patient's symptom profile (in particular their level of cognition and disease/burden awareness) and subsequent impact on QoL is likely to be heterogeneous. Therefore, this assumption was formally tested using a sensitivity analysis, as reported in Section 12.5.12.2 of the CS, where the HSUV for the 'wheelchair dependent' health state was equal to the HSUV for the 'severely immobile' health state. When compared with the base case results (Section 12.5.1 of the CS), the ICER for the HSUV sensitivity analyses were lower for all three age cohorts.

As reported in response to the ERG clarification questions **A27, B47,** and **Appendix A** patient utility data from the UK MPS Society Survey are now available, and have been incorporated into the revised CUA base case (CUA2, please see **Appendix B** and **Appendix C**). The UK MPS Society Survey patient utilities are deemed more relevant to the decision problem given these data are:

- derived from UK AM patients

- reported by carers (family members) who care for the patients on a daily basis
- were collected via a structured, formal survey conducted by the UK MPS Society

B38. <u>Priority Question</u>: Please provide the exact questions asked at the elicitation exercise. Please also clarify whether the clinicians explicitly took into account potential improvements in health state, such as moving from walking with aids to walking unaided, when the estimate of the increased years in walking without aids due to VA treatment was elicited. Unless the question explicitly excluded patients who improved, it is likely that the clinicians assessed the typical patient progressing to the next health state and that the gains modelled will be an overestimate of the benefit of VA.

Full details of the questions asked at the elicitation workshop are described in the DOF reference submitted with the CS ('DOF Chiesi – UK Expert Elicitation Panel.pdf' (61)).[c] For completion and ease, we have extracted the questions here:

QoL 1: Questions related to disease progression for patients under BSC alone were as follows:

For paediatrics aged 6–11 years (at the time of treatment initiation/under specialist care) under BSC alone:

1. How many years does a typical AM patient spend in a 'walking unassisted' health state before progressing to a 'walking with assistance' health state (Transition A in model schematic)?
2. How many years does a typical AM patient spend in a 'walking with assistance' health state before progressing to a 'wheelchair' health state (Transition B in model schematic)?
3. How many years does a typical AM patient spend in a 'wheelchair' health state before progressing to a 'severe immobility' health state (Transition C in model schematic)?
4. How many years does a typical AM patient spend in a 'severe immobility' health state before progressing to the 'death' (Transition D in model schematic)?

These four questions were repeated for:

- adolescents aged 12–17 years (at the time of treatment initiation/under specialist care) under BSC alone, and
- adults aged ≥18 years old (at the time of treatment initiation/under specialist care) under BSC alone

[c] In the DOF reference source 'DOF Chiesi – UK Expert Elicitation Panel.pdf' the questions display slightly different titles for the health states when compared to the questions displayed in this ERG clarification response. Following discussion, the experts at the elicitation panel concluded that 'walking' should be termed 'walking unassisted' for further clarity. In addition, 'walking with aids' should be redefined as 'walking with assistance', which covers a broad range of assistance from the use of traditional walking aids, such as a walking stick or occasional wheelchair use, to help from another person or adaptations in the home (e.g. hand rails). Another difference relates to the final transition along the primary functional health states – severe immobility to long-end stage. The experts found it difficult to distinguish between the 'severe immobility' state and the 'long-end stage'. They also remarked that the level of care provided to a patient in 'long-end stage' would be highly variable and based on the wishes of the patient and caregivers. Therefore, it was agreed that 'long-end stage' should be termed as 'death' and that the final transition (Transition D) should reflect to time spent in 'severe immobility' before death.

For questions related to adolescents and adults under BSC alone, the elicited paediatric BSC transitions were displayed on a wall and were used as a starting point, and experts asked whether they felt there was any difference from these. Where experts felt there was no difference, the same fitted distribution was entered onto the wall as a response for the adolescents and/or adults (i.e. completion by copy). Where experts felt there was a difference in one or more of the transitions, a full elicitation was conducted. The same proportionate difference was then used as a starting point for any other transitions. If the experts felt this was reasonable, this would be entered as the final answer (i.e. completion by proportionate difference). If only minor modifications to the median and credibility intervals were required, this was done as directed by the experts. However, if there was substantial discussion or disagreement, a full elicitation was conducted. Details of which questions were answered by full elicitation, completion by copy, or completion by proportionate difference are described on page 22/176 of the 'DOF Chiesi – UK Expert Elicitation Panel.pdf' (61), as provided with the CS.

QoL 2: Questions related to disease progression for patients under velmanase alfa + BSC were as follows:[d]

For paediatrics aged 6–11 years (at the time of treatment initiation/under specialist care) under velmanase alfa + BSC:

1. How many years does a typical AM patient spend in a 'walking unassisted' health state before progressing to a 'walking with assistance' health state (Transition A in model schematic) relative to those receiving BSC alone?
2. How many years does a typical AM patient spend in a 'walking with assistance' health state before progressing to a 'wheelchair' health state (Transition B in model schematic) relative to those receiving BSC alone?
3. How many years does a typical AM patient spend in a 'wheelchair' health state before progressing to a 'severe immobility' health state (Transition C in model schematic) relative to those receiving BSC alone?
4. How many years does a typical AM patient spend in a 'severe immobility' health state before progressing to the 'death' (Transition D in model schematic) relative to those receiving BSC alone?

These four questions were repeated for:

- adolescents aged 12–17 years (at the time of treatment initiation/under specialist care) under BSC alone, and
- adults aged ≥18 years old (at the time of treatment initiation/under specialist care) under BSC alone

The experts were first asked which transitions they felt velmanase alfa + BSC would have an effect over and above BSC alone. A full elicitation was conducted for the first of these, with

[d] In the DOF reference source 'DOF Chiesi – UK Expert Elicitation Panel.pdf' the questions relating to the time spent in health states for patients under velmanase alfa + BSC do not display the term 'relative to those receiving BSC alone'. During the elicitation panel, experts stated it would be more cognitively intuitive to provide their probabilities relative to the values they provided for patients receiving BSC alone. The questions were therefore altered during the elicitation panel to reflect this change.

the same relative effects suggested as a starting point for the remaining transitions, with resulting modification or full elicitation as appropriate. Details of which questions were answered by full elicitation, completion by copy, or completion by relative effect are described on page 22/176 of the 'DOF Chiesi – UK Expert Elicitation Panel.pdf' (61), as provided with the CS.

QoL 3: Questions related to disease improvement for patients under velmanase alfa + BSC were as follows:

Consider 10 patients in a 'walking with assistance' health state being treated with velmanase alfa + BSC:

- How many of these 10 patients will move from a 'walking with aid' state to a 'walking unassisted' state as a result of two years of active treatment with velmanase alfa + BSC? (Transition E)

Consider 10 patients who are in a 'wheelchair' health state being treated with velmanase alfa + BSC:

- How many of these 10 patients will move from a 'wheelchair' state to a 'walking with assistance' state as a result of two years of active treatment with velmanase alfa + BSC? (Transition F)

Notably, the experts were asked to elicit their feedback on disease progression under velmanase alfa + BSC separate to their feedback on disease improvement (i.e. backward transitions) under velmanase alfa + BSC. This is demonstrated by questions relating to disease progression falling under 'QoL 2' and questions relating to disease improvement falling under a different QoL - 'QoL 3'. Therefore, the final clinicians' (group) probabilities concerning disease progression under velmanase alfa + BSC for the typical patient progressing to the next health state are not an overestimate of the benefit of velmanase alfa. A 'typical' patient receiving velmanase alfa was defined as those who are responders according to the post hoc multi-domain responder analysis at Month 12 of the rhLAMAN-05 trial.

B39. Please clarify the approach used to generate the clinician proxy utility values, including how many clinicians provided answers, what information was used to define the health states, which EQ-5D valuation set was used (3L or 5L), and the associated uncertainty.

One clinician completed the EQ-5D-5L questionnaire (via proxy) for seven AM patients based on the clinician's own observations of the patient and information provided by the patients' carers at last patient visit.

These data were not collected formally via a study, but shared by the clinician as part of the UK KOL interviews conducted to support development of the cost utility model. When classifying the seven patients' walking ability, the clinician used their own observations of the patient and/or information provided by the patients' carers at last patient visit to categorise patients into one of the four ambulatory health states used in the cost utility analysis i.e. 'walking unassisted', 'walking with assistance', 'wheelchair dependent' and 'severe immobility'.

These KOL audit data are associated with uncertainty as they are proxy data only based on an individual clinicians' observations from memory of the patient at last patient visit, in an AM population from several countries. Chiesi proposes that the UK MPS Society Survey EQ-5D-5L data are most relevant to the decision problem, and therefore become the base case patient HSUVs for the updated cost utility analysis (CUA2, please see **Appendix B** and **Appendix C**). Therefore, we would also refer the ERG to consider our responses to questions **A27, B47** and **Appendix A** where the UK MPS Society Survey data are reported in detail.

B40. Please clarify how the resource use data and the associated uncertainty presented in Table 66 p232 was derived from KOLs.

UK KOLs during teleconference interviews were asked to provide the frequency of consultations as part of BSC for AM patients in the UK. Full methods for the UK KOL interviews are described in Section 12.2.5.2 of the CS. Specifically, resource use data for Table 66, were collected in the stage 2 interviews from 'Section 3.4 Resource Utilisation' questions, as provided in the DOF reference submitted with the CS (DOF Chiesi – UK KOL interviews.pdf', pages 83–84, 107–108 and 132–133 (49)). A simple pooling of the UK estimates was provided, with the mean frequency used to populate Table 66. The inclusion of resource use uncertainty was omitted from the PSA in error. Please see the response to question **B26**, and **Appendix B** and **Appendix C** for the revised CUA (CUA2).

B41. Please clarify whether KOLs/experts were given a training exercise before the elicitation process and also if the clinicians were provided with an evidence dossier. Please also clarify whether any clinician strongly objected to the 'consensus' distribution (note the final distribution should align with that of a rational impartial observer privy to all discussions not a consensus and therefore strong disagreement is possible).

An evidence dossier was collated, describing the concepts of expert elicitation, a statement of what would be asked of the experts and a detailed summary of direct/indirect evidence of relevance to the unknown quantities of interest (QoL), as described in Section 12.2.5.1 of the CS. Experts were asked to read the evidence dossier carefully and return a consent form confirming their participation, declaring that they had read the information in full. The experts were also asked to provide feedback on the dossier. The feedback received (such as additional studies to include in the direct/indirect evidence) from the experts was then incorporated into the final dossier used to support the elicitation panel. The evidence dosser provided to the experts is provided in the DOF reference submitted with the CS ('DOF Chiesi – UK Expert Elicitation Panel.pdf', pages 31–67 (61)).

Experts were given a training exercise before the elicitation process, as stated in Section 12.2.5.1 of the CS. The training involved two components: 1) Experts were provided with training materials/pre-reading as a part of the evidence dossier and 2) A training exercise was also conducted at the start of the elicitation workshop in order to familiarise the experts with the process of elicitation. The training exercise was devised to simulate an elicitation using the 'Roulette method'. The presentation slides used to support this training exercise are provided in the DOF reference submitted with the CS ('DOF Chiesi – UK Expert Elicitation Panel.pdf', pages 78–88 (61)).

All final group probability distributions were deemed by the experts to be a plausible representation (in the eyes of a rational impartial observer) of their group probabilities. No clinician strongly objected to any of the final group probability distributions.

Model Output

B42. Priority Question: Please provide an example of how the weighted ICER was calculated.

The weighted ICER is calculated by weighting the absolute costs and QALYs across the paediatric, adolescent and adult sub-populations by the expected proportion of patients in each group (taken from the budget impact analysis calculation and reported in 12.5.1 of the CS). The corresponding incremental costs, incremental QALYs and ICER are then calculated.

B43. Priority Question: Please provide an example of how the credible intervals associated with each ICER were calculated.

The credible intervals associated with each PSA expected ICER were calculated by taking the PSA results and identifying the 2.5% percent ICER estimate and the 97.5% percent ICER estimate from the ranked output of the simulation. If any ICERs are undefined, dominated or dominant, then this is stated in the output of the credible interval.

B44. Priority Question: Please clarify the estimated incremental undiscounted QALYs gained associated with the use of VA compared with BSC.

The estimated incremental undiscounted QALYs gained for velmanase alfa compared to BSC are provided in **Appendix B,** section 12.5.7, Table 84.

Other

B45. Priority Question: Please clarify the likely distribution of health states that a cohort of people with AM diagnosed in the future would reside in, and the likely age distribution of these patients.

As described in Section 13.1 of the CS, based on analysis of the UK MPS Society Patient Registry data for live AM patients whom have an age at diagnosis data point (n=21), [redacted] (52). Therefore, these data can be used to infer the likely age distribution of people with AM diagnosed in the future, with the notable caveat that changes to UK clinical practice (such as the availability of new national guidance for the treatment of AM) may alter/speed up the route to AM diagnosis in the future. For example, as reported in the UK MPS Society Survey Report (**Appendix A** and associated DOF (9)), [redacted]

The largest AM patient population available for which patients' ambulatory health states are reported in appropriate detail to inform the cost utility model, is from the starting distribution at baseline of rhLAMAN-10 (n=33). Therefore, these data (in Table 29) are deemed the best estimate of the likely distribution of health states that a future AM cohort would reside in. [redacted]

[redacted]

Table 29: Starting health state distribution at baseline (from rhLAMAN-10)

	Walking unassisted, % (n/N)	Walking with assistance, % (n/N)	Wheelchair dependent, % (n/N)†	Severe immobility, % (n/N)
Paediatrics	77.8 (7/9)	22.2 (2/9)	0 (0/9)	0 (0/9)
Adolescents	72.7 (8/11)	27.3 (3/11)	0 (0/11)	0 (0/11)
Adults	61.5 (8/13)	38.5 (5/13)	0 (0/13)	0 (0/13)

Source: rhLAMAN-10.
†Although three patients used a wheelchair in rhLAMAN-10 (according to CHAQ), they were not strictly wheelchair bound (as per the eligibility criteria of the study).

B46. Please provide information on the age of patients in the UK MPS Society registry.

Table 30 describes the current age of all live AM patients [redacted] registered in the UK MPS Society Registry who live in the UK, as per the MPS Society Registry DOF reference submitted with the CS (52). The ages of the [redacted] unique patients who responded to the UK MPS Society Survey are presented in response to the clarification question **A27**.

Table 30: Age of live AM patients (UK address) registered with the UK MPS Society Registry

Age†	Date registered with MPS Society	Year of birth
[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]

†At the time of data extraction from the UK MPS Society Patent Registry (29/11/2017)

B47. Please clarify what utility data the UK MPS Society survey is expected to provide and which model health states it will populate.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 31: QoL tools to assess patient utility: responses by carers (by proxy)

Patient ID	Prior treatment of the patient	Walking ability of the patient	Survey completed		
			EQ-5D-5L†	EQ-5D-Y†	HUI-3†
[redacted]					

[redacted]

Table 32: QoL tools to assess patient utility: responses by patients (by self-report)

Patient ID	Prior treatment of the patient	Walking ability of the patient	Survey completed		
			EQ-5D-5L	EQ-5D-Y	HUI-3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

To provide further data to support and validate the CUA presented in the CS, analysis of AM patients' utilities according to their walking ability (ambulatory health state) was conducted by means of simple pooling, whereby patients with the same walking ability were combined and descriptive statistics used to assess pooled data (e.g. mean, range, standard deviation). The EQ-5D-5L (and EQ-5D-Y) provided by carers (by proxy) was the most complete patient utility dataset and therefore chosen for onward analysis and incorporation into the CUA on the grounds of:

- As only three patients provided self-reported patient utilities, there were insufficient patient-reported data to cover the four ambulatory health states of interest. As noted in **Appendix A**, the patient-reported and carer-reported utilities were generally consistent with one another.
- NICE process methods prefers EQ-5D-5L over other tools for assessing utility
- The HUI-3 dataset is associated with a higher level of uncertainty due to incomplete surveys and the subsequent exclusion of 3 patients: Patients CH001, CH002 and CH009 could not have their HUI-3 utility value calculated due to missing data in their survey responses

When assessing patient EQ-5D-5L utility as reported by the carer (by proxy) stratified by the four ambulatory health states by simple pooling, the following scenarios were examined:

- Scenario 1[e]: Patient utility as reported by the carer (by proxy) regardless of prior treatment
- Scenario 2: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC, i.e. patients who had received HSCT or velmanase alfa were excluded from the pooled analyses. A resulting missing data point for the 'walking with assistance' health state was imputed using the EQ-5D-5L utility for this health state as reported previously in a unpublished UK KOL audit referred to in the original CS (49)
- Scenario 3: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC, i.e. patients who had received HSCT or velmanase alfa were excluded from the pooled analyses. A resulting missing data point for the 'walking with assistance' health state was imputed using the mean of the EQ-5D-5L utility values

[e] Referred to as the 'base case' in the full UK MPS Society Survey Report in Appendix A

calculated for the 'walking unassisted' and 'wheelchair dependent' states from the UK MPS Society Survey

- Scenario 4: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC, i.e. patients who had received HSCT or velmanase were excluded from the pooled analyses. A resulting missing data point for the 'walking with assistance' health state was imputed using a ratio of utility for 'walking with assistance' relative to 'walking unassisted' as reported previously in an unpublished UK KOL audit referred to in the original CS (49)

Table 33–Table 36 shows the results of the pooled analysis, across the four scenarios described above.

Table 33: Scenario 1† – EQ-5D-5L patient utility: carer-reported

Health state	Obs (n=9)	Mean	SD	Min	Max
WU	5‡	0.794	0.200	0.567	1.000
WWA	1	0.758	N/A	0.758	0.758
WC	1	0.100	N/A	0.100	0.100
SI	2	-0.011	0.053	-0.048	0.027

Abbreviations: N/A, not applicable; Max, maximum; Min, minimum; Obs, observations; SI, severe immobility; SD, standard deviation; WC, wheelchair dependent; WU, walking unassisted; WWA, walking with assistance
†Referred to as the 'base case' in the full UK MPS Society Survey Report in Appendix A. ‡Group contains utility values mapped from EQ-5D-Y for two patients (CH001 and CH008) as per the methods detailed in Appendix A.

Table 34: Scenario 2 – EQ-5D-5L patient utility: carer-reported

Health state	Obs (n=5)	Mean	SD.	Min	Max
WU	2	0.906	0.00	0.906	0.906
WWA	N/A	[redacted]	N/A	N/A	N/A
WC	1	0.100	N/A	0.100	0.100
SI	2	-0.011	0.053	-0.048	0.027

Abbreviations: N/A, not applicable; Max, maximum; Min, minimum; Obs, observations; SI, severe immobility; SD, standard deviation; WC, wheelchair dependent; WU, walking unassisted; WWA, walking with assistance
†Value from unpublished UK KOL audit data (49) as reported in the original company submission, descriptive statistics unavailable.

Table 35: Scenario 3 – EQ-5D-5L patient utility: carer-reported

Health state	Obs (n=5)	Mean	SD.	Min	Max
WU	2	0.906	0.000	0.906	0.906
WWA	N/A	0.503†	N/A	N/A	N/A
WC	1	0.100	N/A	0.100	0.100
SI	2	-0.011	0.053	-0.048	0.027

Abbreviations: N/A, not applicable; Max, maximum; Min, minimum; Obs, observations; SI, severe immobility; SD, standard deviation; WC, wheelchair dependent; WU, walking unassisted; WWA, walking with assistance
†Value = mean of 0.906 (WU) and 0.1 (WC).

Table 36: Scenario 4 – EQ-5D-5L patient utility: carer-reported

Health state	Obs (n=5)	Mean	SD.	Min	Max

Health state	Obs (n=5)	Mean	SD.	Min	Max
WU	2	0.906	0.00	0.906	0.906
WWA	N/A	0.345†	N/A	N/A	N/A
WC	1	0.100	N/A	0.100	0.100
SI	2	-0.011	0.053	-0.048	0.027

Abbreviations: N/A, not applicable; Max, maximum; Min, minimum; Obs, observations; SI, severe immobility; SD, standard deviation; WC, wheelchair dependent; WU, walking unassisted; WWA, walking with assistance
†Value = reported WU utility (0.906) multiplied by ratio of WU utility to WWA utility (ratio = 0.380) from unpublished UK KOL audit data (49) as reported in the original company submission, descriptive statistics unavailable.

[redacted]

B48. Please clarify whether any resource use data was recorded in rhLAMAN-05 or rhLAMAN-10. If yes, clarify why this was not considered within the modelling.

No resource data were not collected.

Section C: Textual clarifications and additional points

C1. Has any follow-up been undertaken on the patient who suspended VA treatment in September 2016 (p38)?

The patient who suspended velmanase alfa treatment in September 2016 was lost to follow-up.

C2. Please clarify the source of the quotation, "It is the simple things ...” and provide a reference to support the statement: 'Mobility was identified as a key factor in the overall health and QoL of patients with AM' (section 7.1.3.1 p.52).

The quotation "It is the simple things ...” was taken from page 146 of the UK KOL interviews (reference 17 in the UK MPS Society Survey Report, **Appendix A**) which is referenced in the paragraph preceding the quotation. The conclusion that "Mobility was identified as a key factor in the overall health and QoL of patients with AM” was based on answers to question 12 (a) from the third round of KOL interviews.

C3. Please clarify if the total patient population is 33 (as stated on p23) or 34 (as stated on p72)?

The total patient population is 34 (rhLAMAN-05, n=25; phase I/II, n=9). The reference to a patient population of 33 in rhLAMAN-10, as stated on p23 in CS, is not the total patient population as it excludes one patient who was not included in the integrated analysis as they did not enrol from the compassionate use programme.

C4. Please confirm that patients in rhLAMAN-10 came from other locations than just Denmark (Table 13 p. 100).

The CEV for patients enrolled in the compassionate use programme was conducted in Denmark. However, patients travelled from other locations to undergo the CEV.

C5. There appears to be a typo in Table 26 p137: the last banded row states “serum IgG” but the data underneath states 12 month CHAQ disability index score. Please clarify which is the correct data, and provide any missing data.

Yes, this is a typo. The data are 12 month CHAQ disability index scores and no data are missing.

C6. There appears to be a lack of consistency between the statements “This limitation is known as a ‘ceiling effect’ and suggests that improvement is more difficult to observe in patients who have baseline values approaching the normal range.” and “The results for the 3-MSCT and 6-MWT may have also been confounded by the lack of patient selection at baseline according to mobility and motor performance. This led to a potential unbalance in the severity of patients in favour of placebo, with a higher proportion of more compromised patients randomised to the velmanase alfa group; however, as previously mentioned, all patients were reasonably mobile and recorded as being able to walk (with or without aids/assistance) at baseline. Ultimately, the treatment

effect may have been eroded by a combination of the ceiling effect, limiting the ability to observe improvement in the velmanase alfa group, and higher-functioning patients in the placebo group who may have possessed a greater ability to perform well in these tests." If the first statement is true, the velmanase alfa group should have the potential to show more effect compared to the placebo group, not less, and this would appear to suggest that the velmanase alfa group has an advantageous bias in comparative analyses between treatment and placebo. Please clarify your interpretation of the evidence.

Our interpretation of the evidence is that several confounding factors may have affected the ability of a 12-month randomised controlled period to detect significant differences between the velmanase alfa and placebo arms in relation to the endurance endpoints (3-MSCT and 6-MWT). Such confounding factors include:

- Presence of a 'ceiling effect'
- Lack of patient selection at baseline according to mobility and endurance
- Lack of patient selection at baseline according to other markers of AM disease severity
- Potential weaknesses of the individual tests in an AM patient population (e.g. the tests require a certain level of cognition and motivation, which can be lacking in a cognitively impaired population)

Due to the small patient numbers in rhLAMAN-05, and the heterogeneous nature of AM, there is a paucity of information to confirm if these confounding factors impact both the velmanase alfa arm and placebo arms of rhLAMAN-05 equally.

C7. Please clarify why the text in section 12.5.3 (p250) states "at 10 years (aged 16), 19.53% of patients under BSC alone have died, in contrast to 12.08% of the cohort treated with velmanase alfa" whereas the results for VA in Table 79 gives this as 11.67%.

The value reported in Table 79 (11.67%) is the correct result. The text has been corrected in **Appendix B**.

References

1. Malm D, Nilssen O. Alpha-mannosidosis. Orphanet J Rare Dis. 2008 Jul 23;3:21.
2. Malm D, Riise Stensland HM, Edvardsen O, Nilssen O. The natural course and complications of alpha-mannosidosis--a retrospective and descriptive study. J Inherit Metab Dis. 2014 Jan;37(1):79-82.
3. University of Tromsø and the University Hospital of North Norway. Alpha-mannosidosis Mutation Database. Available at: https://apex.jupiter.no/apex/f?p=101:1:::::: Accessed: March 2017. 2016.
4. Malm D, Halvorsen DS, Tranebjaerg L, Sjursen H. Immunodeficiency in alpha-mannosidosis: a matched case-control study on immunoglobulins, complement factors, receptor density, phagocytosis and intracellular killing in leucocytes. Eur J Pediatr. 2000 Sep;159(9):699-703.
5. Govender R, Mubaiwa L. Alpha-mannosidosis: a report of 2 siblings and review of the literature. J Child Neurol. 2014 Jan;29(1):131-4.
6. Michelakakis H, Dimitriou E, Mylona-Karayanni C, Bartsocas CS. Phenotypic variability of mannosidosis type II: report of two Greek siblings. Genet Couns. 1992;3(4):195-9.
7. Riise Stensland HM, Klenow HB, Van Nguyen L, Hansen GM, Malm D, Nilssen O. Identification of 83 novel alpha-mannosidosis-associated sequence variants: functional analysis of MAN2B1 missense mutations. Hum Mutat. 2012 Mar;33(3):511-20.
8. Berg T, Riise HM, Hansen GM, Malm D, Tranebjaerg L, Tollersrud OK, et al. Spectrum of mutations in alpha-mannosidosis. Am J Hum Genet. 1999 Jan;64(1):77-88.
9. MPS society. Data on file: UK MPS Society Survey. 2018.
10. Broomfield AA, Chakrapani A, Wraith JE. The effects of early and late bone marrow transplantation in siblings with alpha-mannosidosis. Is early haematopoietic cell transplantation the preferred treatment option? J Inherit Metab Dis. 2010 Dec;33 Suppl 3:S123-7.
11. Avenarius DF, Svendsen JS, Malm D. Proton nuclear magnetic resonance spectroscopic detection of oligomannosidic n glycans in alpha-mannosidosis: a method of monitoring treatment. J Inherit Metab Dis. 2011 Oct;34(5):1023-7.
12. Grewal SS, Shapiro EG, Krivit W, Charnas L, Lockman LA, Delaney KA, et al. Effective treatment of alpha-mannosidosis by allogeneic hematopoietic stem cell transplantation. J Pediatr. 2004 May;144(5):569-73.
13. Mulrooney DA, Davies SM, Walk D, Charnas LR. Late occurrence of chronic immune-mediated axonal polyneuropathy following bone marrow transplant for juvenile-onset alpha-mannosidosis. Bone Marrow Transplant. 2003 Nov;32(9):953-5.
14. Mynarek M, Tolar J, Albert MH, Escolar ML, Boelens JJ, Cowan MJ, et al. Allogeneic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients. Bone Marrow Transplant. 2012 Mar;47(3):352-9.
15. Will A, Cooper A, Hatton C, Sardharwalla IB, Evans DI, Stevens RF. Bone marrow transplantation in the treatment of alpha-mannosidosis. Arch Dis Child. 1987 Oct;62(10):1044-9.
16. Yesilipek AM, Akcan M, Karasu G, Uygun V, Kupesiz A, Hazar V. Successful unrelated bone marrow transplantation in two siblings with alpha-mannosidosis. Pediatr Transplant. 2012 Nov;16(7):779-82.
17. Chiesi Farmaceutici S.p.A. Data on file: Response to Clinical Question 137D. 2017.
18. Mazzone E, Martinelli D, Berardinelli A, Messina S, D'Amico A, Vasco G, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2010 Nov;20(11):712-6.
19. Fox JE, Volpe L, Bullaro J, Kakkis ED, Sly WS. First human treatment with investigational rhGUS enzyme replacement therapy in an advanced stage MPS VII patient. Mol Genet Metab. 2015 Feb;114(2):203-8.

20. Chiesi Farmaceutici S.p.A. Data on fie: Response to Clinical Questions 137C. 2017.
21. 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 Jun 20;8:88.
22. Chiesi Farmaceutici S.p.A. Data on file: Responses to Clinical Question 149. 2017.
23. European Medicines Agency. Vimizim® (elosulfase alfa) European Public Assessment Report. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002779/WC500169242.pdf. Accessed: December 2017.
24. Enright PL. The six-minute walk test. Respir Care. 2003 Aug;48(8):783-5.
25. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD. 2005 Mar;2(1):125-9.
26. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012 Sep 01;186(5):428-33.
27. Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. Cardiopulm Phys Ther J. 2013 Sep;24(3):21-9.
28. McDonald CM, Henricson EK, Abresch RT, Florence J, Eagle M, Gappmaier E, et al. The 6-minute walk test and other clinical endpoints in duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. Muscle Nerve. 2013 Sep;48(3):357-68.
29. Lachmann R, Schoser B. The clinical relevance of outcomes used in late-onset Pompe disease: can we do better? Orphanet J Rare Dis. 2013 Oct 12;8:160.
30. Wells AU, Behr J, Silver R. Outcome measures in the lung. Rheumatology (Oxford). 2008 Oct;47 Suppl 5:v48-50.
31. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011 Dec 15;184(12):1382-9.
32. Dempster H, Porepa M, Young N, Feldman BM. The clinical meaning of functional outcome scores in children with juvenile arthritis. Arthritis Rheum. 2001 Aug;44(8):1768-74.
33. 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 Oct 15;47(5):501-5.
34. Harmatz P, Ketteridge D, Giugliani R, Guffon N, Teles EL, Miranda MC, et al. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. Pediatrics. 2005 Jun;115(6):e681-9.
35. Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, et al. The 6-Minute Walk Test and Person-Reported Outcomes in Boys with Duchenne Muscular Dystrophy and Typically Developing Controls: Longitudinal Comparisons and Clinically-Meaningful Changes Over One Year. PLoS Curr. 2013 Jul 08;5.
36. Nightingale EJ, Pourkazemi F, Hiller CE. Systematic review of timed stair tests. J Rehabil Res Dev. 2014;51(3):335-50.
37. Roig M, Eng JJ, MacIntyre DL, Road JD, Reid WD. Associations of the Stair Climb Power Test with muscle strength and functional performance in people with chronic obstructive pulmonary disease: a cross-sectional study. Phys Ther. 2010 Dec;90(12):1774-82.
38. Bolton JW, Weiman DS, Haynes JL, Hornung CA, Olsen GN, Almond CH. Stair climbing as an indicator of pulmonary function. Chest. 1987 Nov;92(5):783-8.

39. Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest. 1992 Dec;102(6):1774-9.
40. Chiesi Farmaceutici S.p.A. Data on file: PAREXEL International. Research report Europe. Part A – Patient Concerns. 2016.
41. Lam C, Young N, Marwaha J, McLimont M, Feldman BM. Revised versions of the Childhood Health Assessment Questionnaire (CHAQ) are more sensitive and suffer less from a ceiling effect. Arthritis Rheum. 2004 Dec 15;51(6):881-9.
42. Brunner HI, Klein-Gitelman MS, Miller MJ, Trombley M, Baldwin N, Kress A, et al. Health of children with chronic arthritis: relationship of different measures and the quality of parent proxy reporting. Arthritis Rheum. 2004 Oct 15;51(5):763-73.
43. Kolko DJ, Kazdin AE. Emotional/behavioral problems in clinic and nonclinic children: correspondence among child, parent and teacher reports. J Child Psychol Psychiatry. 1993 Sep;34(6):991-1006.
44. Klepper SE. Measures of pediatric function: Child Health Assessment Questionnaire (C-HAQ), Juvenile Arthritis Functional Assessment Scale (JAFAS), Pediatric Outcomes Data Collection Instrument (PODCI), and Activities Scale for Kids (ASK). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S371-82.
45. Ding T, Hall A, Jacobs K, David J. Psychological functioning of children and adolescents with juvenile idiopathic arthritis is related to physical disability but not to disease status. Rheumatology (Oxford). 2008 May;47(5):660-4.
46. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. Eur Respir Rev. 2013 Dec;22(130):487-94.
47. Burton BK, Berger KI, Lewis GD, Tarnopolsky M, Treadwell M, Mitchell JJ, et al. Safety and physiological effects of two different doses of elosulfase alfa in patients with morquio a syndrome: A randomized, double-blind, pilot study. Am J Med Genet A. 2015 Oct;167A(10):2272-81.
48. Hendriksz CJ, Burton B, Fleming TR, Harmatz P, Hughes D, Jones SA, et al. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. J Inherit Metab Dis. 2014 Nov;37(6):979-90.
49. Chiesi Farmaceutici S.p.A. Data on file: UK key opinion leader interviews. 2017.
50. Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. Orphanet J Rare Dis. 2014 Mar 07;9:32.
51. Kanters TA, Redekop WK, Kruijshaar ME, van der Ploeg AT, Rutten-van Molken MP, Hakkaart L. Comparison of EQ-5D and SF-6D utilities in Pompe disease. Qual Life Res. 2015 Apr;24(4):837-44.
52. MPS society. Data on file: MPS Society Registry – registered patients in England. 2017.
53. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007 Jun 15;175(12):1304-45.
54. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008 Feb 01;177(3):253-60.
55. Deitz JC, Kartin D, Kopp K. Review of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2). Phys Occup Ther Pediatr. 2007;27(4):87-102.
56. Brahler CD-F, B., Mrowzinski, S., Aebker, S., Kreill, M. . Numerous Test Items in the Complete and Short Forms of the BOT-2 Do Not Contribute Substantially to Motor Performance Assessments in Typically Developing Children Six to Ten Years Old. Journal Of Occupational Therapy, Schools & Early Intervention. 2012;5(1):73-84.

57. Pakhale S, Bshouty Z, Marras TK. Comparison of per cent predicted and percentile values for pulmonary function test interpretation. Can Respir J. 2009 Nov-Dec;16(6):189-93.
58. Cassidy JT, Nordby GL, Dodge HJ. Biologic variation of human serum immunoglobulin concentrations: sex-age specific effects. J Chronic Dis. 1974 Dec;27(11-12):507-16.
59. Borgwardt L, Lund AM, Dali CI. Alpha-mannosidosis - a review of genetic, clinical findings and options of treatment. Pediatr Endocrinol Rev. 2014 Sep;12 Suppl 1:185-91.
60. Chiesi Farmaceutici S.p.A. Data on file: Response to ERG clarification question A39. 2018.
61. Chiesi Farmaceutici S.p.A. Data on file: UK Expert Elicitation Panel. 2017.
62. Chiesi Farmaceutici S.p.A. Data on file: Velmanase alfa: clinical trial KOL interviews. 2017.
63. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. Health Soc Care Community. 2006 Nov;14(6):508-22.
64. BioMarin Europe Ltd. Highly Specialised Technologies Evaluation Programme. Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA [ID744]. Submission of evidence by BioMarin Europe Limited. Available at: https://www.nice.org.uk/guidance/hst2 (Accessed: November 2017). 2014.
65. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis. 2012 Dec;12(12):919-24.
66. Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. Pediatrics. 2012 Aug;130(2):e273-80.
67. National institute for Health and Care Excellence. Final evaluation determination. Elosulfase alfa for treating mucopolysaccharidosis type IVa. Available at: https://www.nice.org.uk/guidance/hst2/documents/final-evaluation-determination-document (Accessed: February 2018).

Appendices

The appendices are provided as separate files which are enclosed within the response to NICE/ERG.

Appendix A: UK MPS Society Survey Report

Appendix B: Updated base case and sensitivity analyses

Appendix C: Updated cost utility analysis

Appendix D [redacted]

Appendix E [redacted]

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Highly Specialised Technology Evaluation

Velmanase alfa for treating alpha-mannosidosis [ID800]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: The MPS Society

Brief de*scrip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

The Society for Mucopolysaccharide Diseases (known as the MPS Society) is the only organization in the UK providing vital practical support and advocacy to the families and carers of over 1,300 children and young adults affected by mucopolysaccharide and lysosomal storage diseases - a group of 25 rare, incurable genetic conditions. The MPS Society was established in 1982, with the aims of providing support, information and advice to affected families, advocating for their rights in areas of health, social care and special educational needs, and enabling them to cope practically and emotionally with these devastating degenerative diseases. The MPS Society also promotes awareness of MPS and related lysosomal storage diseases (LSD), especially among health and social care professionals. The MPS Society supports over 95% of all diagnosed MPS patients living in England, Scotland, Wales and Northern Ireland.

The MPS Society does not receive any statutory funding in England, therefore the MPS Society relies upon a rolling programme of grant applications to Trusts and Foundations, together with monies raised by members and the public through fundraising activities.

The MPS Society receives unrestricted educational grants from approximately six pharmaceutical companies not exceeding 18% of total income.

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Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- ✓an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) **Head of Advocacy and Patient Services**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: ***None***

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Alpha mannosidosis has a wide spectrum of severity and its effects are extremely varied in patients. Individuals will suffer from progressive physiological effects and for some progressive neurological deterioration is also present. Some of the more prevalent symptoms experienced by patients include; sleeplessness, behavioural difficulties, significant problems with bone growth and formation often resulting in Osteoarthritis, severe joint stiffness and swelling that restricts movement and causes acute pain. Spinal difficulties such as Scoliosis and Kyphosis can also be present.

For many patients with mild symptoms there was a delay in their diagnosis, with many only receiving a confirmed diagnosis in their teens. However, many have received interventions for individual symptoms such as hearing, bone growth issues and respiratory (ENT problems).

HSCT is available and widely used in children to prevent disease progression and possible future neurological deterioration. However, for those individuals who are diagnosed later in life the risks of HSCT may be too high and mildly affected patients may not require HSCT as neurological issues are not prevalent

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Individuals can need a high level of care and the burden for carers can be significant.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

Alpha mannosidosis is a progressive disease which varies in severity and how it affects individuals.

Nearly all patients have some level of progressive physical issues which affects their mobility, hands and spine.

Repeated hospital appointments, surgeries and medical interventions are burdensome for both patients, carers and the wider family.

Most have some level of hearing loss requiring hearing aids and use of BSL

Most needs some level of 1:1 support at school and require an Education Healthcare Plan

Not many adults are able to undertake either full time or part time work due to stamina, mobility issues and learning difficulties. However, some have undertaken voluntary work.

Many carers have had to give up work to undertake their caring roles, either to accommodate frequent hospital trips or to become their fulltime carer.

<u>What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?</u>

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Improved respiratory function and energy – patient has reported that they have more energy and do not have as many chest infections and their respiratory function has improved.

Improved self-esteem and confidence- Improved mobility and respiratory function has had a positive effect on self-esteem and confidence and has aided independence and communications.

Improved mobility and effects on bones and joints – The treatment has improved mobility for patients with positive effects reported on reducing swelling around joints. For some they no longer requiring the use of aids and equipment for daily activities. Improved respiratory function has enhanced mobility and stamina.

Hearing and infections – Patient has reported no longer experiencing repeated ear infections (used to have one every 2-3 months) and an improvement in her hearing with a positive impact on her communication.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

T**he course and outcome of the condition- Alpha Mannosidosis is a progressive disease. Velmanase alfa has shown stabilisation of disease progression and in some area clinical improvement.**

Physical symptoms – Improved lung / respiratory function and increased energy. Reduced joint swelling and improved physical ability *"I no longer use calipers, nor sticks nor (at one point) a wheelchair, nor do I qualify for a blue parking badge now. I am now more independent and able to walk further" "Since being on the trial I can now do more, I have more energy and don't get as breathless"*

Mental health & Quality of life– stabilisation of the disease improves patient outcomes and their quality of life. Patient reported outcomes have shown that since being on treatment they have become more social and have in fact increased their working capacity and their communication has also improved. Increased mobility, reduced reliability on aids for mobilising aids individuals quality of life and has led to greater independence and improves their self-esteem and wellbeing.

Impact of carers – Prior to enrolment on the clinical trial a patients parents were told at diagnosis that their child's prognosis was poor, their intellect was set and that they would by this stage be in decline (without treatment). None of this has been the case.

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

Difficulties in taking or using the technology – Patients may need a portacath to avoid weekly cannulation for difficult veins or needle phobia.

Side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate) -
There is a small possibility of an allergic reaction and SAEs. These have shown to be managed by slowing the infusion rate and using prophylactic antihistamine. Most members have indicated that benefits of treatment far outweigh the potential risk of a severe adverse event.

Impact on others (for example family, friends, employers)
As the disease stabilised and improvements were shown in individual cases, the caring role was reduced as individuals developed more independence. The mental stress, worry and unknown future without treatment is burdensome for carers. Improvement on ERT takes away the constant fear of the child / adult deteriorating and dying.

F**inancial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)**
It is anticipated that once a patient is stable on treatment homecare can be started. This will lessen the impact on personal and family life and for those in employment should offer some flexibility in fitting treatment around work and home life.

If home treatment or treatment nearer to home is available the financial impact will hopefully be reduced.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Velmanase alfa is available for those aged 6 years and over.

Treatment with Velmanase alfa is not beneficial for those patients who have received a transplant (HSCT)

In our opinion Velmanase alfa would not be appropriate for patients who have severe or rapidly progressive neurological manifestations of the disease.

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6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

For patients diagnosed in early childhood, HSCT is offered as a treatment option. The MPS Society is aware of 3 of 5 children under 16 years in England who have received HSCT.

Of the 20 adult patients in England 3 had received HSCT in childhood. For those diagnosed in adulthood there is no alternative treatment option to ERT available.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

HSCT is a risky procedure and for patients with alpha mannosidosis is usually only offered to children. Velmanase alfa offers an alternative treatment and is the only available treatment for adults with this condition.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We do not see any disadvantages to the treatment compared with disease progression and early death.

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7. Research evidence on patient, family or carer views of the technology
(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

I am aware of the Natural History Study that was undertaken by MPS Commercial on behalf of the company. I believe this is being submitted by the company.

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

The key difference is stabilisation, improvement of symptoms and enhanced quality of life. This is reported as being due to improved respiratory function, increased energy and stamina. Improved mobility, joint movements and reduced pain has improved general mobility and reduced the reliance on aids.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

If the technology was not made available the disease would continue to progress and disease burden would continue for both the patient and carers.

(iii) Are there groups of patients that have difficulties using the technology?

(iv) Are there any situations where patients may choose not to use this technology?

We believe that all patients who meet the criteria for access will want to have access to this treatment.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Total number of patients in UK = 26 (25 living in England, 1 living in Wales)

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Of the 25 patients in England ; 5 are under 15 years (We are aware of 3 patients who have been treated with HSCT); Of the remaining adult patients (16-56 years) we are aware of 3 who have been treated with HSCT.

1 patient in England was on the clinical trial but came off.

This leaves 17 patients who may want access to treatment if they meet the clinical criteria.

Equality
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 this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

The clinical evidence and recommendations given by the European Medical Agency should be considered within NICE's appraisal of Velmanase alfa.

Alpha mannosidosis is an ultra-orphan disease with only 25 patients in England of whom 17 may be eligible for reimbursed ERT.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Our members look forward to NICE considering positively, reimbursement of Velmanase alfa and trust that the appraisal will give appropriate attention and be a fair process for a disease where patient numbers are considerably low.

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Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

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To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: NA

Brief de*scrip*tion of the organisation:

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- ✓a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: **None**

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis **No diagnosis until age 15**
- appropriate treatment **No specific treatment until ERT. Prior to that: supportive care and treatment was provided for individual symptoms rather than being looked at collectively.**
- helpful information about the condition **Helpful information was gained from MPS Society after some years and a chain of consultant's referrals.**

and the impact these difficulties have on patients and their families or carers.

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The impact of this illness from a patient's view is social, physical and spiritual:
Social: **because the sufferer is isolated from their peers at school and therefore in later life.**
Physical: because the sufferer has to rely on others.
Spiritual: because of the demoralising nature of the illness.

The impact of this illness from a family's view is also social physical and spiritual:
Social: Families of the same age tend to socialise and their children will play and interact. But with this illness, the child's peer group interaction is not fully achieved and the families' socialisation becomes difficult. Holidays are also difficult as the growing teenager will not want to go on holiday with parents – nor can they be 'left' at home.

Physical: It's exhausting – but that's what parents do for their children.

Spiritual: sympathy, assistance, guidance and encouragement given constantly (and willingly) combined with what seems to be an inevitable decline has its toll on the parents.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health: **As above, It's exhausting – but that's what parents do for their children.**
- emotional wellbeing: As above **sympathy, assistance, guidance and encouragement given constantly (and willingly) combined with what seems to be an inevitable decline has it's toll on the parents: including depression.**

- everyday life **We were in the fortunate position of being flexible: as my wife had the higher income, I could work at home or take time out of the office to make hospital visits etc. Schooling was special needs and further special education to achieve a level of understanding of the world and greater socialisation.**
We have not yet needed to adapt our home.
We have suffered financially.

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages:
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition: -

physical symptoms: - **reduced pain, joint swelling, respiratory function which have all aided mobility**
- level of disability: **access to treatment has improved or stabilised many of her symptoms enabling her to be more independent.**
- mental health: **improved mental health for both our daughter and for us as parents as we now see a future.**
- quality of life (lifestyle, work, social functioning etc.): **improved quality of life for both. Our daughter is more independent and able to socialise more which has lessened the burden on us to provide that support and to deal with the pain of watching her deteriorate.**
- other people (for example friends and employers): **Many people who know our daughter have commented on how well she looks, how her mobility has improved and her confidence with communicating with the wider community.**
- other issues not listed above

3. Disadvantages
Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse. **We are aware of the limitations in ERT crossing the blood brain barrier and implications that this may have on any future neurological deterioration**
- difficulties in taking or using the technology – **We are aware of some difficulties if people are needle phobic**
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate) **Not aware**
- impact on others (for example family, friends, employers) **Home treatment should alleviate any burden on families to take child / young adult to hospital on a weekly basis.**
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

Home treatment should lessen the financial burden associated with accessing weekly treatment in a hospital setting.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.
Not known, its has been positive for us.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?
We are aware that the technology does not help those with severe neurological involvement.

6. Comparing the technology with alternative available treatments or technologies NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.
There is no comparable

(i) Please list current standard practice (alternatives if any) used in the UK.

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I have little knowledge of 'standard practice'. Our daughter has an infusion into a porto-cath once each week.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall **As listed above, our daughter has shown a number of improvements in multiple areas.**
- improvement in certain aspects of the condition **Her mobility, stamina, confidence and respiratory function have all improved.**
- ease of use (for example tablets rather than injection) **As our daughter has a porto-cath we experience no issues with vein access.**
- where the technology has to be used (for example at home rather than in hospital) **home infusion would be better than attending hospital**
- side effects (please describe nature and number of problems, frequency, duration, severity etc) **None**

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall **None**
- worsening of specific aspects of the condition **None**
- difficulty in use (for example injection rather than tablets) **None**
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe). **None**

7. Research evidence on patient, family or carer views of the technology
(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available? **The technology described above would improve all aspects of suffering, caring and treatment if implemented correctly.**

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available? **Patients would continue to deteriorate unnecessarily and their carers and families would have to continue to struggle to meet needs and watch as their child deteriorates, taking on more caring responsibilities and the burden this may cause.**

(iii) Are there groups of patients that have difficulties using the technology? **Yes! Those who cannot understand how to use the technology and those who physically cannot.**

(iv) Are there any situations where patients may choose not to use this technology? **Possibly for those whose symptoms the treatment may not improve.**

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?
I have no information about this question

Equality
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 this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed; **Those who live on the border of one country (England) but who's facilities (by proximity) are accessed in another country (Wales).**
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; **Those who's postcode dictates greater distances travelled to access the treatment**
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities. **The greater the disability, the more difficult to access.**

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.
I cannot stress more strongly that early intervention in the form of preventative medical technology is socially, morally and (in the long term, financially) beneficial for sufferers, their carers and for the health service.

Appendix D – NHS organisation statement template

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Velmanase alfa for treating alpha-mannosidosis [ID800]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a commissioners perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation NHS England

Please indicate your position in the organisation:

- commissioning services in general?
- commissioning services specific to the condition for which NICE is considering this technology?

Links with, or funding from the tobacco industry - please declare any direct or indirec links to, and receipt of funding from the tobacco industry:

none

Potential impact on the NHS if NICE recommends the technology

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

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The main cost will the cost of the drug but there are costs of monitoring treatment especially if a managed access scheme is required.

Would there be any need for education and training of NHS staff?

Some training of staff on this specific drug

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this highly specialised technology?

We would expect velmanase to be used (i.e. prescribing initiated and monitored) within the existing expert centres for lysosomal storage disorders. It is likely that there are a small number of adult patients currently, in the absence of disease modifying therapy, being cared for in local or regional hospitals.

Appendix D - professional organisation statement template

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Velmanase alfa for treating alpha-mannosidosis [ID800]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation:
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No links with the tabacco industry.

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What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Velmanase alfa is a rare inherited metabolic condition. It is a lysosomal storage disorder and patients are managed within the NHS England designated lysosomal storage disorders unit. There are around 20 patients in the UK and those within the ages studied in the clinical trial ie approximately 5 and above and not having received a bone marrow transplant would be assumed to be eligible for treatment. The condition is currently treated in the NHS by allogeneic stem cell transplant for those patients presented with severe manifestations in infancy. There is a spectrum of severity reflected in the age of presentation for those presenting at later ages with phenotypically milder disease. Management would essentially consist of supportive care including management of infections, surgery such as spinal surgery (cervical spine decompression), ventricular peritoneal shunts, joint replacements, hernia repairs, carpal tunnel release, ENT procedures including tonsillectomy and grommet, rehabilitation, respiratory support including ventilation, psychology mental health support and educational provision. Individuals would be managed through the specialist paediatric lysosomal storage disorders unit with some patients now in the adult age group transitioning to the adult units. This is a very rare condition with no existing standard treatment other than bone marrow transplant and therefore there may be geographical differences in the

nature of best supportive care. However, these would reflect local practice and not necessarily specific differences in opinion.
Bone marrow transplantation does offer a treatment for appropriate patients and is effectively a way of replacing enzyme from normal transplanted cells. It is not available to everyone, not everyone has a donor and is not without complications. The disease is progressive, requiring interventions for infections, joint problems reduced mobility and respiratory problems. The standard management addresses the complications of the enzyme deficiency but does not alter the nature history of the disease. Since there is understood to be a phenotypic spectrum it may be that patients presenting later in adulthood are milder in expression of the disease and may not benefit from intervention equally, however, this population is not well defined.

The product is enzyme replacement therapy and would therefore be delivered through the existing infrastructure of the specialist lysosomal storage disorder units with the nurses there who were changed in enzyme delivery including management of infusion reactions. Patients would subsequently transition to homecare through the existing homecare provision. This would not necessitate any changes to the organisation of the storage disorders unit or homecare and since there are relatively small number of patients spread throughout the UK they are unlikely to require significant expansion of services. The technology is not currently available in the NHS and is used under clinical trial protocols. Use of commercial product would require clinical guidelines for initiating, monitoring, measuring the effectiveness of and stopping treatment.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Enzyme replacement therapy has the advantage of providing missing enzyme to reduce substrate and therefore alter the natural history of the condition. This is predicted to slow down the progression and maintain patients with ambulatory capacity for longer and potentially also reduce the frequency and impact of infections. Over time in patients treated from a young age it would be expected to reduce comorbidities and therefore impact of managing complications of the natural history such as surgical interventions. Rules for starting and stopping the treatment would need to be agreed, however, there is precedent for appropriate design and use of rules in other lysosomal storage disorders through managed access programmes. The technology is not particularly difficult to use, I would expect patients to require a relatively small (perhaps one to three infusions) in the hospital before transitioning to home care. This would have the advantage of facilitating patient education and acclimatising them to regular intravenous infusions. Patients are likely to go on requiring some elements of supportive care and will require regular follow up and monitoring the specialist centres. Evidence from clinical trials shows that long term enzyme replacement therapy slows the progression in adults. The clinical trial recruited patients who were not dissimilar to those encountered in clinical practice. Individuals were followed for improvement in her immune function including correction of hypergammaglobulinaemia, reduction in relevant polysaccharide substrates, improvements in three minute stair climb and improvement in mobility through reduction in need of walking aids. The study also examined pain and respiratory function. This is a combination of surrogates which may predict long term outcome by overall life expectancy but importantly risk of progression of requiring a wheelchair or ventilation but also real end points such as pain for patients. The study showed greater trend for improvement in paediatric and adult patients. Patients receiving enzyme replacement therapy can expect infusion reactions which require management usually using a combination of steroids and anti-histamines. This tertiary centres are experienced in the management of such reactions and do not usually hinder the use of enzyme replacement in the home setting.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Centres not experienced with the infusion of this enzyme would require some familiarisation with reconstitution and delivery of the drug. However, this is sufficiently similar to other drugs given within the storage disorders unit for this not to be excessive. Patients would then be given initial infusions in hospital subsequent to transfer to home care. Given the relatively small number of patients this would probably be reasonably absorbed within the current infrastructure.

Equality

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 this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Appendix D - professional organisation statement template

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Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a commissioners perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation Central Manchester foundation trust

Please indicate your position in the organisation:

- commissioning services in general?
- commissioning services specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery (e.g. medical director, public health director, director of nursing)?
- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirec links to, and receipt of funding from the tobacco industry:

No but I have been a member of a Chiesi advisory board.

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

It is part of highly specialized provision more specifically part of the LSD services. There are no current alternatives beyond symptomatic care and no other disease modifying therapies. There is no geographical variation in practice with respiratory, immune, musculoskeletal aspects of this disease being managed. This is new technology with the only patients currently treated being on a compassionate use basis. Bone marrow transplantation is a potential alternative in those patients in early childhood where there is a suitable donor, though the long term effects of this therapy are unknown.

Appendix D – NHS organisation statement template

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To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

The only patients with access to this technology are patients on compassionate use at this moment in time. It has only been used with the indications of the clinical trial. Delivery is via home infusion using the pre-established lysosomal ERT providers. The data available on its use has so far been limited to presentations both oral and posters at international conferences this would indicate an improvement in respiratory, infective and musculoskeletal outcomes. This ERT would seem as far as the data available is able to describe to be modify and improve the visceral symptoms associated with this disease.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

For the patients not on therapy already there would be minimal impact, For untreated patients who were felt to potentially benefit from therapy it would mean regular (weekly) IV infusions at home and increased monitoring in terms of blood tests.

Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment) to enable this technology to be used?

In terms of administration the impact of Velmanase alfa will be minimal, given that it is both envisaged to be delivered at home i.e. conforming to the pre established template of other lysosomal disease ERTs and that the number of patients with this extremely rare disease (incidence estimated as between 1 in 300 to 1 in 500,000) is low.

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Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

This ERT would potentially impact on the visceral complications of all known patients. There 3 known paediatric patients under treatment in Royal Manchester Children's though 5 patients have transitioned to the regional adult services one of whom is on compassionate use.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

There is potential impact, given the finite limits in the drug budget for specialized commissioning, outside this given the extremely limited number of patients the impact on service provision is likely to be minimal.

Would there be any need for education and training of NHS staff?

There would be no need for additional training for NHS staff, as these patients are already being looked after and the technology is well established in other lysosomal disease.

Equality

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 this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this highly specialised technology?

NICE National Institute for Health and Care Excellence

Clinical expert statement

Velmanase alfa for treating alpha-mannosidosis [ID800]

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

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

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

Information on completing this expert statement

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

About you	
1. Your name	[redacted]
2. Name of organisation	**Willink Biochemical and genetics unit St Mary's Hospital**

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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop progression and development of the visceral complication of mannosidosis
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The improvement of respiratory function, resolution of underlying immunological abnormalities and prevention of the destructive polyarthropathy and some amelioration of reduction in overall storage
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Supportive care
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway is well defined within specialist centres
• What impact would the technology have on the current pathway of care?	Would
11. Will the technology be used (or is it already used) in the same way as current care	As with previous enzyme replacement therapies under the auspices of metabolic consultants

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There is no therapy aiming at preventing/ ameliorating the progression of the disease, purely reactive symptomatic therapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Would be used through the national commissioned services for lysosomal disease
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal investment for introduction, given there is a well prescribed pathway via the recognised national commissioned service
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than	Currently this is uncertain but this would be in keeping with other similar therapies in the past

current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with aggressive, progressive central neurological involvement should be excluded
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	There is no therapy currently that this can be compared to outside the Bone marrow transplant. This later option appears to be most efficacious when done early though there is little data available about the long term outcome of BMT. The delivery of this therapy will on occasion necessitate the use of antihistamines and other agents to mitigate infusion related reactions. Velmanase is delivered as an intravenous infusion and in some patients this may necessitate the insertion of a central line especially in the paediatric population. Monitoring is by clinical outcomes which are already assessed during routine evaluation though the establishment of a readily available biochemical marker outside the auspices of the company is yet to be established.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	National guidance is to be developed, especially in light of wider spread use that commissioning would entail.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Potential removal of storage tissue from cardiac and renal tissues may not be apparent to patients, though there is little apparent clinical consequence of cardiac tissue storage thus far known in the patient population.
17. Do you consider the technology to be innovative in its potential to make a	Yes as it provides the first therapy that looks to potential reverse somatic storage in alpha mannosidosis.

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	The progression visceral manifestations of the disease
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The major side effects are related to the infusion of Velmanase with the need for intravenous access, the potential infusion related reactions and the alteration in patient activity that often accompanies intravenous infusions.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	In terms of monitoring those on clinical trial shave as a rule been more extensively monitored than is current clinical practice.
• If not, how could the results be extrapolated to the UK setting?	If Velmanase is introduced the degree of monitoring would increase to ensure the utility of the treatment, as well as monitoring for potential complications would increase.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The outcomes that could be expected to be improved by ERT were musculoskeletal, respiratory and immunological. These were investigated
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The use of oligosaccharides as a marker disease/ response is in keeping with previous similar disease groups where measurement of primary storage compounds has been considered to reflect tissue burden.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known to me.
20. Are you aware of any relevant evidence that might not be found by a systematic	No

review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	They are comparable
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Alpha mannosidosis is a panethnic disease but like many rare autosomal diseases there is a concentration in ethnic groups where consanguineous marriage is a cultural norm
23b. Consider whether these issues are different from issues with current care and why.	No
Topic-specific questions	
24. Is allogeneic HSCT usually	No, it is not normally performed in those over 5 years of age, therefore I agree that this is this age group the

performed in patients with apha-mannosidosis aged >5 years? If no, do you agree that allogeneic HSCT is not be a suitable comparator for velmanase alpha?	risk benefit ratio would mean that HSCT is not a suitable comparator.

Key messages

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

- Alpha mannosidosis is a generally a slowly progressive lysosomal storage disorder outside the aggressive severe neurological childhood variant.
- Quality of life has been impaired by the somatic manifestations especially the polyarthropathy and respiratory disease
- It' is a true rare disease with a prevalence of 1 in 500,000 and thus data either from natural history or trials is extremely limited.
- The slow progressive nature of the visceral disease makes it extremely hard for clinically meaningful endpoints to be demonstrated in the limited time that clinical trials are run over. Though trial data does demonstrate reversal of a number of disease manifestations.
- If approved there is already a recognised national service that could deliver the therapy.

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

Clinical expert statement

Velmanase alfa for treating alpha-mannosidosis [ID800]

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

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

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

Information on completing this expert statement

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

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal Free London NHS Foundation Trust/ University College London**

3. Job title or position	**Consultant/Senior Lecturer**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
The aim of treatment for this condition	
5. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim is to halt the accumulation of storage material and therefore reduce the rate of progression of the patient from mobile and ambulant through walking with aids, requiring a chair to becoming non ambulant. Similarly, there would be an aim to reduce the rate of respiratory deterioration and dependence on ventilatory assistance. This condition is also associated with a degree of immune dysfunction and improvement would be anticipated to reduce the risk of infection synergising with positive effects on ambulation and ventilation to improve life expectancy
6. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Improvement in 6 minute walk test> 25 m Improvement in length of time in ambulant phase without walking aids Reduction in the use of walking aids Improvement in FVC >5% Reduction in number of infections

x cm, or a reduction in disease activity by a certain amount.)	
7. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The unmet need is to reduce the rate of progression of deterioration in physical status in the condition and need for interventions provided in best supportive care. Stem cell transplantation is not safe or available for all patients with the condition and is not curative.
What is the expected place of the technology in current practice?	
8. How is the condition currently treated in the NHS?	The condition is currently treated in the NHS by allogeneic stem cell transplant for those patients presented with severe manifestations in infancy. There is a spectrum of severity reflected in the age of presentation for those presenting at later ages with phenotypically milder disease. Management would essentially consist of supportive care including management of infections, surgery such as spinal surgery (cervical spine decompression), ventricular peritoneal shunts, joint replacements, hernia repairs, carpal tunnel release, ENT procedures including tonsillectomy and grommet, rehabilitation, respiratory support including ventilation, psychology mental health support and educational provision. Individuals would be managed through the specialist paediatric lysosomal storage disorders unit with some patients now in the adult age group transitioning to the adult units.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	I am not aware of formal recommendation in NHS for the management of this condition. Variour review articles are available including guidelines for appropriate anaesthetic support.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	This is a very rare condition with no existing standard treatment other than bone marrow transplant and therefore there may be geographical differences in the nature of best supportive care. However, these would reflect local practice and not necessarily specific differences in opinion
• What impact would the technology have on the current pathway of care?	After diagnosis patients would be assessed for initiation of therapy and for baseline parameters and within the specialist centre receive upto 3 infusions of enzyme replacement therapy with subsequent therapies being received at home. In the long term an effective therapy initiated early in the natural history of the condition would be expected to reduce the requirement for some elements of supportive acre including some surgical interventions
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is a new therapy which will be given in a different way to current practice: available even when no but donor, older and milder patients and as an ongoing modality Other supportive care and interventions will be delivered in the same way although predicted at a lower rate. The infrastructure for care delivery already exists through the delivery of care for other similar conditions

• How does healthcare resource use differ between the technology and current care?	The technology is not difficult to use, I would expect patients to require a relatively small (perhaps one to three infusions) in the hospital before transitioning to home care. This would have the advantage of facilitating patient education and acclimatising them to regular intravenous infusions. Patients are likely to go on requiring some elements of supportive care and will require regular follow up and monitoring the specialist centres The requirement for specialist bone marrow transplantation resource would not be required. Resource for other elements of supportive care might be reduced
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescribed and coordinated through a tertiary specialist centre with regular delivery of the enzyme in the home
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Centres not experienced with the infusion of this enzyme would require some familiarisation with reconstitution and delivery of the drug. However, this is sufficiently similar to other drugs given within the storage disorders unit for this not to be excessive. Patients would then be given initial infusions in hospital subsequent to transfer to home care. Given the relatively small number of patients this would probably be reasonably absorbed within the current infrastructure.

10. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The disease is progressive, requiring interventions for infections, joint problems reduced mobility and respiratory problems. The standard management addresses the complications of the enzyme deficiency but does not alter the nature history of the disease. The clinical trial recruited patients who were not dissimilar to those encountered in clinical practice. Individuals were followed for improvement in her immune function including correction of hypergammaglobulinaemia, reduction in relevant polysaccharide substrates, improvements in three minute stair climb and improvement in mobility through reduction in need of walking aids. The study also examined pain and respiratory function. This is a combination of surrogates which may predict long term outcome by overall life expectancy but importantly risk of progression of requiring a wheelchair or ventilation but also real end points such as pain for patients.
• Do you expect the technology to increase length of life more than current care?	Enzyme replacement therapy has the advantage of providing missing enzyme to reduce substrate and therefore alter the natural history of the condition. This is predicted to slow down the progression and maintain patients with ambulatory capacity for longer and potentially also reduce the frequency and impact of infections. Over time in patients treated from a young age it would be expected to reduce comorbidities and therefore impact of managing complications of the natural history such as surgical interventions Evidence from clinical trials shows that long term enzyme replacement therapy slows the progression in adults
• Do you expect the technology to increase health-related quality of	Improvement in ambulatory state , reduced dependence on walking aids and other support tove and improved infection rate would be expected to improve quality of life without the necessity of high risk BMT or sequalae of infection, graft versus hot disease

life more than current care?	
11. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Since there is understood to be a phenotypic spectrum it may be that patients presenting later in adulthood are milder in expression of the disease and may not benefit from intervention equally, however, this population is not well defined. The study showed greater trend for improvement in paediatric and adult patients.
The use of the technology	
12. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Bone marrow transplantation does offer a treatment for appropriate patients and is effectively a way of replacing enzyme from normal transplanted cells. It is not available to everyone, not everyone has a donor and is not without complications. The product is enzyme replacement therapy and would therefore be delivered through the existing infrastructure of the specialist lysosomal storage disorder units with the nurses there who were changed in enzyme delivery including management of infusion reactions. Patients would subsequently transition to homecare through the existing homecare provision. This would not necessitate any changes to the organisation of the storage disorders unit or homecare and since there are relatively small number of patients spread throughout the UK they are unlikely to require significant expansion of services. The technology is not currently available in the NHS and is used under clinical trial protocols. Use of

or ease of use or additional tests or monitoring needed.)	commercial product would require clinical guidelines for initiating, monitoring, measuring the effectiveness of and stopping treatment
13. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	. Rules for starting and stopping the treatment would need to be agreed, however, there is precedent for appropriate design and use of rules in other lysosomal storage disorders through managed access programmes.
14. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
15. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Current needs are met only in reactive and supportive way which is therapy after the vent to address complications. Enzyme replacement therapy would be predicted to reduce the rate of progression of the disease hence redicing the complication rate and requirement for supportive care interventions

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	This a step change in delivering a therapy with improved safety compared to BMT which will be easily delivered, interfere with the natural progression of the condition improving physical status and functioning
• Does the use of the technology address any particular unmet need of the patient population?	Treatment to address the natural history of the patients in the age/ physical status range who are unable to receive HSCT
16. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Patients receiving enzyme replacement therapy can expect infusion reactions which require management usually using a combination of steroids and anti-histamines. This tertiary centres are experienced in the management of such reactions and do not usually hinder the use of enzyme replacement in the home setting.
Sources of evidence	

17. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	nNA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improved 6 minute walk test Disability score Pain score
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	This is not known for alpha mannosidosis but would be predicted
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	

18. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
19. How do data on real-world experience compare with the trial data?	I am not aware of a body of real world data at this point
Equality	
20a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
20b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions	
21. Is allogeneic HSCT usually performed in patients with apha-mannosidosis aged >5 years? If no, do you agree that allogeneic HSCT is not be a suitable comparator for velmanase alpha?	HSCT is not usually performed in older patients and is therefore not a suitable comparator
Key messages	
22. In up to 5 bullet points, please summarise the key messages of your statement. • • • • •	

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Velmanase alfa for treating alpha-mannosidosis [ID800]

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☐ x a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Then MPS Society
4. Did your nominating organisation submit a submission?	☐ x yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ X yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **x** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	I was diagnosed approximately 3 years ago in August 2015. My younger sister was diagnosed also around this time. The diagnosis is still relatively new to us, after years of undiagnosed medical symptoms, going back to childhood where I had problems with balance and co-ordination, fine and gross motor skills. Once we saw a specialist who knew about alpha mannosidosis our diagnosis was quite quick although it to a long time to get to this conclusion. The diagnosis was a very big shock and has taken some time to actually digest. We are still processing the whole situation. Mentally, not knowing what will happen in the future gives added stress but we look on the positive side of life!

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	When we were young at primary school age we would be in the lowest school groups and my sister got a key worker (to help with classes) but this was in secondary school. In my college years I got some support. But because of my social skills of being shy and not able to make friends easily, I had a difficult time. There were groups of girls in my class who were very unkind to me. At University I received a lot of help. I had a note taker for classes. My tutors had more understanding of my needs. We don't have any external carers but we get a lot of support from our parents . My sister and I have had struggles through our education and life but we like to keep positive. Adaptions to individual and family life. -physical health – after the diagnosis, we have been advised to do exercises and eating healthily and look after our general health and well being. We were doing this anyway. -emotional wellbeing – it has been a struggle with making friends and getting them to understand what our needs have been. I have felt isolated at many times and this would feel sad. Over the years we have learned to research other groups of people who have similar needs. So we have contacted them and have now made some good friendships. -everyday life including -Through real hard work and effort from the Job Centre and an Organisation that helps young people with disability into work, I have managed to keep a part-time job for over a year. I am really proud and happy to have achieved this. As my degree has been in Textile Design, I have also started my own little business in Machine Knitting things such as cushions, hats and scarves. I am living with my parents. I would like to one day have my own place. At the moment we have had no adaptations to the home. If we need to in the future we will get advice about what to do. Financially, I have a part time job. My dealings with money and finance are always overseen by my parents. I try to keep myself aware of scams and not to be a victim of vulnerable financial situations such as cold calling.

	As I have said before, I did find it difficult to be part of friendship groups when I was younger. Now will lots of research, we are beginning to make good friends. I would also like to have a partner in life and have a family. Both my sister and I are affected in different ways.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	We have appointments every 6months for a check up in Manchester. We also have blood tests, scans and weight and blood pressure taken. As a child I suffered from Glue Ear and had grommets 4 times. I also had my tonsils out when I was 16. We have not been involved in any treatment as yet.
11. Is there an unmet need for patients with this condition?	I would like to know more about my condition
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and	There are many advantages of potential ERT treatment. At the moment we are living 'with a ticking time bomb'. Meaning we have no idea what is going to happen with us, as we get older. So at least with treatment we would have peace of mind. Emotionally we would be able to feel that we are part of the whole society and not just this very exclusive group of people with the condition.

emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	Not currently receiving treatment. We are aware of the treatment moving to home therapy which can be more accommodating for work etc
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology?	None at present

Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	I think that all patients who are eligible should be able to access this treatment

Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**none**
Other issues	
17. Are there any other issues that you would like the committee to consider?	no
Key messages	

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

- Patients without early symptoms can struggle to get diagnosed in childhood
- The disease may not always be visible physically but can cause psychological issues
- Patients are able to have a good quality of life if their disease is managed effectively
- Treatment can offer patients a future
- I hope that treatment will allow me to follow my dreams of remaining independent, physically well and hopes of a family.

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Velmanase alfa for treating alpha-mannosidosis [ID800]

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**
3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology?
Current treatment of the condition in the NHS	
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	Although most patients will be managed in metabolic centres, lack of disease modifying therapy likely means that some (an unknown number) medically stable patients are managed in regional or district hospitals.

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	Availability of a treatment is likely to concentrate management of patients into the centres where the treatment is available
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	Not in use.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technoloigy should only be used in lysosomal storage disorder centres familiar with the use of enzyme replacement therapies.

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

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	Date completed (26/03/2018)

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Declared competing interests of the authors

. No other author declares a conflict.

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Rider on responsibility for report

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

This report should be referenced as follows:

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Contributions of authors

Matt Stevenson and Rebekah Pennington critiqued the health economic analysis submitted by the company. Sue Harnan and Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens critiqued the statistical aspects including the elicitation of experts' beliefs. Mark Clowes critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

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Abbreviations

3-MSCT	3-minute stair climb test
6-MWT	6-minute walk test
ADA	Anti-drug antibody
AEs	Adverse events
AIC	Academic-in-confidence
AM	Alpha-Mannosidosis
ANCOVA	Analysis of Covariance
BMT	Bone marrow transplant
BOT-2	Bruininks-Oseretsky test of motor proficiency 2nd edition
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CEV	Comprehensive evaluation visit
CHAQ	Childhood Health Assessment Questionnaire
CI	Confidence interval
CIC	Commercial-in-confidence
CPQ	Cost per quality-adjusted life year gained
CrI	Credible interval
CSt	Cohort study
CS	Company's submission
CSF	Cerebrospinal fluid
CSR	Clinical study report
DB	Double-blind
DSA	Deterministic sensitivity analyses
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
EQ-5D-Y	EuroQol 5-Dimensions-Youth
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GFAp	Glial fibrillary acidic protein
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HST	Highly Specialised Technology
HTA	Health Technology Assessment

HUI3	Health Utility Index-3
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IgG	Immunoglobulin G
IRRs	Infusion-related reactions
ITT	Intention-to-treat
IV	Intravenous
KOLs	Key opinion leaders
LSD	Lysosomal storage disorder
MC	Multicentre
MCID	Minimal clinically important differences
MDT	Multidisciplinary team
MPS IH	Severe mucopolysaccharidosis I
MPS Society	Society for Mucopolysaccharide Diseases
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NICE	National Institute for Health and Care Excellence
NFLp	Neurofilament protein
NMA	Network meta-analysis
OGS	Oligosaccharides
OL	Open-label
PC	Placebo-controlled
PEF	Peak expiratory flow
PFT	Pulmonary function test
PK	Pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PTA	Pure tone audiometry
PTS	Patients
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SC	Single centre
SD	Standard deviation
SHELF	Sheffield Elicitation Framework
SI	Severe immobility

SRT	Substrate replacement therapy
STA	Single Technology Appraisal
UK	United Kingdom
VA	Velmanase alfa
VAS	Visual analogue scale
WC	Wheelchair dependent
WU	Walking unassisted
WWA	Walking with assistance

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) adequately describes the decision problem. The CS assesses the clinical effectiveness of velmanase alfa within its licensed indication for the treatment of patients with alpha-mannosidosis and the cost-effectiveness of velmanase alfa for patients aged six years and older. The comparator of best supportive care (BSC) was appropriate although the company did not include haematopoietic stem cell transplant as a comparator; clinical advice to the ERG suggested that it could be a comparator in some cases. Evidence relating to all outcomes listed in the final scope produced by the National Institute for Health and Care Excellence (NICE) was included within the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence base comprised one 12 month, double-blind, placebo controlled RCT (rhLAMAN-05, n=25) and one long-term, single arm, open label study (rhLAMAN-10, n=33). Some patients were enrolled in both studies. In rhLAMAN-05 participants were treated with velmanase alfa 1mg/kg or placebo infusions once per week.

Both studies used the biomarker serum oligosaccharides as a co-primary outcome, with the clinical outcomes 3-minute stair climb test (3-MSCT) as the second co-primary outcome. 6-minute walk test (6-MWT) and functional vital capacity (FVC) were prioritised secondary outcomes in rhLAMAN-05 and secondary outcomes in rhLAMAN-10. Other outcomes measured in both trials were other pulmonary function tests (PFTs), Bruininks-Oseretsky test of motor proficiency, 2nd edition (BOT-2), Leiter-R (cognition), Pure Tone Audiometry (PTA), Childhood Health Assessment Questionnaire (CHAQ), and the EuroQol five-dimension-five-levels (EQ-5D-5L) quality of life questionnaire. Infections and psychiatric outcomes were not measured as efficacy outcomes.

In rhLAMAN-05, there was a statistically significant decrease in serum oligosaccharides (adjusted mean difference in relative change between velmanase alfa and placebo group −70.47% (95% confidence interval (CI): −78.35, −59.72), p<0.001; adjusted mean difference in absolute change -3.50 µmol/L (95% CI: -4.37; -2.62), p< 0.001**)**. However, there were no statistically significant decreases in the clinical co-primary and prioritised secondary outcomes or on the other secondary outcomes relating to motor function, cognition and hearing. The adjusted mean difference in relative change and adjusted mean difference in absolute change results respectively were: 3-MSCT: 3.01% (95% CI: −9.86, 17.72), p=0.648 and 2.62 steps/min (95% CI: -3.81, 9.05), p=0.406; For 3-MWT estimates were: 1.86% (95% CI: −6.63, 11.12), p=0.664 and 7.35 meters (95% CI: -30.76; 45.46), p=0.692; FVC% 8.40% (95% CI −6.06, 25.08), p=0.269 and 5.91% predicted (95% CI −4.78, 16.60), p=0.278. The company stated that the trial met the endpoint of "*a statistically significant reduction in serum oligosaccharides (at a*

significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis".

In rhLAMAN-10, the relative change from baseline results (SD) at last observation were: serum oligosaccharides -62.8% (33.61), p<0.001; 3-MSCT 13.77% (25.83), p=0.004; 6-MWT 7.1% (22.0), p=0.071; FVC% predicted 10.5% (20.9), p=0.011. Other statistically significant results at last observation were: EQ-5D-5L Index (11.2% (24.7218), p=0.036); BOT-2 total (13.0% (33.9), p=0.035; Leiter-R (visualisation and reasoning) (5.338 (10.45) p= 0.006), and serum IgG levels, a surrogate for infections, 44.07% 95% CI (32.58, 55.57), p=<0.001.

The company also provided pre-planned analyses in rhLAMAN-10 including age subgroups (<18 years vs ≥18 years) and a patient status analysis. Post-hoc analyses included a multi-domain responder analysis in both studies and an evaluation by age (<18 years vs ≥18 years). The multi-domain responder analysis showed more patients were responders in the velmanase alfa arm of rhLAMAN-05 than the placebo arm (87% vs 30% respectively), and more patients <18years were responders than ≥18 years in rhLAMAN-10 (100% vs 71%). The age subgroup analyses showed observed differences between groups, but interaction tests were not performed in rhLAMAN-05 and were only performed for serum oligosaccharides (non-significant interaction) and 3-MSCT (a significant interaction) in rhLAMAN-10.

To address ERG concerns about the omission of infection rates from the trials, the company provided additional post-hoc analyses of serum IgG, use of antibiotics and a questionnaire provided to caregivers. These data were interpreted by the company as indicating improvements in infection rates were likely.

The proportion of patients receiving velmanase alfa and experiencing any AE is high (88%-100%); approximately one half experienced a treatment-related AE and one third a SAE. However, most AEs were reported as being mild or moderate.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG believes the CS is complete with respect to evidence relating to velmanase alfa. The ERG judged both studies to be at some, or unknown, risk of bias. The clinical advice provided to the ERG suggested that serum oligosaccharides are a surrogate with pharmacokinetic relevance, but low clinical relevance. They also considered infection rates and psychiatric outcomes (not measured as efficacy outcomes in the studies) as clinically relevant outcomes.

The ERG noted that the patient spectrum of the evidence base is likely to be younger than the population in England due to the inclusion criteria (5-35 years old), and it may be easier to detect an effect in younger patients as disease progression is more rapid. It is unclear whether some of the patients included

in the studies may have been eligible for HSCT in some clinical practices in England. The company provided draft start/stop criteria which, if applied in clinical practice, would be likely to exclude some patients who continued treatment in the studies. In clinical practice, therefore, fewer patients may be eligible for long term treatment, but for those who are, the studies are likely to have underestimated population-level efficacy.

The ERG does not think it is clear whether rhLAMAN-05 met its definition of efficacy as there was no definition given for a "*trend for improvement*". The ERG noted that the observed differences between treatment groups in clinical outcomes in rhLAMAN-05 did not meet the minimal clinically important differences (MCID) defined by the company post-hoc.

Whilst statistically significant differences from baseline were reported at last observation in some outcomes, results from rhLAMAN-10 are difficult to interpret because it is a single arm study and thus it is unclear how patients would have progressed without treatment. The duration of follow-up varied a great deal for patients, with variable numbers, sometimes comprising different patients altogether, at time points beyond 12 months. There are also instances of patients missing from some analyses. The last observation analysis generally included all patients and for the four main outcomes (Serum oligosaccharides, 3-MSCT, 6-MWT, FVC % predicted) there was little difference between the 12 month and the last observation analyses (though the mean length of follow-up in the last observation analysis is unclear).

The ERG had a number of concerns regarding the multi-domain responder analysis including: dichotomising continuous data based on arbitrary cut-off values; the assumption that the domains are of equally importance; the use of a potentially clinically irrelevant surrogate outcome (serum oligosaccharides) with demonstrably poor association with clinical outcomes in the studies; the omission of infection rates and central nervous system outcomes from the domains; and the post-hoc nature of the analysis and MCIDs.

The ERG did not agree with the company's reasons for not conducting interaction tests by age in rhLAMAN-05 and given that only two outcomes were tested in rhLAMAN-10, the ERG conclude that it is statistically unclear if efficacy is different in the chosen age groups for most clinical outcomes.

The ERG was concerned that the data relating to infection rates was not ideal. In rhLAMAN-05 there was a higher observed adverse event rate of infections and infestations in the velmanase alfa arm than in the placebo arm in rhLAMAN-05(48 events (87% of patients), versus 23 events (70% of patients) respectively).

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a health model constructed in Microsoft Excel® that compared treatment with velmanase alfa to treatment with BSC. The primary outcome measure was cost per quality-adjusted life year (QALY) gained using an NHS and personal social services perspective. The model uses a state transition approach with one-hundred yearly time cycles. There are five primary health states: (i) walking unassisted; (ii) walking with assistance; (iii) wheelchair dependent; (iv) severe immobility and (v) death. In addition, patients can experience severe infection, which can result in transition to a short end stage where death occurs four weeks' later, and patients can also undergo surgery, which can result in either death or transitioning to severe immobility health state. Key clinical parameters of the model that were assumed to be influenced by velmanase alfa treatment were informed largely through elicitation of experts' beliefs with, or interviews with, clinical experts. These included: improvement in health state; the additional time in a health state before progression; the reduction in the probability of major surgery; the reduction in surgical-mortality and surgical complications; the reduction in mortality and complications associated with severe infections; and the reduced requirement for ventilation. Resource use and unit costs were populated from published literature. Based on the deterministic version of the company's revised model, post clarification, the incremental cost-effectiveness ratio (ICER) for velmanase alfa versus BSC was estimated to be: £[redacted] per QALY gained for a paediatric cohort; [redacted] per QALY gained for an adolescent cohort; and [redacted] per QALY gained for an adult cohort. Probabilistic estimates were similar to the deterministic estimates.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent of these include: (i) the use of utility data taken from a UK Society for Mucopolysaccharide Diseases survey ([redacted]) rather than those from rhLAMAN-10[1] ([redacted]); (ii) the use of an inappropriate discount rate of 1.5% per annum rather than one of 3.5% per annum; (iii) the assumption of a utility increase of 0.10 for those patients receiving velmanase alfa; (iv) a model implementation error relating to the transition probabilities after treatment discontinuation; and (v) a model implementation error relating to the expected costs after discontinuation of velmanase alfa treatment. In addition to the five issues previously described, there is considerable uncertainty in many key parameters relating to the effectiveness of velmanase alfa.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Given the rarity of the disease, the availability of RCT evidence is commendable.

The ERG considers the general model structure adopted by the company to be appropriate. The company fixed errors identified by the ERG in the clarification process.

1.6.2 Weaknesses and areas of uncertainty

The small number of patients in the studies and the relatively short (for a treatment that will be given life-long) length of follow-up leads to uncertainty around the estimates of efficacy. The lack of statistical significance is perhaps not surprising in some instances given the small sample size, though the small observed differences between treatment arms is still a concern. The company assert that improvements over the natural course of the disease are likely over time, and the biological rationale for this is plausible. However, the available evidence is difficult to interpret because of the small number of patients followed-up for longer than 12 months, and the inclusion of different patients at different time points.

The rationale for some of the assumptions used within the company's model were unclear or contentious. Many of these assumptions could be seen as being favourable to velmanase alfa. In addition, two programming errors were identified by the ERG after the clarification process. Clinical advice received by the ERG suggested that haematopoietic stem cell transplant may be an appropriate treatment for some patients; however, this was not included in the company model as a comparator.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made five changes to the company model. These were: (1) the use of utility data collected in the rhLAMAN-10[1] study ([redacted]) in preference to data taken from the MPS survey ([redacted]); (2) changing the discount rate from 1.5% per annum to 3.5% per annum; (3) removing the company's assumption that patients receiving velmanase alfa treatment have a gain in utility of 0.10; (4) the correction of a model implementation error whereby the transition rates between those patients receiving BSC were different dependent on whether the patient had received velmanase alfa previously; and (5) the correction of a model implementation error whereby the incorrect costs were used after the discontinuation of velmanase alfa. The differences these changes make to the company's base case are shown in Table 1. The amendments made by the ERG within its base case increased the estimated ICERs for velmanase alfa versus BSC to: [redacted] per QALY gained for a paediatric cohort; [redacted] per QALY gained for an adolescent cohort; and [redacted] per QALY gained for an adult cohort.

In addition, the ERG performed multiple sensitivity analyses which are presented in Table 2. These analyses indicated that the ICER was sensitive to the following assumptions relating to velmanase alfa treatment; the duration for which it was assumed that treatment with velmanase alfa could potentially result in an improvement of health state; the benefit associated with surgical outcome; the benefit

associated with serious infection; and any underlying utility gain that may be conferred by velmanase alfa. There are limited data on these parameters. It was also noted that the ICER was sensitive to assumptions made regarding which health state patients were in when receiving velmanase alfa and also the assumed average ages of patients.

The ERG noted four structural assumptions that it could not amend within the timescales of the Highly Specialised Technology appraisal relating to: (i) the prohibition of patients receiving BSC improving health state (although the rate of velmanase alfa would also need to improve by the same amount); (ii) that the model output did not predict the elicited input data regarding time in health state; (iii) that the number of vials required were not based on a distribution but was assumed fixed and known for a patient of given age and sex; and (iv) that patients discontinuing velmanase alfa treatment were assumed to do so at six months rather than at 1 year as would be the case given the proposed stopping rule. It is not known how amending the model to accommodate these changes would impact on the ICER. The ERG did not perform any analyses with haematopoietic stem cell transplant as a comparator.

The ERG highlights that all ICERs contained in this document are based on the list price of velmanase alfa, whereas there is a PAS agreed. The results when the PAS is incorporated are provided in a separate document.

Table 1: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case [redacted])**	**Adolescent (CS base case £[redacted])**	**Adult (CS base case [redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906;[redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; WU – Walking Unassisted; WWA – Walking With Assistance

Table 2: Scenario analyses run on the ERG's base case

	CPQ given individual change		
Analyses	**Paediatric (base case [redacted])**	**Adolescent (base case [redacted])**	**Adult (base case [redacted])**
Assuming 100% in the WU health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WWA health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WC health state	[redacted]	[redacted]	[redacted]
Assuming the average age per age band observed in rhLAMAN-10[1]	[redacted]	[redacted]	[redacted]
Assuming no improvements in health state after 12 months	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to surgery.	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to serious infection.	[redacted]	[redacted]	[redacted]
Assuming the costs of a severe infection are set to £2742	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to ventilation costs.	[redacted]	[redacted]	[redacted]
Assuming the UK MPS survey as the source for caregiver requirements.	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility	[redacted]	[redacted]	[redacted]
Including personal expenditure by the family	[redacted]	[redacted]	[redacted]
Including caregiver productivity losses	[redacted]	[redacted]	[redacted]
Assuming that patients treated with velmanase alfa have a utility gain of 0.05	[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; MPS – Mucopolysaccharidosis; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

2 BACKGROUND

2.1 Critique of company's description of the underlying health problem

The company's submission (CS) (section 6.1)[2] provides a good and comprehensive description of alpha-mannosidosis (AM). AM is an ultra-rare, inherited, lysosomal storage disorder (LSD), a phenotype of which was first identified in the late 1960s.[2] Numbers of patients with AM are unknown but the most frequently-reported prevalence is between one in 500,000 and one in 1 million live births.[3, 4] The number of cases in the UK is also unknown: based on registry data from the Society for Mucopolysaccharide Diseases (MPS Society), the CS[2] reports that there are only [redacted] cases of AM currently registered in England and Wales, and there is [redacted] in those countries (pages 20, 21, 41 and 43 of the CS). There is no known predisposition based on gender or ethnicity.[4]

The disorder is the result of a deficiency of the lysosomal enzyme alpha-mannosidase. This deficiency is caused by mutation of the MAN2B1 gene, which leads to reduced production of alpha-mannosidase; this in turn leads to increased excretion in urine of mannose-rich oligosaccharides, and the accumulation of these un-degraded oligosaccharides in various tissues, especially the central nervous system, liver and bone marrow.[3, 5]

As a disorder, AM is complex: it is characterised by immunodeficiency, facial and skeletal abnormalities (especially scoliosis and deformation of the hips and feet), and impairment of a person's mental and hearing abilities, and their motor function (including muscular weakness, joint abnormalities and ataxia).[3, 4] However, the clinical presentation of the disorder is highly heterogeneous and patients can present with a very wide range in terms of levels of impairment.[3, 4]

The disorder is diagnosed by measuring acid alpha-mannosidase activity in leukocytes or fibroblasts and by analysis to detect mutations in the alpha-mannosidase gene, MAN2B1.[4] Elevated urinary excretion of mannose-rich oligosaccharides is suggestive of AM but is not used for diagnosis.[4] The majority of patients are diagnosed in childhood.[3, 4] The literature has distinguished between mild, moderate and severe 'types' or forms of the condition,[3-5] but there is no universally-accepted typology.[4] It is accepted that the 'severe' form tends to be diagnosed before the age of 5 years and is characterised by rapid and lethal progress and leads to early death (in childhood), while the 'moderate' and/or 'mild' forms are characterised by slow progression (and therefore survival into adulthood), and a very wide range of impairments to a person's mental and hearing abilities, their eyesight, and their mobility. The CS[2] does not accept the distinctions by 'type' (e.g. types I and II) because of the heterogeneous nature of AM, but proposes that the condition be considered as a 'continuum' with extremes of severity. This is consistent with the literature in terms of the clinical presentation of the disease[4] and does not affect

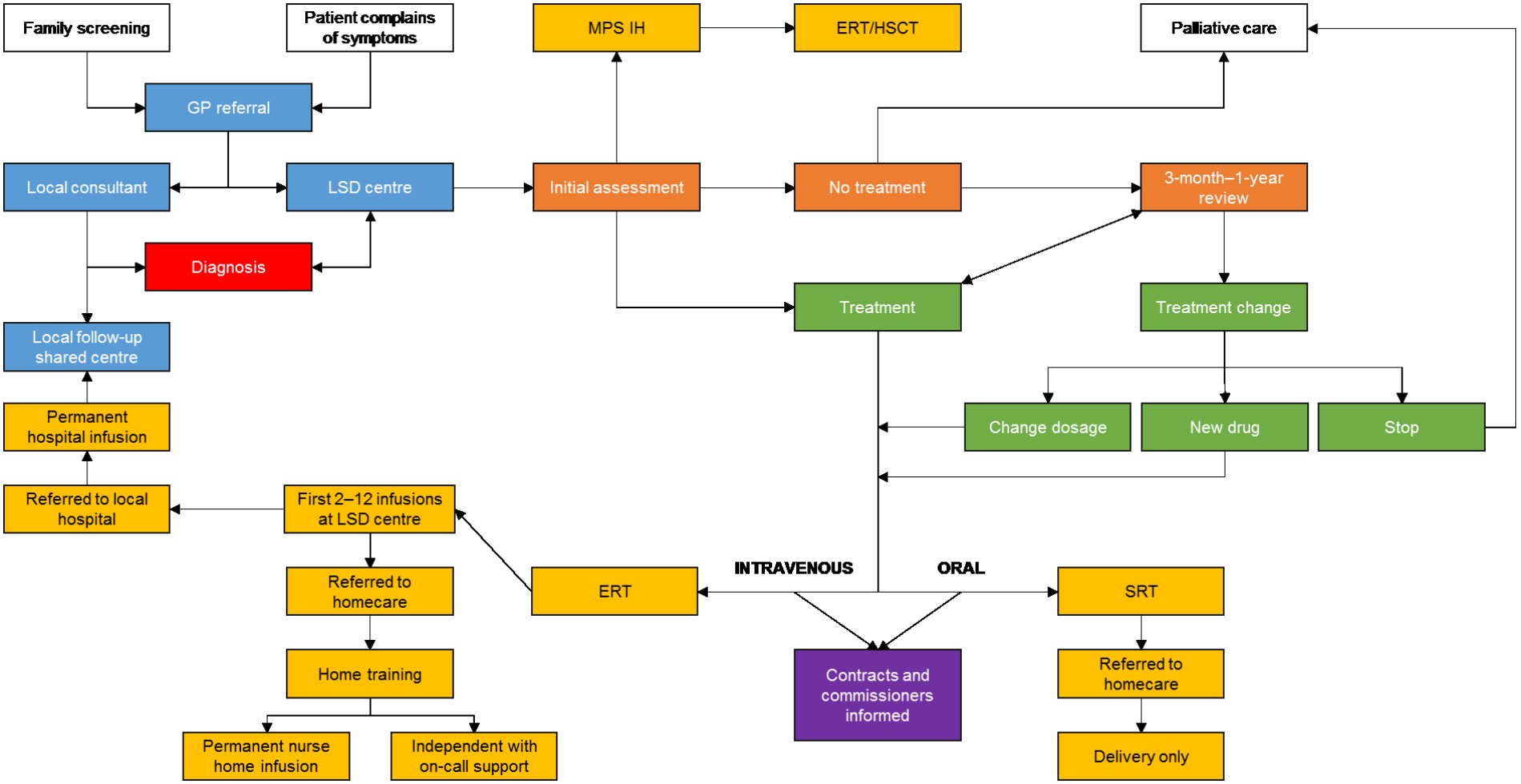
the decision problem because this distinguishes between patients based on treatment options only (CS,[2] Section 2.1).

Given the adverse effect on the immune system, AM patients are pre-disposed to recurrent infections.[3, 4, 6] The disorder also has a major impact on a person's quality of life: they can experience severe impairment to their cognitive ability, mobility, functional capacity, eyesight and hearing,[3, 4] as well as experiencing more pain as the disease progresses.[3] The number and severity of infections, comorbidities and impairments increase with time on account of the progressive nature of the disease. As a consequence of the mental and physical problems experienced by patients diagnosed with AM, they require constant support and are not socially independent, including in adulthood.[4] As a result, there is inevitably a major quality of life burden for carers also, although no published research was presented in the CS to support this (Section 7.1.3.2, page 53 and Section 7.2.3.2, page 57).[2] Given the progressive nature of the disorder, the long-term prognosis is poor and the available data, including unpublished AIC data presented in the CS[2] (page 49), suggest that the disorder is life-limiting.[3, 4]

2.2 Critique of company's overview of current service provision

The CS[2] provides a good overview of current service provision (Section 8.1, 8.2 and 8.3, pages 61-68). The CS[2] states correctly that there is currently no NICE guidance on the management of the condition and no licensed pharmacological or disease-modifying treatments for AM (pages 20, 22-23 and Section 8.3). Patients follow the NHS England lysosomal storage disorder (LSD) services care pathway,[7] as outlined in Figure 1; they are managed at designated LSD service centres in England and specialist hospitals for managing metabolic diseases in Wales (CS[2], page 64). Services depend on a patient's age and location (CS[2], Section 8.3, pages 66-68).

Figure 1: Lysosomal storage disorder (LSD) service care pathway



Source: Reproduced from CS[2], Figure 2 page 63, which was adapted from NHS England Standard Contract for LSD services.[7]
Abbreviations: ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; LSD, lysosomal storage disorder; MPS IH, severe mucopolysaccharidosis I; SRT, substrate replacement therapy

Bone marrow transplant (BMT) and allogeneic Haematopoietic Stem Cell Transplant (HSCT) represent the only treatment options for some patients, but there is substantial morbidity and mortality associated with these procedures.[4, 5, 8] The CS[2] (page 23) states that in the UK, allogeneic HSCT is only clinically indicated for patients aged five years or less, without additional comorbidities/recurrent infections, and who have a matched sibling or umbilical cord donor. However, the CS[2] (Section 8.3.3, pages 67-68) also states that broader clinical criteria might be applied in practice.

Given the lack of treatment options, current service provision principally consists of symptom management for the pain and impairments associated with the disorder. This is represented by best supportive care (BSC) and includes walking aids, physiotherapy, infection management and, where appropriate, surgical intervention (CS, Section 8.2.4 and pages 64-65).[2] Given the highly heterogeneous nature of the disorder, and the highly individual nature of its presentation, patients must be managed on a case-by-case basis.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The remit detailed in the final scope issue by the National Institute for Health and Care Excellence (NICE)[9] is to appraise the clinical and cost-effectiveness of velmanase alfa within its licensed indication for AM. The technology is not yet licensed; the CS[2] (page 38) states that a UK marketing authorisation is expected in April 2018.

The ERG notes that the final NICE scope[9] specified patients aged 6 years or older and that the CS provides clinical trial data on patients aged 5 years or older (CS,[2] Section 9). However, the CS[2] (pages 21 and 33) states that the anticipated licence is now for velmanase alfa as an enzyme replacement therapy (ERT) for the treatment of non-neurological manifestations in patients of any age with mild to moderate AM, who are not clinically indicated for HSCT.

Therefore, there is uncertainty regarding the generalisability of the results to child patients aged less than 5 years, who were excluded from the trials (rhLAMAN-05[10] and rhLAMAN-10[1]) presented in the CS.[2] Given the absence of discrete diagnostic criteria for severe, moderate and mild forms of the disorder, there might also be an issue distinguishing between patients with 'severe' AM and patients with 'moderate or mild AM'. Clinical advice to the ERG suggested that patients diagnosed under 5 years of age tend to be classified as having a 'severe' form of the disorder, with those diagnosed at 5 years or older being considered to have moderate or mild form, which ultimately progresses to 'severe' in later life. Clinical advice received by the ERG also confirmed that the clinical evidence relates to trials of patients with 'moderate or mild' AM.

3.2 Intervention

The intervention evaluated by the company is velmanase alfa (Lamzede®). Velmanase alfa is a white powder that is reconstituted to provide a final concentration of 10 mg/5 ml (2 mg/ml) per vial. The recommended dose of velmanase alfa is 1 mg/kg of body weight, once every week, to be administered by intravenous (IV) infusion at a controlled speed. As velmanase alfa is dosed by weight, (1mg/kg of body weight) dose adjustments are required as/if the patient's weight changes. Velmanase alfa is intended to be used continuously throughout a patient's lifetime, subject to the 'start' and 'stop' criteria described in the CS[2] (pages 182-83). A patient is excluded from treatment if they do not have a confirmed diagnosis of AM; has experienced a severe allergic reaction to velmanase alfa or to any of its excipients; if they are diagnosed with an additional progressive life-limiting condition where treatment would not provide a long-term benefit; or if the patient is unable to comply with the associated monitoring criteria. Treatment may be stopped due to reasons of non-compliance, non-response and/or

deterioration of functional capacity. The list price for velmanase alfa is £866.67 per vial with the number of vials required per week dependent on the patient's weight.

3.3 Comparators

The final NICE scope[9] indicated that the only comparators are BSC or HSCT, where clinically indicated. However, the CS[2] (pages 21 and 33) states that the anticipated licence is for patients for whom HSCT is not indicated, and therefore this therapy does not represent a valid comparator. If this position is accepted, the ERG believes that the rhLAMAN-05[10] and rhLAMAN-10[1] trials, which compared velmanase alfa (plus BSC) with placebo (plus BSC), are appropriate to address the decision problem. For brevity, velmanase alfa in combination with BSC intervention has henceforth been abbreviated to velmanase alfa, and placebo in combination with BSC has been termed BSC.

Clinical advice received by the ERG and submitted to NICE within expert statements suggests that HSCT could present a valid comparator for a minority of these patients, including those aged 5 years or more. The ERG also notes that there are no universally-accepted criteria regarding patients for whom 'allogeneic HSCT is not suitable and/or not possible' (CS[2], pages 23 and 68). The CS[2] (page 23) states that, '*allogeneic HSCT is typically only reserved for AM patients with extensive disease presenting in early infancy (≤5 years), and who do not have additional comorbidities/recurrent infections, and where a matched sibling or matched umbilical cord donor is available … Additionally, the risk of allogeneic HSCT-associated morbidity and mortality increases with age … Therefore, patients over the age of 6 are less likely to have any treatment options'*. The ERG notes that the clinical evidence is drawn from trials of AM patients aged 5 years or older who have never been exposed to allogeneic HSCT (CS[2], pages 97 and 100). There is therefore no comparison of clinical effectiveness or cost-effectiveness of velmanase alfa for patients who are suitable for HSCT.

3.4 Outcomes

Nearly all clinical outcomes listed in the final NICE scope[9] were addressed in the clinical section of the CS;[2] however, infections were only reported as adverse events and language was not measured. The ERG received clinical advice that infections are an important outcome as they are a source of mortality and morbidity and should have been included as an efficacy outcome. The potential status of oligosaccharides as a surrogate outcome for patients' functional outcomes[3] was not demonstrated by the submitted evidence from the only randomised controlled trial (rhLAMAN-05[10]). The company's model aggregates the patients simulated experiences into quality-adjusted life years (QALYs) as stipulated in the final scope.[9] The clinical advisors were further surprised that psychiatric problems such as acute psychosis were missing both from the NICE scope[9] and from the trials, as this is also a problem for many patients.

3.5 Other relevant factors

The company have applied for a patient access scheme which will take the form of a simple discount on the price per vial resulting in a cost of [redacted] (excluding VAT) per 10mg vial rather than the list price of £886.61 (excluding VAT) per 10mg vial. Societal costs are included in a sensitivity analyses.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

Whilst the lack of a registered protocol and poor reporting of methods in the CS[2] introduces the potential for bias, the ERG is satisfied, after clarifications[11] from the company, that the review is conducted to a high enough standard and will have captured all relevant studies relating to AM.

4.1.1 Searches

The company conducted a systematic literature review to identify published and unpublished evidence on the clinical effectiveness of treatments for AM in patients over 6 years. Searches were conducted on 25th January 2017 and then updated 31st October 2017.

Databases searched included all those recommended by NICE (Medline; EMBASE; Cochrane Library, plus a number of additional registers for the cost-effectiveness review – see Section 5.1.1). These were complemented by hand searches of Health Technology Assessment (HTA) publications and relevant conference proceedings listed in full in the CS Appendices (17.1.5.1)[2] and clinical study reports provided by Chiesi; and followed by manual checking of reference lists of included studies to identify any further potentially-relevant studies. The ERG queried whether any "forward" citation tracking (of later publications citing those included) had been conducted, but the company replied that this was not the case (clarification response,[11] Question A1).

There were some minor errors in the reporting of the searches (and specifically the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart) which were resolved via the company's response to the clarification letter (clarification response,[11] Questions A2 and A3). However, the search strategies (reported in Appendix 1 of the CS[11]) are well-designed and the ERG considers them to be unlikely to have missed any relevant studies.

4.1.2 Inclusion criteria for clinical studies

Table 3 provides the inclusion criteria used by the company which is a reproduction of Table 4 of the CS.[2] The selection criteria were in line with the decision problem, but quite broadly defined. The review did not restrict by intervention type, and it was therefore unclear how the final selection of studies was made. The ERG asked for clarification on the inclusion criteria for the review; the company replied that "Only studies that assessed the clinical effectiveness of velmanase alfa in humans were deemed relevant to the decision problem, and therefore presented in Section 9.3 of the CS onwards." (Question A8)[11]

The company also listed the excluded studies which comprised seven studies related to HSCT and six studies related to the treatment of the consequences of AM.

There was a mismatch between the reported number of included studies in the text (16 (19 publications)) and in the flow chart (17 (25 publications)). The company clarified that the flow chart total was correct, but that a box detailing the source of the additional studies (an update conducted in October 2017 (1 study, 6 publications)) had been omitted in error (see clarification question A3).[11]

In their clarification response, the company confirmed that study selection was conducted by two independent assessors with recourse to a third reviewer if consensus was not reached after discussion and re-review of discordant decisions (response A6).[11]

Table 3: The Inclusion criteria employed by the company

Inclusion criteria	
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age).
Interventions	Not restricted (see Appendix 1, Section 17.1.6 for details on treatments to include).
Outcomes	Aligned to the outcomes presented in the decision problem (Table 2).
Study design	RCTs, non-RCTs, observational/real-world studies, case series and case reports
Language restrictions	Unrestricted
Search dates	Unrestricted
Exclusion criteria	
Population	Patients aged <6 years with AM (all patients were included at first pass regardless of age).
Interventions	Unrestricted
Outcomes	Publications reporting solely on outcomes outside the NICE scope were not considered relevant.
Study design	Studies not meeting the inclusion criteria for study design.
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: AM, alpha-mannosidosis

4.1.3 Critique of data extraction

In their clarification response, the company confirmed that data extraction was conducted by two independent assessors with recourse to a third reviewer in cases of discordant data (response A6).[11] It was not reported whether a data extraction form was piloted or standardised, and no list of relevant data fields was provided. However, given the data presented, the ERG is satisfied that data was extracted in an acceptable manner.

4.1.4 Quality assessment

The company confirmed that the quality assessment of the studies was conducted in the same manner as data extraction (response A6),[11] and the ERG is satisfied that the process was of an acceptable standard.

However, the ERG does not agree with all the judgements provided by the company, nor the use of an RCT checklist for the assessment of rhLAMAN-10[1] which is a non-controlled study more akin to a cohort study. Table 4 and Table 5 provide the ERG's judgements on the quality of rhLAMAN-05[10] and rhLAMAN-10[1] compared with the company's appraisal. Table 5 also includes responses to a quality assessment checklist for cohort studies provided by the company in their clarification response A5.[11]

Overall, the ERG judges rhLAMAN-05[10] to be of reasonable quality, with some faults. The ERG judged rhLAMAN-05[10] to be at low risk of bias in three domains, compared to six domains judged at low risk by the company. The ERG judged there to be a lack of clarity about randomisation procedure (i.e. how the random sequence was generated), allocation concealment (even after the company's clarification response to A4)[11] and blinding of outcome assessors, whereas the company judged these to be at low risk of bias (see Table 5).

The ERG and company's judgement of risk of bias in rhLAMAN-10[1] differed in three domains. Overall, the ERG judged rhLAMAN-10[1] to be in some respects a well conducted study, but with some key limitations that make the results subject to high risk of bias. The ERG judged an unclear risk for outcome measurement as some measures were subjective (e.g. Childhood Health Assessment Questionnaire (CHAQ)) and the trial was open label. The ERG judged there to be a lack of clarity around attrition as numbers are inconsistent across Figures 18-21 in the CS.[2] The ERG also judged that the results are possibly confounded and inconsistent with other data (CS, page 137-39);[2] there is a lack of consistency across functional outcomes, for example, 3-minute stair climb test (3MSCT) shows significant improvement but 6-minute walk test (6MWT) does not, and there is no quality of life gain despite statistically significant improvements in function; the findings for 6MWT are not correlated with oligossacharide levels as suggested elsewhere (Beck 2013).[3]

Table 4: Critical appraisal of rhLAMAN-05[10] (randomised and controlled trial) (reproduced in part from CS, Table 22)

Study name	rhLAMAN-05[10]			
	CS critical appraisal[2]		ERG critical appraisal	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Randomisation (in a 3:2 ratio) into active and placebo groups was stratified by age and was used to allocate the patients into blocks. Within the blocks, a standard randomisation into active and placebo was performed.	Unclear	CSR: 9.4.6: It is not clear how the randomisation sequence was generated, e.g. by referring to a random number table, using a computer random number generator, etc.
Was the concealment of treatment allocation adequate?	Yes	rhLAMAN-05[10] was double-blind study.	Unclear	Assumption is that vials are identical, but the description provided is not explicit: C.S.R 9.4.2.4[11] (packaging) and 9.4.6 (randomization and blinding): To preserve the blinding no batch number was included, but the batch was identified by the trial reference code (rhLAMAN-05[10]) and the retest date… The subject number, identification and randomization were documented at Larix (a Contract Research Organisation). Three sets of sealed code/label with the randomization number containing information about the treatment for the particular subject were prepared for each subject. One set was kept at the dosing site (during the entire trial period), one set was kept at Larix and one set was kept at the Sponsors Quality Assurance. The randomization code list was kept at Larix and was disclosed to the contract manufacturing organization (CMO) performing the packaging of the trial. The code for a particular subject could be broken in a medical emergency ...

				also clarification response A4[11]: The randomisation code list was kept at the CRO and was disclosed to the contract manufacturing organisation (CMO) performing the packaging of the trial. The code for a particular subject could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject. However, blinding was not broken for any patient in the trial.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Overall, the demographic characteristics were similar between the two groups. In terms of functional capacity (by categorical values arbitrary adopted for 3-MSCT and 6-MWT), PFTs and BOT-2, the two groups were less balanced, with a higher proportion of more compromised patients randomised to the active treatment group.	No	As noted, the patient groups are not balanced for 3MSCT, 6MWT, FVC, BOT-2 or CHAQ Disability Index (CSR, Table 11-1)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Patients and investigators remained blinded to treatment assignment during the study. The blinding for a particular patient could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the patient.	Unclear	Patients and care providers appear to be blinded (see allocation concealment above, CSR[10] sections 9.4.2.4 and 9.4.6), possibly as well as outcome assessors at data review (CSR[10] sections 9.6 and 11.1), but it is not specified if all outcome assessors (e.g. 3MSCT) are blinded. CSR[10] 9.6: After completion of data cleaning, a blinded data review meeting was held to define protocol deviations and patient populations to be analysed. Afterwards, the database was locked, the randomisation codes were opened and the planned statistical analysis was performed.

				CSR[10] 11.1: During the blinded data review, all patients were included in the PK analysis set, but only the 15 patients treated with Lamazym were then analysed.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	NR	No	No reported drop-outs
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	NR	No	However, the following outcomes were not listed in the protocol, but were reported: BOT-2 motor function; Leiter-R cognitive ability; EQ-5D; CHAQ Disability Index and VAS; and PTA hearing loss tests: https://clinicaltrials.gov/ct2/show/record/NCT01681953[12]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety evaluation was based on a modified ITT analysis and included all patients who received ≥1 dose of trial drug and whose efficacy was evaluated post-baseline.	Yes	CSR[10] 9.7.1: statistical analysis of everyone who had at least 1 dose of study drug (CS, 9.6.2, page 154[2]) and protocol deviations did not suggest any patient was not analysed in the correct group (CSR 10.2.1). Appropriate multiple imputation methods were used to account for missing data.

Abbreviations: CS, company submission; CSR: Clinical Study Report; 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency, 2nd edition; ITT, intention-to-treat; PFT, pulmonary function test; PK: Pharmokenetics; PTA: Pure Tone Audiometry; CHAQ: Childhood Health Assessment Questionnaire; VAS: Visual Analogue Scale; EQ-5D: EuroQol five-dimension questionnaire.

Table 5: Critical appraisal of rhLAMAN-10[1] (cohort) using the CASP tool for cohort studies (reproduced in part from clarification response to question A5[11])

	rhLAMAN-10[1]			
Study name	**CS critical appraisal[2]**		**ERG critical appraisal**	
Study question	**Response (yes/no/not clear/N/A)***	**How is the question addressed in the study?**	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Did the study address a clearly-focused issue	NR[2, 11]	NR[2, 11]	Yes	CSR[1], page 3: 'the evaluation of the long-term efficacy of Lamazym treatment in patients with AM who were previously enrolled in trials with Lamazym and were currently receiving the treatment according to the AfterCare Program agreed with the National Authorities'
Was the cohort recruited in an acceptable way	Yes[2]	Patients who were receiving active treatment as part of the compassionate use programme (after-trial study following the Phase I-II and rhLAMAN-05[10] trials) were invited to attend a CEV in order to obtain a long-term data point. These data were combined with the data bases of the Phase I-II trial, rhLAMAN-05[10], rhLAMAN-07 and rhLAMAN-09 to form the integrated data base (see Section 9.4.1.3 for details)[2]	Yes	See CS response in column 3 of this table.
	Yes[11]	Patients were enrolled from the previous rhLAMAN studies[11]		
Was exposure accurately measured	NR[2]	NR[2, 11]	Yes	Full details of different levels of exposure depending on 'parent' trial are reported: CS, section 9.7.2.2, page 157;[2] CSR[1], 12.1, page 150. However, treatment compliance was not assessed as part of this study: CSR[1], 11.3, page 66.
	Yes[11]			
Were outcomes accurately	Yes[11]	A clear definition of all measured outcomes were reported[11]	Unclear	The study measured objective outcomes, e.g. serum oligosaccharides, and subjective outcomes, e.g. CHAQ by 'patients' legally authorized

measured to minimise bias? e.g. same for different groups, are measures subjective / objective				guardians' (CSR[1] 9.5.1.1.4, page 41) and BOT-2 by a physiotherapist and occupational therapist (CSR[1], 9.5.1.1.2, page 38). The measures and outcome assessors were the same for all groups.
Have all confounding variables been identified and taken into account?	Not clear[11]	Identification of potential confounding factors was difficult due to disease heterogeneity, exemplified by variation in severity across the numerous disease manifestations, together with the small population size of the trial. [11]	Unclear	Analyses were conducted by time on treatment and age (CS, pages 139-40 and 148-50).[2] The principal potential confounders were the large variability in range of function etc. at baseline and the small patient numbers (p.103 and 136), as well as possible 'training' (Beck 2013[3]) and potentially 'ceiling effects' for certain outcomes (page 165). It is not possible to control for all of these confounders in small populations with ultra-rare disease.
Was follow-up complete enough and long enough	Yes[11]	The follow-up period ranged from 1 to 4 years[11]	Yes and No	There was no reported attrition and follow-up to 4 years. However, only a small number of patients had 2-year (n=19/33) or 4-year follow-up (n=9/33) (CSR[1], pages 150-51) and exposure is likely to be lifetime in duration. There is some lack of clarity around attrition as n numbers are inconsistent across Figures 18-21 in the CS,[2] and detailed in **Error! Not a valid result for table.** here.
How precise are the results and are they credible?	Yes[11]	For all efficacy outcome results, p-values and variances were reported wherever applicable[11]	Unclear	Results are possibly confounded and inconsistent with other data (CS, page 137-39).[2] There is a lack of consistency across functional outcomes, e.g. 3MSCT shows significant improvement but 6MWT does not, and there is no quality of life gain despite statistically significant improvements in function; the findings for 6MWT are not

				correlated with oligossacharide levels as suggested elsewhere (Beck 2013[3]).
Can results be applied to the local population?	NR[2, 11]	NR[2, 11]	Yes	The study inclusion criteria potentially led to the recruitment of a more mobile population than reported in other studies (e.g. Beck 2013[3]), but clinical advice suggests the trial data are still applicable to England and Wales.
Do results fit with other available evidence	NR[2, 11]	NR[2, 11]	Unclear	This non-controlled study was recruited from a series of 'parent' trials (rhLAMAN-02[13], 03[13], 04[14] and 05[10]), which currently represent the only other relevant data on velmanase alfa in this patient group. The absence of a clear correlation between oligosaccharides and 6MWT is inconsistent with the findings of a larger, longitudinal study in AM patients (Beck 2013[3]).

Abbreviations: AM: alpha-mannosidosis; CS: company submission; CSR: Clinical Study Report; 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency, 2nd edition; CHAQ: Childhood Health Assessment Questionnaire; VAS: Visual Analogue Scale; EQ-5D: EuroQol five-dimension questionnaire.

*Note, there were two parts to rhLAMAN-10[1]: a) the inclusion of patients already enrolled in ongoing long-term studies and b) the inclusion of patients on compassionate use programmes.

Where applicable, the first row is for a) and the second row for b)

4.1.5 Evidence synthesis

There was no formal synthesis of the data, which the ERG believes was acceptable as there was only a single relevant phase III/IV trial (CS, section 9.8, page 161).[2] The narrative synthesis tabulated results and described these with a good degree of clarity.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The clinical effectiveness review included five studies of velmanase alfa: a Phase I-II trial comprising three individual studies (rhLAMAN-02[13], rhLAMAN-03[15], rhLAMAN-04[14]), and two further Phase III trials, one of which was an RCT (rhLAMAN-05[10]) and the other of which is a long term non-controlled study (rhLAMAN-10).[1] Table 6 details these studies. Of note, patients were eligible to enrol in subsequent trials: patients in rhLAMAN-02[13] could enrol in rhLAMAN-03[15] (and all ten did, exclusively forming the rhLAMAN-03[15] trial); patients in rhLAMAN-03[15] could enrol in rhLAMAN-04[14] (9/10 of whom did, exclusively forming the rhLAMAN-04[14] trial); patients in rhLAMAN-04[14] and -05[10] could enrol in rhLAMAN-07 or -09 (references not provided by the company for either study) or a compassionate use programme (where no efficacy outcomes were assessed). rhLAMAN-07 and -09 were set up to ensure patients could continue treatment in countries that did not want the company to offer a compassionate use programme; -07 was for French patients, and -09 for Norwegian and Polish patients. Both studies include long-term follow-up for safety, with -09 also following-up patients for efficacy (see clarification response Question A18[11]). rhLAMAN-10[1] is an integration of data collected for rhLAMAN -02[13], -03[15], -04[14], -05[10], -07 and -09, and a single efficacy assessment point for patients who enrolled in the compassionate use programme after participating in rhLAMAN-02[13], -03[15] or -04.[14] In this way, all patients had baseline and follow up data. Flow charts of patients through the trials rhLAMAN-02[13], -03[15], -04[14], -07, -09 and -10[1] are provided in Appendix 1.

4.2.1 Description of the design of rhLAMAN-05[10]

rhLAMAN-05[10] was a Phase III multicentre, double blind, placebo-controlled RCT. Patients were randomised to velmanase alfa treatment (1mg/kg by infusion) weekly, or to weekly placebo in a 3:2 ratio stratified by age in a block randomisation. Treatments were administered for 12 months. Inclusion criteria are provided in the footnote to Table 6.

4.2.2 Description of the design of rh-LAMAN-10[1]

rhLAMAN-10[1] was an integrated database(N=33) incorporating data from the Phase I/II trial (rhLAMAN-02[13]/03[13]/04[14]), rhLAMAN-05[10], rhLAMAN-07 and rhLAMAN-09 to form the rhLAMAN-10[1] integrated data set, along with additional patients who entered the compassionate use programme and had a long-term efficacy assessment as part of rhLAMAN-10.[1] The study design is an open label non-controlled study akin to a cohort study as there is no comparator arm and patients are

followed up over time. All patients were receiving velmanase alfa treatment at the standard dose (1 mg/kg); patients who had been treated with placebo in rhLAMAN-05[10] commenced treatment with VA. At the time of analysis, patients were expected to have follow-up times ranging from a minimum of 1 year to a maximum of 4 years. Inclusion criteria were determined by the original studies' criteria (see footnotes to Table 6); of note, the Phase I/II trial included patients aged 5-20 years, whereas rhLAMAN-05[10] included patients aged 5-35 years. Other inclusion criteria are largely similar.

4.2.3 Outcomes in rhLAMAN-05[10] and -10[1]

Outcomes measured in rhLAMAN-05[10] and -10[1] are described in Table 7. Minimal clinically important differences (MCID) were defined post-hoc in response to request from the European Medicines Agency (EMA). These are described on pages 105 to 108 of the CS,[2] and the methods used to define the MCIDs are described in brief in the CS Appendix 2, Section 17.7.3.1.[2] and are summarised in Table 7 of this report. Of note, there were no pre-existing MCIDs defined for alpha mannosidosis; the MCIDs were based on literature review of similar conditions and clinical opinion. Of the outcomes measured in the trials, no MCIDs were provided for motor function (BOT-2), hearing (PTA), cognition (Leiter R), infections (only measured as an adverse event), EQ-5D (though MCID provided for CHAQ) or mortality.

Table 6: Summary of key trials of velmanase alfa

Trial Name	Trial design	Inclusion criteria	N	Duration	Intervention	Comparator	Main outcomes
rhLAMAN-02[13] (NCT01268358) Borgwardt et al, 2013[16] (JA)	Phase I, SC, OL Randomised dose escalation	AM[f] pts aged 5-20[a]	10	1-5 weeks[b]	5 dosing groups (n=2 in each) VA, U/kg: 6.25; 12.5; 25; 50; 100	Baseline	**Safety:** AEs, vital signs, haematology, biochemistry, urinalysis, Anti-drug antibody (ADAs)
rhLAMAN-03[15] (NCT01285700) Borgwardt et al, 2013[16] (JA)	Phase IIa, SC, OL Randomised multiple dose	AM[f] pts aged 5-20 (all from rhLAMAN-02[13])[a]	10	6 months efficacy assessment + 6 months extension[c]	2 dosing groups (n=5 in each), weekly, IV VA, U/kg 25 50	Baseline	**Efficacy:** OGS in serum, urine, CSF; CSF neurodegeneration markers; Brain MRS; Functional capacity; cognitive development; pulmonary function; hearing; PK profile **Safety:** as rhLAMAN-02[13]
rhLAMAN-04[14] (NCT01681940) Borgwardt et al, 2014[17] (CA)	Phase IIb, MC,[d] OL	AM[f] pts aged 5-20 (all from rhLAMAN-02[13]/-03[15])[a]	9	6 months	VA 1 mg/kg	Baseline	**Efficacy (primary):** Serum and CSF OGS; 3-MSCT; 6-MWT; pulmonary function; **(secondary):** mannose-rich OGS by MRS and MRI in white matter, grey matter and centrum semiovale; CSF neurodegeneration markers; BOT-2 and hearing loss; Leiter-R; CHAQ
rhLAMAN-05[10] (NCT01681953) Guffon et al, 2017[18] (CA)	Phase III; RCT, MC,[e] DB, PC	AM[f] pts aged 5-35[g]	25	12 months	VA 1 mg/kg (randomised 3:2, VA: placebo)	Placebo	**Efficacy (primary):** Serum OGS; 3-MWT; **(secondary):** 6-MWT; FVC; PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; EQ-5D
rhLAMAN-10[1] integrated dataset (NCT02478840)	Phase III; NC, SC, OL,	AM[f] Recruited from rhLAMAN-02[13], -03[15], -04[14], and -05.[10] Pts who chose the compassionate	33	Integration of data collected in other rhLAMAN studies, or a one-week assessment for those	VA 1 mg/kg	Baseline	**Efficacy (primary):** Serum OGS; 3-MWT; **(secondary):** 6-MWT; FVC; PFTs; BOT-2; Leiter-R; CSF OGS; CSF

Guffon et al, 2017[18]; Borgwardt 2017a[19]; Borgwardt 2017b[19] ; Borgwardt 2017c[20] ; Lund 2017[21]; Harmatz 2017[19]; Borgwardt 2017d[22]; Cattaneo 2016[23]; Ardigo 2016 [24]; Borgwardt 2016[25] (all CAs)		use programme after rhLAMAN-04[14] were also eligible. Pts enrolled in rhLAMAN-07 or -09 were included in the dataset.[a g]		who joined the compassionate use programme			neurodegeneration markers; PTA; CHAQ; EQ-5D

3-MSCT, 3 minute stair climb test; 6-MWT, six minute walk test; ADA, anti-drug antibody; AEs, adverse events; AM, alpha-mannosidosis;N, number; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; DB, double-blind; MC, multicentre; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NC, non-controlled study; OGS, oligosaccharides; OL, open-label; PC, placebo-controlled; PFT, pulmonary function test; PK, pharmacokinetics; PTA, pure tone audiometry;RCT, randomised controlled trial; SC, single centre; pts, patients; VA, velmanase alfa;

[f] AM confirmed by α-mannosidase activity <10% of normal activity in blood leucocytes

[a] Inclusion criteria: Physical ability to perform 6-MWT, 3-MSCT and PFTs; Ability to mentally cooperate in the cognitive and motor function tests; Ability to hear and follow a request (hearing aids can be worn); signed, informed consent of legal guardian; Exclusion criteria: known chromosomal abnormality and syndromes affecting psychomotor development, other than AM; HSCT; conditions that would preclude participation in the trial including clinically significant cardiovascular, hepatic, pulmonary or renal disease, echocardiogram with abnormalities within half a year, other medical condition or serious intercurrent illness, or extenuating circumstances; pregnancy; psychosis in previous 3 months

[b] Patients in the 6.25U/kg group started in week 1 and continued treatment to week 5. Patients in the 12.5 U/kg started in week 2 and continued treatment to week 5, and so on, with a higher starting dose each subsequent week.

[c] To maintain treatment until enrolment in rhLAMAN-04[14]

[d] Five EU sites in Denmark, UK, France, Spain, and Belgium.

[e] Six countries in the European Union: Denmark, France, Spain, Belgium, Germany and Sweden

[g] Inclusion criteria: ability to physically and mentally co-operate with the tests; echocardiogram without abnormalities that would preclude participation in the trial; ability to comply with protocol; Exclusion criteria: known chromosomal abnormality and syndromes affecting psychomotor development, other than AM; HSCT; conditions/circumstances that would preclude participation in the trial; pregnancy; psychosis (including remission); participation in other interventional trials testing IMP (including VA) within the last three months; Adult patients who would be unable to give consent, and who do not have any legal protection or guardianship; Total IgE >800 IU/ml; Known allergy to the IMP or any excipients (sodium-phosphate, glycine, mannitol)

Table 7: Outcomes listed in the NICE scope,[9] their measurement in rhLAMAN-05[10] and -10[1], MCIDs (defined post-hoc) and inclusion in patient status analysis. Partly reproduced from Table 7 of the CS[2]

NICE Scope[9]	Measure used in rhLAMAN-05[10] and -10[1]	Description of test	MCID (Absolute change)	Based on	Patient status analysis (rhLAMAN-10[1] only)
Not listed	Serum Oligosaccharide	The levels of oligosaccharides in serum are measured to evaluate VA activity and its efficacy in clearing oligosaccharides.	Cut off: ≤4µmol/L	Arbitrary, based on rhLAMAN-05[10] baseline values	Yes
Mobility	3-MSCT	3-MSCT – evaluation of the number of steps climbed in 3 minutes to assess mobility/functional capacity.	Increase ≥7 steps/min	Used MCID defined post-hoc for a trial MOR-004 of elosulfase alfa in patients with MPS IVA (similar condition). Based on 20% of baseline value in MOR-004 (27-35 steps/min at baseline)	Yes
	6-MWT	6-MWT – evaluation of the distanced walked in 6 minutes to assess mobility/functional capacity.	Increase ≥30 meters	Literature review: Chronic lung disease MCID = 54-80 meters; pulmonary hypertension MCID = 33 meters; chronic heart failure MCID = 30.1 meters; Duchenne muscular dystrophy MCID = 28.5-31.7 meters (based on statistical distributions) MPS IV: 22.5 meters, but rhLAMAN-05[10] patients have higher baseline (466 meters vs 20 meters) Pompe disease range MCIDs = 24-54 meters	Yes
Motor function	BOT-2	BOT-2 assessment to evaluate motor skills.	NR	NR	No
Hearing and language	Hearing: PTA Language: NR	PTA to assess hearing loss.	NR	NR	PTA: yes
Cognition	Leiter R test	Leiter-R test to assess cognitive ability.	NR	NR	No

Lung function	FVC	Assessment of FVC (L and % of predicted), FEV_1 (L and % of predicted) and PEF (L/s) to evaluate lung function.	Increase ≥10% of FVC % predicted	FVC >80% considered normal. Systemic scleroma, change of 10% from baseline is a real change not measurement error; idiopathic pulmonary fibrosis MCID = 2-6% of predicted (3-9% relative change from baseline) reflected changes in global health status; Pompe disease reported global health changes at similar levels, though MCIDs were set higher (exact figure not reported in CS[2]).	No
Rates of infections	Adverse event	Not clear how AEs reported to clinical team (see clarification response A32).[11]	NR	NR	No
Mortality	Adverse event	No patients died during follow-up	NR	NR	NA
Quality of life	CHAQ disability index	Evaluation of QoL using CHAQ and EQ-5D (assessments were completed by parent/caregiver on behalf of patient, i.e. indirect measures only).	Decrease ≥0.13 on the 0-3 scale	MCID in Juvenile arthritis -0.13: 35.7% of adult patients in rhLAMAN-10[1] had arthralgia	Yes
	CHAQ pain		Decrease ≥0.246 on the 0-3 scale	MCID for Pain (VAS) ≥8.2% in juvenile arthritis (≥0.246 on the 0-3 scale)	Yes
	EQ-5D	NR	Increase NR	NR	No
Adverse events	NR	Not clear how AEs reported to clinical team (see clarification response A32).[11] Clinical team report directly to CRO within 24 hours	NA	NA	NA

MPS IVA; mucopolysaccharidosis IVA; MCID, minimal clinically important difference; VAS, visual analogue scale; CRO, clinical research organisation in charge of running trial; NR, not reported; CHAQ, childhood health assessment questionnaire; QoL, quality of life; CS, company submission; L, litres; 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; min, minutes; PTA, pure tone audiometry.

4.2.4 Critique of the design of rhLAMAN-05[10] and rhLAMAN-10[1]

4.2.4.1 Population

Impact of patient age on detection of effect: The clinical advisors to the ERG felt that the inclusion and exclusion criteria (see footnotes to Table 6) were acceptable but noted that the trial excluded very young patients (<5 years old) and older patients (>35 years old). This probably biased the cohort towards younger patients, and it is possible that it might have been easier to detect an effect in younger patients, as disease progression is more rapid.

Exclusion of severe disease and licence-indicated population: The exclusion of the very young (<5 years) will mean severe disease (which presents at a younger age) patients are excluded. The exclusion of patients who could not complete 3-MSCT or 6-MWT or could not mentally cooperate will also lead to the exclusion of patients with severe disease, and those with mobility problems at the higher end of the spectrum. As such, the spectrum is likely to comprise patients with mild to moderate disease, in accordance with the population proposed for reimbursement.

It should be noted that the anticipated licence will not restrict treatment by age, as the EMA recognises that early treatment could be beneficial. However, the company are not seeking reimbursement for patients under 6 years of age, and currently there is insufficient evidence in this group to judge the clinical effectiveness.

Generalisability concerns: The ERG asked for clarification about the exclusion criterion of "patients with IgE>800 IU/mL". The company clarified that this was to exclude patients who are at high risk of anaphylactic reactions "*or for whom the high background concentrations of immunoglobulin E (IgE) would make it difficult to clearly identify an increase due to a reaction to velmanase alfa.*" (response A15)[11] This reduces the generalisability of safety findings to patients with IgE>800 IU/mL.

Previous treatment: The ERG asked for clarification about why 3 months was chosen as an adequate time for patients who had been on previous IMP treatments (including velmanase alfa). The ERG was satisfied with the company's response, indicating that "*Given that most ERTs are given as weekly or bi-weekly infusions, a total of 12 weeks since the last infusion would ensure that a time significantly longer than 5 times the longest theoretical half-life would have elapsed, ensuring a complete drug wash out*." (response A14).[11]

4.2.4.2 Intervention

The intervention appears to match the proposed licenced posology and dose.

Start/stop criteria: The company described a set of start/stop criteria for continuation of treatment, which are reproduced in Appendix 1. There is uncertainty around the proposed criteria as a review by key opinion leaders in the UK is ongoing. (see clarification response A11).[11] However, the clinical advisors to the ERG felt that the criteria were largely sensible as treatment would be stopped for those with life-limiting conditions, those who cannot tolerate the treatment, those who cannot not comply with monitoring (either for practical reasons or due to worsening of disease) and those gaining no benefit after one year of treatment.

However, the clinical advisors to the ERG also suggested that advance brain disease might be an additional reason for stopping treatment, though the ERG further note that it is possible that this could result in non-compliance with monitoring, which is itself a stopping criterion.

The ERG asked how application of the stopping criteria to the patients in the evidence base might affect the results of rhLAMAN-05[10] and -10.[1] The company stated that results at 12 months would not be affected as the criteria are only applied at 12 months, but that some patients who continued treatment after 12 months may have met the stopping criteria. The company stated that the stopping criteria are likely to result in more favourable outcomes in the long term than those reported in the studies as patients with lower efficacy are excluded from treatment. However, an analysis excluding these patients was not provided. (Clarification response A13).[11]

Following the clarification response[11] (question B1) the manufacturer confirmed that patients who move into the severe immobility health state would continue to receive velmanase alfa treatment for one year to reflect "*that once a person moves into the severe immobility state, there will be a period where their health status in confirmed by their specialist consultant, and the decision is made in collaboration with the patient and their carer to withdraw active treatment.*" The company further confirmed that treatment with velmanase alfa would be withdrawn if a patient entered the short end stage.

4.2.4.3 Comparator

The placebo comparator in rhLAMAN-05[10] seemed appropriate for some of the patients, but the clinical advisors to the ERG, and the experts who submitted expert statements to NICE expressed a view that HSCT is potentially a valid comparator for a (small) proportion of these patients. Within their submission[2] and clarification response,[11] the company stated that the comparator HSCT is not valid as patients recruited to the trial must have been unsuitable for HSCT in order to be eligible. However, no further details to verify this statement were given (e.g. specific reasons for not giving HSCT to younger patients), and it is assumed that such decisions were made by the individual clinicians treating each patient. The studies largely comprise European patients, and it is unclear if HSCT practice in the European countries that were included in the trials were similar to UK practice. The ERG asked for

clarification on whether any of the patients would be eligible for HSCT according to usual UK practice, but the answer provided did not directly address this issue (clarification response A12).[11] As such, the ERG believes it remains unclear if any patients in the trial would have been deemed eligible for HSCT in clinical practice in England.

Use of HSCT in the UK now and in the future: The clinical advisors to the ERG expressed an opinion that HSCT should be considered more often as a treatment option in the UK as the safety of the procedure is much improved over recent years. One advisor who treats paediatric patients stated that in his clinical practice it is more of a decision not to conduct as HSCT, rather than a decision to conduct one. Both clinical advisors to the ERG agreed with the view expressed in the CS that patients under 5 are most likely to receive HSCT as these patients usually have severe disease.[2] However, their view was that as patients get older (≥5 years), the decision is based on a balance of risk from the procedure, expected benefit in terms of severity of disease, and the availability of a suitable donor (the same list of factors is also provided in the CS[2]). They believed there is no clear age cut-off which would preclude an HSCT. The views expressed in the Expert Statements provided to NICE,[26, 27] where clinicians stated that "*HSCT was not normally performed in those aged 5 years or over*" and "*is not usually performed in older patients*" which suggest that it is an option for a small proportion of patients.

Other data relating to HSCT efficacy: The clinical advisors to the ERG noted that data relating to the efficacy of HSCT in AM patients is likely to be very scarce. The company conducted such a review and found seven studies/case reports related to HSCT, the largest of which included 17 patients, and the remainder of which included 1-4 patients (see Appendix 2, CS).[2] The ERG asked for clarification about HSCT evidence in the UK. The company provided a table (reproduced here as Table 8) detailing three patients, and their current age and status. All received HSCT at age <6 years, and all had a current status of "walking unassisted". The cognitive and mental health of these patients was not provided, however, whereas in the wider literature measurement of cognitive function was a key outcome of HSCT trials.

The company further provided information from their systematic review, relating to patients aged ≥6 years (from any country), and these can be found in Appendix 2 of the CS,[2] Tables 123-125. In summary, HSCT was successfully performed in several patients over 6 years of age (contrary to the company's view that HSCT would not be performed in patients of this age) with reports of improved symptomatology (including cognitive), though no RCT evidence was available and follow-up was sometimes short. The ERG has not conducted a full critique of this evidence.

Table 8: Reproduction of Table 2 from the clarification response:[11] UK MPS Society Survey patients in receipt of allogeneic HSCT for AM

MPS Survey patient code	Current age (years)†	Age at diagnosis (years, months)‡	Weight (kg)‡	Walking ability‡	Age at receipt of allogeneic HSCT§
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AM, alpha-mannosidosis; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; UK, United Kingdom.
†At time of survey completion; ‡Responses taken from phase 3 of the survey responses, as they are the most up to date data; §Treatment described as bone marrow transplant in survey responses
Source: Data on file: UK MPS Society patient and carer survey, 2018.[28]

No comparator arm in rhLAMAN-10[1]: Comparisons to baseline in rhLAMAN-10[1] are subject to common drawbacks of single-arm observational studies:

- Regression to the mean: It is possible that patients experience temporary worsening in some of the outcomes measured in the trials due to infections. For example, infections can lead to worsening in pulmonary function tests. If these were present at baseline, subsequent improvements may in part or in totality represent an improvement in these temporary conditions (regression to the mean).
- Placebo effect: The increased number of hospital visits can have a positive effect on wellbeing and general monitoring of health; the hope generated by being on an active treatment may have a strong placebo effect.
- Lack of a comparator arm means it is unclear how patients would have fared without a placebo control, and therefore what the efficacy of the treatment is. This is especially true where the disease is progressive, as is the case for AM.
- Concomitant symptom relief treatments: whilst there are no disease-modifying treatments currently available other than HSCT, patients can start concomitant treatments for symptomatic relief. The clinical advisors to the ERG noted that the introduction of inhaled steroids, which often occurs at some point in management, might improve lung function.
- Training effects: clinical advisors to the ERG indicated that the 3-MSCT, 6-MWT and pulmonary function tests are all subject to patients improving with subsequent tests, as they get used to the expectations of the test.

4.2.4.4 Outcomes

Omission of outcomes relevant to the disease: As stated in Section 3.4, the clinical advisors to the ERG were surprised that infections were not included as a key outcome, as these are a major contributor to mortality and morbidity. This was also an outcome listed in the NICE scope.[9] The clinicians were further surprised that psychiatric problems such as acute psychosis were missing as this is also a problem for many patients. The NICE scope[9] listed language as an outcome, but this was not measured in any trial.

Clinical relevance of serum oligosaccharides: Whilst serum oligosaccharides may have pharmacokinetic relevance, its use as a primary outcome was seen as highly problematic by the clinical advisors to the ERG for a number of reasons:

- The link between oligosaccharide levels and clinical outcomes is poor from a clinical perspective.
- There was no formal assessment of whether oligosaccharide levels were surrogate for clinical outcomes using standard criteria.[29] Correlations between last observation values for serum oligosaccharides and 3-MSCT, 6-MWT and FVC% predicted within rhLAMAN-10[1] were all negligible or marginal (see question A20 in the clarification response[11]). These data were not reported for rhLAMAN-05.[10]
- Serum oligosaccharides are not currently measured in UK practice, and this would have to be implemented as a test on the NHS if it is to be used to monitor response to treatment.
- The cut off of 4µmol/L is arbitrary and has no clinical meaning.

Age matching for outcomes where childhood growth leads to improvement: In cases where outcomes are likely to increase as age increases (e.g. 6-MWT, cognition, motor skills, lung function), age-normalised reference values are usually used. This allows any deterioration due to disease to be observed (in the absence of a control arm) even though such outcomes may improve overall due to growth. The ERG noted that some outcomes were age matched, including lung function, BOT-2 and the Leiter-R test, but that the 3-MSCT and the 6-MWT were not age-matched in the primary analysis.

In their clarification response (response A28),[11] the company explained that there are no reference values for the 3-MSCT and that "*it is of general understanding that the 3-MSCT is less impacted by growth in the scholar age and by the adolescence height burst given that leg length is not a major contributor to staircase climbing performance*" (response A28).[11] They also highlighted baseline data for <18 years and ≥18 years (54 steps/min and 53 steps/min respectively), provided a scatterplot showing the distribution of steps/min by age from rhLAMAN-10[1] baseline data (see Figure 2), and argued that in AM, there is no adolescent growth spurt which might explain there being no noticeable

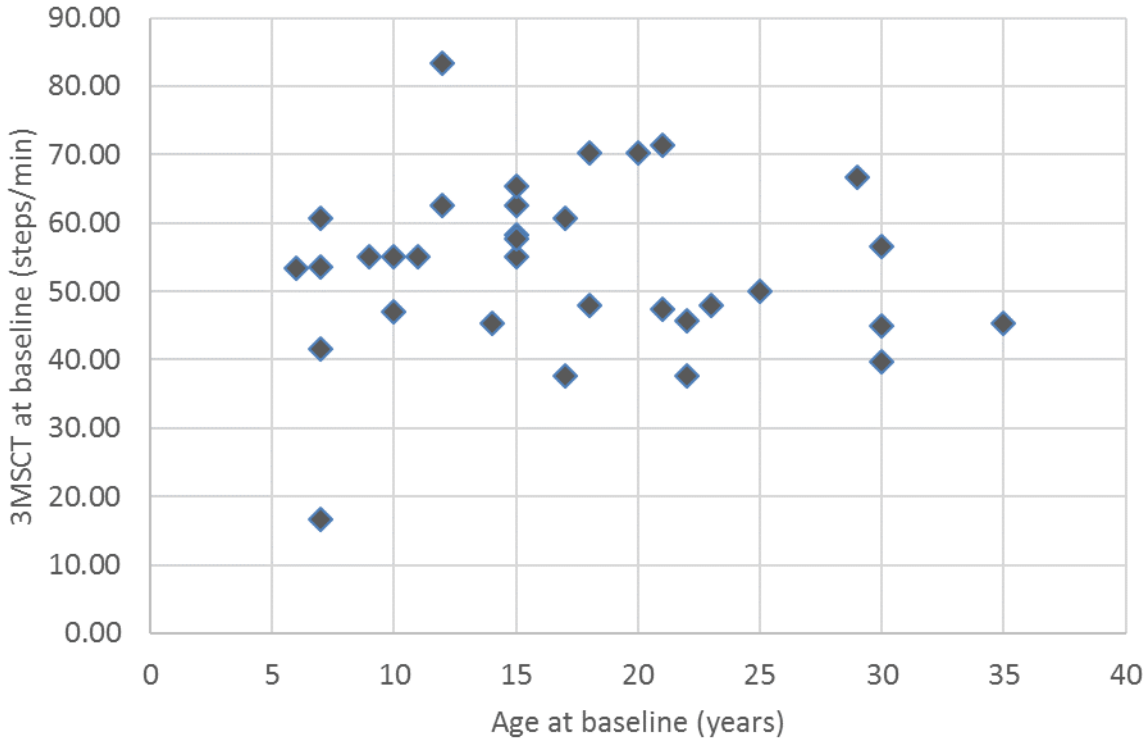
difference between age groups. The ERG note that it was not clear from the clarification response whether a formal assessment of the relationship between 3-MSCT and age was conducted, so it is not possible for the ERG to conclude whether there was, or was not, a correlation.

There are reference values (for age, height and gender) for the 6-MWT, and exploratory analyses using these in rhLAMAN-10[1] were provided in part in the original submission, and in some more detail for data at 12 months and the last observation time in the clarification response A28,[11] and are presented in the results section of this report (Section 4.2.6). The age, height and gender normalised values were generally less favourable than the original non-normalised analysis.

Use of CHAQ in adults: The ERG had initial concerns about the use of CHAQ in adult patients; however, our clinical advisors thought this was appropriate. They explained that CHAQ is filled in by guardians with some questions directed at the patient.

MCIDs and multi domain responder analysis: A critique of the MCIDs and multi domain responder analysis is provided in Section 4.2.7.

Figure 2: Reproduction of Figure 3 from CS: Scatterplot of individual 3-MSCT (Steps/min) and age (years) in rhLAMAN-10[1] at baseline



Source: rhLAMAN-10[1] listings

4.2.5 Description of the analysis of rhLAMAN-05[10] and rhLAMAN-10[1]

4.2.5.1 Analysis of rhLAMAN-05[10]

The statistical plan for rhLAMAN-05[10] is reproduced from Table 12 of the CS,[2] as Table 10 in this report. Follow-up was for 12 months. The co-primary endpoints were serum oligosaccharides and the 3-MWT. The prioritised secondary outcomes were 6-MWT and FVC. The other secondary outcomes were: PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; EQ-5D. Primary outcomes were assessed as the relative change from baseline to month 12. Details of the statistical plan are provided in Table 12 of the CS,[2] and in brief comprised an analysis of covariance (ANCOVA) of log-transformed data. The absolute change from baseline to month 12, the log-transformed relative change from baseline to month 6 and the absolute change from baseline to month 6 were also assessed for these endpoints. Demonstration of efficacy was defined as a statistically significant improvement in both primary outcomes at 6 months, or in serum oligosaccharides with a trend for improvement in the 3-MWT and one prioritised secondary outcome at 12 months. Multiple imputation methods were applied in case of missing data.

Twenty-five patients were recruited but no formal sample size was calculated; the CS[2] states that the number represents a compromise between the total number of patients available who could meet the inclusion criteria and the number required for efficacy assessment.

The company reported a post-hoc analysis of patients aged <18 vs ≥18 years at start of treatment.

4.2.5.2 Analysis of rhLAMAN-10[1]

The statistical plan for rhLAMAN-10[1] is reproduced from Table 13 of the CS,[2] as Table 10 in this report. Data comprises a database of follow-up data from rhLAMAN-07 and -09 (which comprised solely patients from rhLAMAN-04[14] and -05[10] and included long term treatment and follow-up over an unspecified number of years, but probably until treatment becomes available in that jurisdiction) and new data collected from patients who received treatment after rhLAMAN-04[14] and -05[10] on a compassionate use programme (see Table 10 for details of the comprehensive evaluation visit (CEV)).

Absolute and relative change from baseline to each time point were estimated and analysed using paired t-tests, but no sample size calculation was conducted and no data were imputed. Missing values were included in the denominator count when calculating percentages, but only non-missing values were included in analyses of continuous data.

The co-primary outcomes were serum oligosaccharides and the 3-MWT. The secondary outcomes were: 6-MWT; PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; and EQ-5D. Primary outcomes were assessed as the relative change from baseline. The date of the first dose

and the date of the assessment were used to calculate how many days of treatment had elapsed, with the assessment assigned to the nearest designated time point, e.g. 6 months is 183 days, thus any assessment between 1-274 days were assigned to the 6-month time point.

The company provided a table outlining how many patients were available for assessment at each time point. The ERG were not sure if this was the same as the number of patients eligible for assessment at each time point (e.g. did some patients miss assessments), and were further unclear why there were 3 patients at 36 months from the Phase I/II trials and 9 at 48 months; this might be because some patients having been on treatment without assessment (in the compassionate use programme) for 48 months, meaning there was no 36-month data for these patients. The table is reproduced here as Table 9.

Table 9: Number of patients with available data per time point – overall, Phase I/II and rhLAMAN-05[10] (reproduction of Table 14 from the CS)

Study contribution, n (% of total rhLAMAN-10[1])	Total N=33						
	Baseline	Month 6	Month 12	Month 18	Month 24	Month 36	Month 48
rhLAMAN-10[1]	33 (100.0)	24 (72.7)	31 (93.9)	11 (33.3)	10 (30.3)	7 (21.2)	9 (27.3)
Parental study contribution, n (% of total rhLAMAN-10[1])							
Phase I/II‡	9 (27.3)	9 (27.3)	9 (27.3)	9 (27.3)	0	3 (9.1)	9 (27.3)
rhLAMAN-05[10]							
Active	15 (45.5)	15 (45.5)	15 (45.5)	0	10 (30.3)	4 (12.1)	N/A
Placebo→Active	9 (27.3)†	0	7 (21.2)	2 (6.0)	N/A	N/A	N/A

Key: blue cells indicate data derived from rhLAMAN-07 and 09 (baseline to CEV), or rhLAMAN-10[1] data collection.
Abbreviations: N/A, time point not available; VA, velmanase alfa.
†Although 10 patients were included in the rhLAMAN-05[10] placebo group, patient 502 discontinued VA treatment shortly after starting the compassionate use programme. As this patient had no data collected during the active treatment, the patient was excluded from all analyses.
‡Phase I/II trial comprised rhLAMAN-02[13]/03[13]/04.[14]

Pre-planned subgroup analyses included:

- Age group (<18 years vs ≥18 years); this classification is the age of patients at the time of starting treatment
- Parental study (Phase I/II vs rhLAMAN-05[10])
- Anti-drug antibody (ADA) status (positive or negative) for the following outcomes: CSF oligosaccharides, 6-MWT, 3-MSCT and serum IgG
- Patient status analysis: A patient status analysis was also performed for 6-MWT, FVC (% of predicted), FEV1 (% of predicted), CSF oligosaccharides, serum IgG, PTA and CHAQ disability index, where patients were categorised as not impaired/slightly impaired; impaired; seriously impaired. Cut points for this analysis are provided in Appendix 3, and the outcomes listed in Table 7.

Post hoc analyses included:

- *Multi-domain responder analysis,* because AM affects multiple organ systems. Endpoints were classified into one of three domains: Pharmacodynamic: serum oligosaccharide response; Functional: 3-MSCT, 6-MWT and FVC (% of predicted) (FVC is included within the functional domain as muscular effort is required); and quality of life: CHAQ disability index and CHAQ pain (VAS). A patient was classified as a responder in a domain if the MCID was achieved in any one of the component parts. A patient was classified as a responder to treatment if they responded in two domains.

- *analysis of patients according to age* (6-11 years; 12-17 years; ≥18 years)

Table 10: The statistical plans for rhLAMAN-05[10] and rhLAMAN-10[1], reproduced from Tables 12 and 13 of the CS

	rhLAMAN-05[10]	rhLAMAN-10[1]
Duration of follow-up, lost to follow-up information	Patients were followed for 12 months until study end, at which patients were invited to enrol in an after-trial study (rhLAMAN-07 or rhLAMAN-09) or the compassionate use programme. Patients who were receiving placebo in rhLAMAN-05[10] could initiate treatment with VA.	rhLAMAN-10[1] data collection – a one-week assessment visit (the CEV) for patients in the compassionate use programme. • Patients enrolled in the compassionate use programme were not assessed for efficacy. Therefore, patients were invited to enrol in rhLAMAN-10[1] and undergo a CEV, to obtain long-term efficacy data for these patients. • Patients attended a screening visit (Visit 0) on Day 1, at which eligibility was checked and informed consent was signed. After consent was obtained, patients attended the CEV (also on Day 1), at which they underwent pre-infusion evaluations, and then received their infusion of VA. This infusion was the weekly infusion for that week as part of the compassionate use programme. Further evaluations were then carried out over Days 1–6 (Visit 1). Visit 3 (final visit) was held on Day 6 after the evaluations had been completed and before the patient left the trial site. rhLAMAN-10[1] integrated data set analysis • As patients enrolled in rhLAMAN-07 and -09 were subject to annual efficacy evaluations as part of the trial protocol, they were not enrolled in the rhLAMAN-10[1] data collection (as defined by the exclusion criteria). In order to obtain long-term follow-up data, rhLAMAN 07 and 09 were amended to include a CEV. • CEV data from rhLAMAN-07, rhLAMAN-9 and the rhLAMAN-10[1] data collection were pooled and analysed with data from rhLAMAN-02[13], rhLAMAN-03[15], rhLAMAN-04[14], rhLAMAN-05[10], and pre-CEV rhLAMAN-07 and 09 data points. For the integrated data set, details on how the data were aligned to the designated efficacy time points is discussed below this table.

Statistical tests	No formal sample size calculation was performed for this trial. The total of 25 patients represents a compromise between availability of patients who can fulfil the admission criteria and the minimum amount of data that can support an assessment of efficacy and safety of the treatment regimen. The primary analysis of the co-primary endpoints (serum oligosaccharides and 3-MSCT) and prioritised secondary endpoints (FVC [% of predicted] and 6-MWT) was performed on the relative change from baseline to Month 12. Data were log-transformed and then submitted to an ANCOVA with treatment as a fixed factor and corresponding baseline values and age as continuous covariates. The adjusted means in each treatment group, the adjusted mean difference between VA and placebo, their 95% CIs and associated p-values were estimated by the model; however, as no sample size was calculated, p-values should be treated with caution. The absolute change from baseline to Month 12, log-transformed relative change from baseline to Month 6 and absolute change from baseline to Month 6 were also assessed for these endpoints. For primary endpoints, demonstration of efficacy was defined as: • a statistically significant improvement in the two primary endpoints (at significance levels of 0.025 [serum oligosaccharides] and 0.05 [3-MSCT]) at the interim analysis (Month 6), or; • a statistically significant reduction in serum oligosaccharides (at a significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis For the ANCOVA models used in the primary and secondary endpoints, in case of missing data a multiple imputation method was applied before performing the analysis. This approach assumes that measures for withdrawn patients follow the pattern of patients who remained in the study. Imputation was performed by PROC multiple imputation using the Markov Chain Monte Carlo approach by treatment. Each record included baseline, Month 6, Month 12 and the	For each outcome, the absolute and relative changes from baseline to each time point were estimated and analysed using the paired t-test and presented with their p-value and 95% CI; however, as no sample size was calculated, p-values should be treated with caution. Unless otherwise specified, baseline values were defined as the last non-missing value before the first dose of VA (derived from parental Phase I/II and rhLAMAN-05[10] studies). For patients in rhLAMAN-05[10] who were randomised to placebo, the baseline for all scheduled evaluations was the last non-missing value recorded in rhLAMAN-05.[10] Unless otherwise specified, last observation values were defined as the last available value at the end of rhLAMAN trials (derived from the last trial the patient participated in). As such, last observation values presented comprise a range of follow-up times. As the rhLAMAN-07 and rhLAMAN-09 trials were ongoing at the time of the rhLAMAN-10[1] integrated data set, the cut-off date was defined as "the end date of the CEV in rhLAMAN-07, rhLAMAN-09 and rhLAMAN-10".[1] Missing data was not imputed. Unless otherwise specified, missing values were included in the denominator count when computing percentages. When continuous data were summarised, only non-missing values were evaluated for computing summary statistics

	baseline age. One thousand imputations were created and the imputed data sets were then analysed with PROC MIANALYSE.	
Primary outcomes (including scoring methods and timings of assessments)	The co-primary endpoints for rhLAMAN-05[10] were: • Change from baseline to Month 12 in serum oligosaccharides • Change from baseline to Month 12 in the 3-MSCT	The co-primary endpoints for rhLAMAN-10[1] were: • Change from baseline in serum oligosaccharides • Change from baseline in the 3-MSCT
Secondary outcomes (including scoring methods and timings of assessments)	The prioritised secondary endpoints for rhLAMAN-05[10] were: • Change from baseline to Month 12 in 6-MWT • Change from baseline to Month 12 in FVC as a percentage of predicted normal value Additional secondary efficacy endpoints for rhLAMAN-05[10] were: • Change from baseline to other visits in PFTs (FEV_1 [L], FEV_1 [% of predicted value], FVC [L] and PEF [L/s]) • Change from baseline to other visits in BOT-2 (total score and domain scores) • Change from baseline to other visits in the Leiter-R • Change from baseline to other visits in CSF oligosaccharides and CSF biomarkers (tau, NFLp and GFAp) • Change from baseline to other visits in PTA (air conduction left and right ear and bone conduction for the best ear) • Change from baseline to other visits in CHAQ and EQ-5D (total score and domain scores)	• Change from baseline in the 6-MWT (metres and % of predicted) • Change from baseline in PFTs (FEV_1 [L], FEV_1 [% of predicted value], FVC [L], FVC [% of predicted value], and PEF [L/s]) • Change from baseline in BOT-2 (total score and domain scores) • Change from baseline in the Leiter-R • Change from baseline in CSF oligosaccharides and CSF biomarkers (tau, NFLp and GFAp) • Change from baseline in PTA (air conduction left and right ear and bone conduction for the best ear) • Change from baseline in CHAQ and EQ-5D (total score and domain scores)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; ANCOVA, analysis of covariance; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GFAp, glial fibrillary acidic protein; NFLp, neurofilament protein; PEF, peak expiratory flow; PTA, pure tone audiometry; VA, velmanase alfa.

4.2.6 Description of the results of rhLAMAN-05[10] and rhLAMAN-10[1]

The Tables presenting baseline characteristics for each trial are reproduced from the CS in Appendix 4.

The results for rhLAMAN-05[10] are presented in

Table 11 and from rhLAMAN-10[1] in

Table 12.

4.2.6.1 Pre-planned analyses

Serum Oligosaccharides – co-primary endpoint

rhLAMAN-05[10] demonstrated a statistically significant decrease in serum Oligosaccharides at 12 months when considering adjusted mean difference in relative change (−70.47 (95% CI −78.35, −59.72), p<0.001) and adjusted mean difference in absolute change (-3.50 (95% CI: -4.37; -2.62), p< 0.001). Results were also statistically significant at 6 months, Table 11 provides further data including absolute values. The ERG notes that the mean absolute value for the velmanase alfa group was below the (arbitrarily chosen) 4µmol/L MCID cut off but was not for the placebo group.

rhLAMAN-10[1] demonstrated a statistically significant decrease in serum oligosaccharides compared to baseline values at all-time points except 36 months where there was a very low number of patients (n=3) with no imputation conducted.

Table 12 provides further data including absolute values. The ERG notes that the mean absolute value for the velmanase alfa group at last observation was below the 4µmol/L MCID cut off.

Pre-planned subgroup analyses in rhLAMAN-10[1]: The CS reports "*treatment with velmanase alfa resulted in an improvement in patient status; only 9.1% were considered to be seriously impaired for serum oligosaccharides at last observation, compared with 81.8% at baseline Appendix 7 (Section 17.7.2.3). When the ADA status of patients was taken into account, both ADA positive and negative patients experienced a reduction in serum oligosaccharides from baseline to last observation (Appendix 7, Section 17.7.2.4).*" (p140 of the CS).[2]

The relative mean (SD) change from baseline to last observation was similar in both age groups: -66.6% (36.1%) for patients aged <18 years and –57.6% (30.5%) for patients aged ≥18 years. The absolute mean (SD) changes from baseline were –5.26 µmol/L (3.74 µmol/L) and –3.68 µmol/L (2.20 µmol/L), respectively. The clarification response to A36 states that a post-hoc analysis indicated there was no interaction between time and age.[11]

3-MSCT - co-primary endpoint

rhLAMAN-05[10] did not demonstrate a statistically significant difference in 3-MSCT at 6 or 12 months (adjusted mean difference in relative change 3.01% (−9.86, 17.72), p=0.648; adjusted mean difference in absolute change 2.62 steps/minute (95% CI: -3.81, 9.05), p=0.406 both at 12 months). See .

Table 11 for further data including absolute values. To reach the study definition of efficacy, a trend for improvement in 3-MSCT and in one of the two prioritised secondary endpoints was required. The CS interprets the results as a trend towards improvement.[2] The ERG notes that whilst the observed difference favoured velmanase alfa, the mean difference in absolute change from baseline of 2.62 step/minute at 12 months was small (baseline mean: 54 metres), and below the MCID of ≥7 steps/min.

Table 11: Key clinical results from rhLAMAN-05[10]

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
Serum oligosaccharides(µmol/L unless stated otherwise)						
Actual value (SD)	6.8 (1.2)	6.6 (1.9)	2.4 (1.0)	6.2 (1.8)	1.6 (0.8)	5.1 (1.4)
Absolute change from baseline (SD)			-4.3 (1.4)	-0.4 (2.2)	-5.1 (1.2)	-1.6 (1.7)
Relative (%) change from baseline (SD)			-63.6 (14.5)	-1.6 (32.2)	-75.8 (11.2)	-20.3 (24.0)

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
Adjusted mean relative change (95% CI)			-65.85 (-72.05, -58.28)	-7.88 (-27.94, 17.77)	−77.60 (−81.58, −72.76)	−24.14 (−40.31, −3.59)
Adjusted mean difference in relative change (95% CI)			-62.93 (-73.03, -49.06**), p<0.001**		−70.47 (−78.35, −59.72), **p<0.001**	
Adjusted mean absolute change (95% CI)			-4.30 (-5.04, -3.55)	-0.47 (-1.38, 0.45)	-5.11 (-5.66, -4.56)	-1.61 (-2.28, -0.94)
Adjusted mean difference in absolute change (95%CI)			-3.83 (-5.01, -2.65), **p<0.001**		-3.50 (95% CI: -4.37; -2.62), **p< 0.001**	
3-MSCT (steps/min unless stated otherwise)						
Actual value (SD)	52.9 (11.2)	55.5 (16.0)	52.9 (13.8)	53.8 (17.2)	53.5 (15.7)	53.1 (15.6)
Absolute change from baseline (SD)			0.0 (5.3)	-1.7 (5.3)	0.6 (8.6)	-2.4 (5.5)
Relative (%) change from baseline (SD)			-0.5 (9.7)	-2.9 (12.9)	0.5 (16.1)	-3.6 (13.1)
Adjusted mean relative change (95% CI)			0.93 (-7.17, 5.72)	-3.78 (-11.15, 4.19)	−1.07 (−9.05, 7.61)	−3.97 (−13.38, 6.47)
Adjusted mean difference in relative change (95% CI)			2.96 (-7.12, 14.14), p=0.562		3.01 (−9.86, 17.72), p=0.648	
Adjusted mean absolute change (95%CI)			0.11 (-2.79, 3.01)	-1.86 (-5.42, 1.70)	0.46 (95% CI: -3.58, 4.50)	-2.16 (95% CI: -7.12, 2.80)
Adjusted mean difference in absolute change (95%CI)			1.97 (-2.64, 6.59), p=0.384		2.62 (95% CI: -3.81, 9.05), p=0.406	
6-MWT (meters unless stated otherwise)						
Actual value (SD)	459.6 (72.26)	465.7 (140.5)	464.3 (82.68)	466.4 (126.2)	464.0 (82.51)	461.1 (138.7)
Absolute change from baseline (SD)			4.67 (42.80)	0.70 (37.56)	4.40 (46.12)	-4.60 (40.79)
Relative (%) change from baseline (SD)			1.08 (9.65)	1.65 (9.16)	1.17 (9.78)	-0.82 (10.80)
Adjusted mean relative change (95% CI)			0.62 (-4.15, 5.63)	1.29 (-4.56, 7.50)	0.64 (−4.74, 6.32)	−1.20 (−7.63, 5.68)
Adjusted mean difference in			-0.66 (-8.01, 7.28), p=0.860		1.86 (−6.63, 11.12), p=0.664	

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
relative change (95% CI)						
Adjusted mean absolute change (95%CI)			3.79 (-17.52, 25.09)	2.02 (-24.09, 28.13)	3.74 (-20.32, 27.80)	-3.61 (-33.10, 25.87)
Adjusted mean difference in absolute change (95%CI)			1.77 (-31.98, 35.52), p=0.914		7.35 (95% CI: -30.76; 45.46), p=0.692	
FVC% predicted normal value						
Actual value (SD)	81.67 (20.66, n=12)	90.44 (10.39, n=9)	90.38 (18.43, n=13)	91.00 (14.12, n=8)	91.36 (21.80, n=14)	92.44 (18.15, n=9)
Absolute change from baseline (SD)			5.82 (9.56, n=11)	-0.63 (5.50, n=8)	8.17 (9.85, n=12)	2.00 (12.61, n=9)
Relative (%) change from baseline (SD)			9.15 (13.93, n=11)	-1.04 (6.41, n=8)	11.37 (13.13, n=12)	1.92 (15.40, n=9)
Adjusted mean relative change (95% CI)			8.05 (0.3, 16.38)	-2.93 (-14.42, 10.12)	10.11 (1.31, 19.67)	1.58 (−9.48, 13.99)
Adjusted mean difference in relative change (95% CI)			11.30 (-4.10, 29.19), p=0.159		8.40 (−6.06, 25.08), p=0.269	
Adjusted mean absolute change (95%CI)			5.97 (0.11, 11.84)	-2.73 (-11.94, 6.49)	8.21 (1.79, 14.63)	2.30 (-6.19, 10.79)
Adjusted mean difference in absolute change (95%CI)			8.70 (-2.39, 19.78), p=0.124		5.91 (95% CI: -4.78; 16.60),p=0.278	
CHAQ disability						
Actual value (SD)	1.37 (0.82)	1.59 (0.64)	1.31 (0.72)	1.75 (0.53)	1.36 (0.76)	1.76 (0.50)
Absolute change from baseline (SD)			-0.06 (0.38)	0.16 (0.41)	-0.01 (0.32)	0.18 (0.36)
CHAQ pain (VAS)						
Actual value (SD)	0.84 (0.86, n=14)	0.40 (0.56, n=9)	1.00 (0.91)	0.63 (0.76)	0.97 (1.02)	0.50 (0.62)
Absolute change from baseline (SD)			0.20 (0.79, n=14)	0.30 (0.80, n=9)	0.19 (0.69, n=14)	0.15 (0.71, n=9)
EQ-5D-5L index score						
Actual value (SD)	0.61 (0.19)	0.61 (0.18, n=8)	0.66 (0.15, n=14)	0.64 (0.16)	0.64 (0.18, n=14)	0.62 (0.15)

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
Absolute change from baseline (SD)			0.06 (0.12, n=14)	0.04 (0.09, n=8)	0.04 (0.09, n=14)	0.03 (0.16, n=8)
EQ-5D-5L VAS						
Actual value (SD)	66.07 (20.68, n=14)	64.00 (12.87)	71.67 (16.30)	67.00 (13.98)	68.20 (17.34)	67.70 (16.62)
Absolute change from baseline (SD)			5.71 (16.94, n=14)	3.00 (15.85)	2.00 (17.95, n=14)	3.70 (15.71)
BOT2 – motor function						
Actual value (SD)	94.93 (41.68)	109.2 (51.84)	95.13 (38.02)	108.7 (50.02)	101.3 (38.56)	113.4 (50.75, n=9)
Absolute change from baseline (SD)			0.20 (12.80)	-0.50 (12.26)	6.40 (13.38)	-0.33 (9.59, n=9) (as reported)
Relative (%) change from baseline (SD)			2.30 (20.27)	7.98 (33.52)	12.30 (20.55)	3.53 (14.23, n=9)
Adjusted mean relative change (95% CI)					9.99 (3.89, 16.45)	3.73 (–3.39, 11.37)
Adjusted mean difference in relative change (95% CI)					6.04 (–3.21, 16.17), p=0.208	
Leiter R- cognition TEA-VR (years)						
Actual value (SD)	5.73 (1.74)	6.06 (1.61)	5.72 (1.45)	6.16 (1.49)	5.91 (1.45)	6.22 (1.53)
Absolute change from baseline (SD)			-0.01 (0.67)	0.10 (0.52)	0.17 (0.71)	0.16 (0.65)
Relative (%) change from baseline (SD)			1.73 (12.24) 6.16 (	2.10 (8.54)	5.59 (13.66)	3.32 (8.22)
Adjusted mean relative change (95% CI)					4.18 (–0.93, 9.56)	3.89 (–2.33, 10.51)
Adjusted mean difference in relative change (95% CI)					0.28 (–7.43, 8.62), p=0.943	
Leiter R- cognition TEA-AME (years)						
Actual value (SD)	6.30 (2.56)	6.63 (1.80)	6.40 (2.42)	6.91 (2.28)	6.32 (2.12)	6.74 (1.38)
Absolute change from baseline (SD)			0.10 (1.33)	0.27 (0.62)	0.02 (1.41)	0.11 (1.02)
Relative (%) change from baseline (SD)			5.22 (22.13)	2.48 (11.35)	5.63 (23.01)	3.82 (14.61)
Adjusted mean relative change (95% CI)					2.10 (–6.61, 11.62)	4.64 (–6.20, 16.74)
Adjusted mean difference in					–2.43 (–15.33, 12.43), p=0.722	

Analysis	baseline		26 weeks		52 weeks	
	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*	VA (n=15)*	Placebo (n=10)*
relative change (95% CI)						
PTA – hearing best ear						
Actual value (SD)	54.45 (11.35, n=14)	51.77 (11.01)	57.66 (10.09, n=14)	51.06 (13.77)	56.35 (8.94)	51.90 (14.25)
Absolute change from baseline (SD)			3.21 (3.49, n=14)	-0.71 (5.46)	2.36 (5.21, n=14)	0.13 (5.89)
Relative (%) change from baseline (SD)			7.09 (9.19, n=14)	-2.30 (11.52)	6.22 (13.71, n=14)	-0.68 (10.83)
Adjusted mean relative change (95% CI)					6.31 (0.16, 12.83)	–1.94 (-8.62, 5.24)
Adjusted mean difference in relative change (95% CI)					8.40 (–1.17, 18.90), p=0.087	
PTA – hearing left ear						
Actual value (SD)	64.81 (16.13)	60.02 (18.52)	65.41 (13.90)	58.93 (20.69)	65.77 (13.22)	60.78 (16.44)
Absolute change from baseline (SD)			0.59 (7.08)	-1.09 (10.74)	0.95 (8.03)	0.76 (7.83)
Relative (%) change from baseline (SD)			2.43 (11.82)	-1.33 (18.39)	3.29 (14.26)	2.95 (16.51)
Adjusted mean relative change (95% CI)					3.44 (–3.70, 11.10)	0.34 (–8.10, 9.56)
Adjusted mean difference in relative change (95% CI)					3.09 (–8.05, 15.57), p=0.583	
PTA – hearing right ear						
Actual value (SD)	65.33 (16.41)	60.78 (16.59)	66.41 (15.13)	59.34 (21.00)	67.27 (17.17)	58.89 (18.28)
Absolute change from baseline (SD)			1.08 (9.05)	-1.44 (10.61)	1.94 (11.34)	-1.89 (8.99)
Relative (%) change from baseline (SD)			3.68 (15.73)	-2.81 (17.47)	4.85 (17.38)	-2.78 (14.58)
Adjusted mean relative change (95% CI)					4.42 (–4.47, 14.12)	-5.20 (–15.01, 5.74)
Adjusted mean difference in relative change (95% CI)					10.15 (–4.42, 26.93), p=0.171	

3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; AME, attention and memory; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CI, confidence interval;; EQ-5D, EuroQol five-dimension questionnaire; FVC, forced vital capacity; PTA, pure tone audiometry; SD, standard deviation; TEA, total equivalence age; VA, velmanase alfa; VAS, visual analogue scale; VR, visualisation and reasoning

* n=15 for VA and n=10 for placebo at all time points unless indicated otherwise.

Table 12: Key clinical results from rhLAMAN-10[1]

Analysis	Baseline (n=33)		6 months (n=24)		12 months (n=31)		18 months (n=11)		24 months (n=10)		36 months (n=7)		48 months (n=9)		Last observation (n=33)	
		n		n		n		n		n		n		n		n
Serum Oligosaccharides (µmol/L)																
Actual value (SD)	6.90 (2.30)	33	2.60 (0.97)	24	1.61 (1.12)	31	1.59 (1.56)	11	1.45 (0.57)	10	6.20 (5.46)	3	1.57 (0.90)	9	2.31 (2.19)	33
Absolute change from baseline (SD)			-5.01 (2.33) p<0.001		-5.41 (2.87) **p<0.001**		-6.67 (3.83) **p<0.001**		-5.12 (1.12) **p<0.001**		-0.40 (4.19) p=0.884		-7.43 (2.81), **p<0.001**		-4.59 (3.23) , **p<0.001**	
Relative (%) change from baseline (SD)			-64.1 (14.86) **p<0.001**		-72.7 (23.53**) p<0.001**		-76.0 (31.21) **p<0.001**		-77.7 (9.29) **p<0.001**		-13.6 (59.19) p=0.729		-81.8 (11.65), **p<0.001**		-62.8 (33.61) **, p<0.001**	
3-MSCT																
Actual value (SD)	53.60 (12.53)	33	56.56 (14.48)	24	58.48 (14.85)	31	62.58 (17.03)	11	57.33 (18.22)	10	60.67 (18.95)	6	69.70 (15.14)	9	59.98 (16.29)	33
Absolute change from baseline (SD)			3.736 (7.887), p=0.030		4.247 (8.573), p=0.10		11.58 (9.471), p=0.002		1.900 (9.300), p=0.534		11.61 (9.296), p=0.028		17.07 (9.929), **p<0.001**		6.384 (10.54), p=0.001	
Relative (%) change from baseline (SD)			8.315 (18.32), p=0.036		9.317 (19.57), p=0.013		24.48 (18.76), p=0.001		2.487 (16.84), p=0.651		30.88 (32.72), p=0.069		39.11 (31.31), =0.006		13.77 (25.83), p=0.004	
6-MWT																
Actual value (SD)	466.6 (90.1)	33	474.6 (84.1)	24	492.4 (83.7)	31	499.9 (95.6)	11	486.6 (90.7)	10	471.2 (83.5)	6	522.6 (77.1)	9	489.0 (85.7)	33
Absolute change from baseline (SD)			17.6 (62.7), p=0.183		21.9 (65.2), p=0.071		55.5 (66.3), p=0.020		5.0 (58.5), p=0.793		59.3 (85.9), p0.151		69.7 (81.1), p=0.033		22.4 (63.2), p=0.050	
Relative (%)			6.1 (21.1), p=0.169		7.3 (23.3), p=0.090		16.4 (25.7), p=0.061		1.2 (12.3), p=0.766		24.4 (46.1), p=0.252		22.5		7.1 (22.0), p=0.071	

change from baseline (SD)													(35.8), p=0.096			
6-MWT (% predicted for age, height and gender)																
Actual value (SD)	69.04 (11.65)	33	NR		71.8 (10.26)	31	NR		NR		NR		NR		70.20	33
Absolute change from baseline (SD)			NR		2.37 (9.98), p=0.196		NR		NR		NR		NR		1.16 (9.29), p=0.478	
Relative (%) change from baseline (SD)			NR		5.87 (22.14), p=0.150		NR		NR		NR		NR		3.55 (18.30), p=0.273	
FVC % predicted																
Actual value (SD)	84.9(18.6)	29	87.1(18.6)	22	93.2(20.8)	30	84.8(23.6)	8	106.1(18.0)	8	78.8(22.0)	6	98.3(12.4)	7	93.121.7)	31
Absolute change from baseline (SD)			3.5(14.7), p=0.304	20	6.6(12.8, p=0.011	28	4.4(13.9), p=0.403		16.1(14.8), p=0.028	7	5.6(10.3), p=0.243		13.7(19.6), p=0.114		8.1(14.8), p=0.007	29
Relative (%) change from baseline (SD)			6.1(20.3), p=0.194	20	8.5(16.5), p=0.011	28	5.0(20.9), p=0.520		20.7(18.5), p=0.025	7	7.6(15.2), p=0.277		19.8(28.4), p=0.116		10.5(20.9), p=0.011	29
CHAQ disability index*																
Actual value (SD)	1.36 (0.77)	33	1.12 (0.71)	24	1.20 (0.70)	31	1.07 (0.75)	11	1.44 (0.79)	10	1.16 (0.60)	7	0.88 (0.64)	9	1.23 (0.66)	33
Absolute change from baseline (SD)			-0.11 (0.37)	24	-0.10 (0.36)	31	-0.14 (0.41)		0.16 (0.35)	10	-0.32 (0.62)		-0.10 (0.42)		-0.13 (0.440	
Relative (%) change from			-11.2 (44.08)	22	-7.76 (50.68)	29	-7.00 (68.73)		11.83 (23.88)	8	2.28 (76.66)		13.13 (72.270		-2.41 (45.03)	

baseline (SD)																
CHAQ – pain VAS (0-3 scale)*																
Actual value (SD)	0.618(0.731)	32	0.895(0.911)	24	0.761(0.931)	31	0.407(0.409)	9	0.339(0.458)	10	0.390(0.326)	7	0.443(0.644)	9	0.431(0.616)	33
Absolute change from baseline (SD)			0.257(0.776)	23	0.148(0.723)	30	0.060(0.487)	9	-0.393(0.697)	9	-0.249(0.476)		0.063(0.771)	9	-0.173(0.647)	32
Relative (%) change from baseline (SD)			45.77(138.8)	16	3.697(107.3)	20	122.3(380.0)	5	-46.0(60.21)	6	32.61(198.2)		51.69(202.7)	5	-17.0(109.8)	21
EQ-5D-5L Index*																
Actual value (SD)	0.6217(0.1698)	24	0.6596(0.1492)	14	0.6678(0.1785)	21	0.6385(0.1181)	2	0.6437(0.2057)	10	0.7158(0.0743)	4	NR		0.6722(0.1674)	24
Absolute change from baseline (SD)			0.0647(0.1199)		0.0346(0.1044)		0.1950(0.1245)		0.0262(0.1303)		0.0993(0.1422)		NR		0.0505(0.1351)	
Relative (%) change from baseline (SD)			17.2811(32.8088)		6.9320(19.0980)		44.1743(28.6949)		7.2199(21.9332)		21.1495(32.1006)		NR		11.2291(24.7218), p=0.036	
EQ-5D-5L VAS*																
Actual value (SD)	67.9(18.2)	23	71.7(16.3)	15	69.0(16.6)	22	80.0(21.2)	2	70.8(14.3)	10	73.8(18.9)	4	NR		71.6(15.0)	24
Absolute change from baseline (SD)			5.7(16.9)	14	1.6(17.2)	21	6.5(4.9)		9.8(22.7)	9	-2.5(8.7)		NR		3.3(18.1)	
Relative (%) change from baseline (SD)			15.5(30.9)	14	7.7(32.2)	21	8.3(4.9)		26.6(43.3)	9	0.4(16.7)		NR		11.5(33.8)	
BOT-2 total*																

Actual value (SD)	107.0 (47.6)	33	108.5 (47.7)	24	119.1 (44.9)	31	117.3 (66.0)	11	114.3 (33.5)	10	71.8 (27.9)	4	128.3 (59.4)	9	112.1 (46.0)	33
Absolute change from baseline (SD)			3.9 (12.4)		7.5 (16.5), **p=0.017**		12.2 (21.8)		7.3 (24.9)		16.3 (10.4)		7.7 (35.5)		5.1 (23.9)	
Relative (%) change from baseline (SD)			3.8 (17.8)		10.6 (19.3), **p=0.005**		17.9 (32.3)		16.2 (39.8)		31.5 (16.2), **p=0.03**		13.0 (38.3)		13.0 (33.9), **p=0.035**	
Leiter TEA VR*																
Actual value (SD)	5.879(1.565)	33	5.840(1.380)	24	6.296(1.541)	31	5.788(1.574)	11	6.292(1.317)	10	5.131(1.584)	7	5.898(1.437)	9	6.144(1.612)	33
Absolute change from baseline (SD)			0.122(0.577)		0.320(0.717), **p=0.019**		0.333(0.587)		0.308(0.436)		0.333(0.344), **p=0.043**		0.204(0.632)		0.265(0.637), **p=0.023**	
Relative (%) change from baseline (SD)			3.447(10.28)		6.695(12.17), **p=0.005**		6.251(10.75)		6.724(8.951), **p=0.042**		9.037(10.77)		4.140(11.24)		5.338(10.45), **p=0.006**	
Leiter TEA AME*																
Actual value (SD)	6.514(2.176)	24	6.400(2.424)	15	6.860(1.992)	22	3.792(2.180)	2	6.817(1.529)	10	5.250(0.561)	4	NR		6.670(1.757)	24
Absolute change from baseline (SD)			0.100(1.331)		0.167(1.254)		-0.750(1.414)		0.108(1.665)		0.833(1.855)		NR		0.156(1.519)	
Relative (%) change from baseline (SD)			5.219(22.135)		5.849(19.657)		-19.42(34.413)		11.244(33.786)		33.225(47.595)		NR		9.345(32.485)	
Pure tone best ear*																
Actual value (SD)	52.57(12.36)	32	55.44(10.65)	22	53.35(11.41)	31	48.35(16.80)	11	54.76(8.72)	9	56.16(12.86)	7	47.62(13.76)	9	52.16(13.13)	33

Absolute change from baseline (SD)			2.05(4.72)		1.47(6.00)	30	-4.81(9.74)		2.05(6.55)	8	-0.76(8.78)		-3.73(6.21)		-0.49(6.58)	32
Relative (%) change from baseline (SD)			5.76(13.90)		4.26(14.97)	30	-8.89(20.44)		6.85(16.25)	8	-1.71(16.90)		-8.08(12.81)		-0.72(14.54)	32
Serum IgG*																
Actual value (SD)	NR															
Absolute change from baseline (SD)															3.05 (2.39, 3.71), **p=<0.001**	24
Relative (%) change from baseline (SD)															44.07 (32.58, 55.57), **p=<0.001**	

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

***** only statistically significant p values reported.

rhLAMAN-10[1] demonstrated statistically significant changes in absolute and relative change from baseline in 3-MSCT at most time points (

Table 12). Absolute change from baseline ranged from 1.90 (24 months, n=10) to 17.07 (48 months, n=9). The last observation analysis had an absolute change from baseline of 6.38 steps/min (SD 10.54), p=0.001, which is close to the MCID of ≥7 steps/minute, but not much higher than the outcome at 12 months for this study (4.25 steps/min (n=31)).

Pre-planned subgroup analyses in rhLAMAN-10[1]: The CS reports "*The analysis of 3-MSCT by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in an increase in the proportion of patients considered to have no or minor impairment at last observation (60.6%) compared with baseline (39.4%) (Appendix 7, Section 17.7.2.3). When the ADA status of patients was taken into account, improvements in the 3-MSCT were observed in both ADA negative and positive patients (Appendix 7, Section 17.7.2.4).*"

Absolute mean change from baseline in 3-MSCT was consistently greater in patients <18 years of age than in patients ≥18 years of age (Figure 20 of the CS)[2]. The clarification response to question A36[11] indicated that there was an interaction between time and age in a post-hoc analysis, and that there is a difference between results in those aged <18 and those aged ≥18 years.

6-MWT – prioritised secondary endpoint

rhLAMAN-05[10] did not demonstrate a statistically significant difference in 6-MWT at 6 or 12 months (adjusted mean difference in relative change 1.86% (−6.63, 11.12), p=0.664; adjusted mean difference in absolute change 7.35 metres (95% CI: -30.76; 45.46), p=0.692, both at 12 months). Table 11 provides further data including absolute values. To reach the study endpoint, a trend for improvement in 3-MSCT in one of the two prioritised secondary endpoints was acceptable. The CS interprets the results as a trend towards improvement.[2] The ERG note that the observed difference is considerably lower than the MCID of an increase of ≥30 meters.

rhLAMAN-10[1] reported some statistically significant changes in absolute values from baseline time points (18 months; 48 months, last observation, see

Table 12). The ERG notes that the observed difference at the last observation of 22.4 meters (n=33) does not reach the MCID of an increase of ≥30 meters and is similar to the 12-month outcome of 21.9 steps (n=31) of the patients.

Pre-planned subgroup analyses in rhLAMAN-10[1]: The company states that "*The analysis of 6-MWT (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in modest reductions in the number of patients considered to be seriously impaired based on the 6 MWT (% of predicted; 6.1% at baseline to 0% at last observation) (Appendix 7, Section 17.7.2.3). When the ADA status of patients was taken into account, improvements in the 6-MWT (metres and % of predicted) were observed in both ADA negative and positive patients (Appendix 7, Section 17.7.2.4)"* (p143 of the CS)[2]

In the subgroup analysis by age, both velmanase alfa and placebo groups improve in 6-MWT in the <18 years of age group, but to a somewhat greater extent in the velmanase alfa group (2.0 vs 1.2 metres). In the ≥18 years of age group, velmanase alfa patients show a small numerical improvement whilst placebo patients had a decrease in distance walked (0.4 vs -2.8 metres).

Lung function- FVC (% of predicted)

In rhLAMAN-05[10], this was a prioritised secondary endpoint. The results did not demonstrate a statistically significant difference in %FVC predicted at 12 months (adjusted mean difference in relative change 8.40% (−6.06, 25.08), p=0.269; adjusted mean difference in absolute change 5.91% FVC predicted (95% CI: -4.78; 16.60),p=0.278). Table 11 provides further data including absolute values.

The ERG notes that a 5.91% FVC predicted mean difference in absolute change from baseline (baseline 82-90 % FVC predicted) does not meet the MCID of an increase of ≥10% of FVC % predicted.

In rhLAMAN-10[1] the ERG notes that there is some attrition in the analyses of FVC (% of putting these results at some risk of bias, especially given the small patient numbers. For were only 20 patients at 6 months, where there should be 24, only 28 at 12 months where there be 31 (

Table 12). Statistically significant differences in absolute % predicted data were reported at some, but not all, time points, with absolute changes ranging from 3.5% of predicted at 6 16.1% of predicted at 24 months. The last observation analysis was statistically significant, with patients in the absolute change analysis unaccounted for (

Table 12). The ERG note that some analyses reached the MCID of an increase of ≥10% of FVC % predicted.

Pre-planned subgroup analyses in rhLAMAN-10[1]: The CS[2] also reported that "The *analysis of FVC (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in a small increase in the number of patients considered to have no or some impairment based on FVC (% of predicted; 58.6% at baseline to 67.7% at last observation); similar results were observed when the analysis was based on FEV1 (% of predicted) (Appendix 7, Section 17.7.2.3)*." (p144 of the CS).[2]

There were consistently greater increases in FVC (% predicted) in patients <18 years of age compared with baseline and patients greater than 18 years of age (CS Figure 22).

Other PFTs

For rhLAMAN-05[10] the CS[2] states:

"*Overall, a trend for improved lung function compared with placebo was apparent in the velmanase alfa group for all additional PFT endpoints. While patients in both the velmanase alfa and placebo group experienced an improvement in pulmonary function, velmanase alfa demonstrated a numerical advantage over placebo for all PFT secondary endpoints, although no statistically significant differences were observed*."

For rhLAMAN-10[1] the CS[2] states:

"*In addition to FVC (% of predicted), lung function was also measured by FVC (L), FEV1 (% of predicted), FEV1 (L) and PEF (L/s); these results are presented in Appendix 7 (Section 17.7.2.1 for overall results and by age class; Section 17.7.2.2 for results by parental study) and are summarised in Table 15. Together, the results from the PFT secondary endpoints demonstrate that velmanase alfa can produce statistically significant improvements in lung function in patients with AM.*" (p144 of the CS).[2] and that "*The analysis of FVC (% of predicted) by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in a small increase in the number of patients considered to have no or some impairment based on FVC (% of predicted; 58.6% at baseline to 67.7% at last observation); similar results were observed when the analysis was based on FEV1 (% of predicted) (Appendix 7, Section 17.7.2.3).*" (p 144 of the CS).[2]

The ERG notes that for these other lung function measurements, outcomes were only statistically significantly different from baseline at some time points.

CHAQ and EQ-5D

rhLAMAN-05[10] did not provide comparative or adjusted analyses of CHAQ, EQ-5D or any of the sub-domains. Table 11 provides further data. At 52 weeks, velmanase alfa patients had an absolute change in CHAQ disability of -0.01 (SD 0.32) and placebo patients of 0.18 (SD 0.36) (negative changes indicate an improvement in disability). The CS interpreted these data as demonstrating a trend towards improvement.[2] The ERG considers the data inconclusive as no statistical comparison was provided, though also note that the change (worsening) in the placebo arm is larger than the MCID of ≥0.13. Differences between arms for CHAQ pain VAS, and EQ-5D index and VAS were negligible.

rhLAMAN-10[1] did not demonstrate a statistically significant difference in CHAQ, EQ-5D or sub-domains reported except in the last observation analysis of relative change from baseline for EQ-5D-5L index, though this analysis only included 24/33 patients with the reason for this unclear.

Table 12 provides further detail. The change in CHAQ disability exceeded the MCID of ≥0.13 at -0.17 (SD 0.65). No MCID was reported for EQ-5D-5L index.

The CS[2] also highlights data relating to changes to numbers of patients requiring ambulatory assistance taken from the CHAQ. At baseline, ten patients required help, whereas at last observation, 70% of these patients required less help. Conversely, of the 23 who did not require help, 3 (13%) became dependent on some help by the last observation.

In their clarification response A44,[11] the company provided a further analysis where a "walking with assistance" category was created, to more closely mimic the category defined in the model, by combining CHAQ-defined wheelchair users and those requiring walking aids/assistance. The results this analysis are presented in

Table 13. The company state "*It is only in the velmanase alfa arm that a net effect (20%) was observed for an improvement in walking ability after 12 months of treatment, i.e. a higher proportion of patients treated with velmanase alfa transitioned to an improved walking ability state (40%) compared to the proportion of patients treated with velmanase alfa that transitioned to a worse walking ability state (20%).*" (clarification response to question A44).[11]

The company also provided the following statement about rhLAMAN-10[1]:

"*It should be noted that longer-term data (up to 48 months of treatment) are available from the rhLAMAN-10[1] trial. Overall, ten patients required help from a person, walking aids (cane, walker, crutches), or a wheelchair at baseline according to the CHAQ 'Helps and Aids' responses. Of the ten patients, seven (70%) became device- or third party-independent at last observation: 4/5 (80%) paediatric patients and 3/5 (60%) adults. In particular, two paediatric patients and one adult forced to adopt the wheelchair for long distance mobility/functional capacity at baseline discontinued use at last observation. Overall, three patients out of the 23 (13%) who did not require help from a person, walking aids, or a wheelchair at baseline, did so at last observation (one adult and two paediatric patients).*" (A44 clarification response).[11]

Table 13: Post-hoc analysis of proportion of patients in health states defined to closely resemble the model health states (walking with assistance and walking unaided) in rhLAMAN-05[10]

	baseline	12 months	Notes
VA group	WWA 5/15 (33%) WU 10/15 (67%)	WWA 5/15 (33%) WU 10/15 (67%)	2/5 (40%) patients moved to WU 2/10 (20%) patients moved to WWA
Placebo group	WWA 5/10 (50%) WU 5/10 (50%)	WWA 5/10 (50%) WU 5/10 (50%)	2/5 (40%) patients moved to WU, 2/5 (40%) patients moved to WWA

WWA, walking with assistance; WU, Walking unaided; VA, velmanase alfa.

BOT2 – motor function

rhLAMAN-05[10] did not demonstrate a statistically significant difference in BOT2 total score, or any of the sub-domains reported Table 11 of this report and Appendix 7 (Section 17.7.1) of the CS provide further data.[2] The CS interpreted these data as demonstrating a trend towards improvement.[2] The ERG considers the data inconclusive.

rhLAMAN-10[1] reported statistically significant differences at some time points (

Table 12)

Leiter R- cognition

rhLAMAN-05[10] did not demonstrate a statistically significant difference in Leiter R or any of the sub-domains reported. Table 11 provides further data. The CS concludes there was no significant difference in cognition between groups.[2]

rhLAMAN-10[1] reported statistically significant differences at some time points for the Leiter R equivalence age VR, including the last observation analysis, but not for the Leiter R total age AM.

Table 12 provides further details.

Hearing – PTA

rhLAMAN-05[10] did not demonstrate a statistically significant difference in Hearing PTA test. Table 11 provides further details. Whilst the CS[2] notes that results numerically favoured the velmanase alfa group, the ERG considers the data inconclusive.

rhLAMAN-10[1] did not demonstrate a statistically significant difference in Hearing PTA test.

Table 12 provides further data.

The CS states on page 48[2] "*The analysis of PTA measures by patient status (Section 9.4.4.2) demonstrated that treatment with velmanase alfa resulted in modest reductions in the number of patients considered to be seriously impaired based on air conduction in left (72.7% at baseline to 63.6% at last observation) and right ear (66.7% at baseline to 57.6% at last observation) (Appendix 7, Section 17.7.2.3). No change in patient status was seen with regards to bone conduction (best ear).*"

Infection rates

Infection rates, which are listed in the NICE scope[9] as an outcome of interest, were not formally assessed as an efficacy outcome in the rhLAMAN-05[10] or -10[1] studies. However, they were measured as an adverse event. The results are presented in Table 14.

Table 14: infections and infestation adverse events reported by ≥ 2 patients in rhLAMAN-05[10] and -10[1]

Trial	VA group	Placebo
rhLAMAN-05[10]	13 (86.7%) pts 48 events	7 (70.0%) pts 23 events
rhLAMAN-10[1]	24 (72.7%)	NA

The company also provided additional analyses and evidence relating to infections in their clarification response.[11] All analyses were post hoc. The following were provided:

- Evidence that Serum IgG is a relevant biomarker for infection rates in AM: "*The biomarker of serum IgG is well accepted as a surrogate for humoral deficiency and for patients with hypogammaglobulinaemia. Patients with AM may have serum IgG levels below the normal range. The standard therapy for hypogammaglobulinaemia is replacement with immunoglobulins, a treatment which has been demonstrated to reduce infections. An increase in IgG following treatment with velmanase alfa is therefore considered a positive effect."*(p22, clarification response).[11] Results for serum IgG are reported in Section 4.2.6.2.

A post hoc analysis of infections requiring antibiotics in those patients with hypogammaglobulinaemia in rhLAMAN-05.[10] This selected group of patients comprised 5/15 (33.3% (33.3%) from the velmanase alfa arm, and 4/10 (40%) from the placebo arm. The results are presented in

- Table 16, reproduced from the clarification response.[11]
- Caregivers questionnaire – In response to the ERG's request for clarification about why infections were not measured, the company provided an analysis of a questionnaire given to caregivers at the CEV for rhLAMAN-10,[1] which was intended to "*indirectly estimate the occurrence of infections*" (p23 clarification response).[11] Table 5 in the clarification response details the responses of the caregivers. The company summarised the results as *"Although the exact number of infections was not collected, of the 32 patients with completed questionnaires, 22 (68.8%) were reported by their caregivers as having fewer or almost no infections after treatment."* (p23 clarification response).[11]

Additional secondary outcomes

The CS[2] states that "*Although less relevant to the decision problem, the results for the change from baseline in CSF oligosaccharides, tau, neurofilament protein (NFLp) and glial fibrillary acidic protein (GFAp) at Month 12 are presented in Appendix 7 (Section 17.7.1, Table 131) for completeness."*

Preplanned subgroup analyses in rhLAMAN-10[1]

Data relating to the subgroup analyses according to parental study are not presented here but can be found in the CS Appendix 7.[2] Data relating to ADA status are presented in part above in relevant sections.

4.2.6.2 Post hoc analyses

Post hoc analysis of patients aged <18 and ≥18 years in rhLAMAN-05[10]

The results of the post hoc analysis are presented in Table 15. The ERG asked if interaction tests to test whether the two age group results were statistically significantly different to each other were performed, to which the company responded that they were not, but that the ANCOVA model included baseline value and subject age (A36 clarification response).[11]

Table 15: Primary and prioritised secondary endpoints by age class (reproduction of Table 25 from the CS) in rhLAMAN-05[10]

Outcome	Mean change from baseline to Month 12 (SD)			
	<18 years		≥18 years	
	VA (n=7)	Placebo (n=5)	VA (n=8)	Placebo (n=5)
Serum oligosaccharides (µmol/L)				
Relative change, %	−70.6 (14.6)	−7.2 (19.3)	−80.3 (4.4)	−33.4 (22.2)
VA - placebo†	-63.4	-	-46.9	-
3-MSCT (steps/min)				
Relative change, %	5.8 (18.0)	−4.4 (10.8)	−4.1 (13.7)	−2.8 (16.4)
VA - placebo†	10.2	-	-1.3	-
6-MWT (metres)				
Relative change, %	2.0 (7.8)	1.2 (9.4)	0.4 (11.7)	–2.8 (12.8)

Outcome	Mean change from baseline to Month 12 (SD)			
	<18 years		≥18 years	
	VA (n=7)	Placebo (n=5)	VA (n=8)	Placebo (n=5)
VA - placebo†	0.8	-	3.2	-
FVC (% of predicted)				
n	6	4	6	5
Relative change, %	20.5 (11.2)	9.5 (5.6)	2.3 (7.5)	–4.1 (18.7)
VA - placebo†	11.0	-	6.4	-

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; FVC, forced vital capacity; SD, standard deviations; VA, velmanase alfa.
†The differences between the VA and placebo group are provided for descriptive purposes only. For serum oligosaccharides, positive values indicate a treatment effect in favour of placebo. For 3-MSCT, 6-MWT and FVC (% of predictive) negative values indicate a treatment effect in favour of placebo.

Post hoc analysis of serum IgG (not in NICE scope)

Serum IgG was not listed in the NICE scope. The CS reports a post-hoc analysis of serum IgG in rhLAMAN-05[10], where an increase in serum IgG indicates an improvement. The company state in their clarification response that serum IgG is a *"well accepted surrogate for humoral deficiency and for patients with hypergammaglobulinaemia"* (response A20).[11] The CS reports: "*Serum IgG mean (SD) values at baseline were 9.00 g/L (5.02) and 7.27 g/L (1.64) for the velmanase alfa and placebo groups, respectively. At Month 12, treatment with velmanase alfa resulted in a statistically significant increase in serum IgG levels compared with placebo. The adjusted (for baseline value and age) mean change from baseline was 3.59 g/L (95% CI: 2.75, 4.43) in the velmanase alfa group and 0.12 g/L (95% CI: –0.91, 1.16) in the placebo group; the adjusted mean difference was 3.47 g/L (95% CI: 2.12, 4.81; p<0.001).*

When expressed in terms of normal range, 5/15 patients in the velmanase alfa group and 3/10 in the placebo group had low serum IgG levels, comparable with hypogammaglobulinaemia, at baseline. At Month 12, 3/5 patients in the velmanase alfa group reverted to normal serum IgG levels, while the other two patients experienced substantial improvements. In contrast, no patients in the placebo group reverted to normal serum IgG levels after 12 months." (p135 of the CS).[2]

Serum IgG is listed in amongst the main results for rhLAMAN-10[1] but not listed in the study an outcome. It is unclear if this is a post-hoc analysis. The results (

Table 12) show a statistically significant change from baseline at last observation. Only rhLAMAN-05[10] patients were included in the analysis as serum IgG was not recorded in the rhLAMAN Phase I/II trial. The absolute change from baseline was 3.05 (95% CI 2.39 to 3.71) at last observation.

Table 16: Reproduction of Table 4 from the clarification response:[11] Number of patients with low IgG levels experiencing infections requiring antibiotics during the 12 months of rhLAMAN-05[10]

	Velmanase alfa n=15		Placebo n=10	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Number of patients with low IgG	5/15 (33.3)	-	4/10 (40.0)	-
Low IgG patients with infections requiring antibiotic use				
Overall	2/5 (40.0)†	2	2/4 (50.0)	4
>1 month	0/2 (0)	0	2/2 (100.0)	3
Rate of Infections requiring antibiotics per infected patient				
Overall	1		2	
>1 month	0		1.5	

Source: CSR Study rhLAMAN-05[10], Table 11-19, Appendix 16.2.4. Listing 16.2.4.4
†Patient 518 received Cefazolin on Day 234 for use during genua valga surgery has been excluded as the antibiotic use was preventative and not to treat an infection.
IgG, immunoglobulin G.

Post hoc analysis of patients switching from placebo to VA.

The company also describe a subgroup analysis of patients who switched from placebo to velmanase alfa after the completion of rhLAMAN-05.[10] The results of the analyses are given in Table 17 and Table 18, reproduced from the CS.[2]

Table 17: Reproduction of Table 28 form the CS[2]: Change in 3-MSCT, 6-MWT and serum IgG after switching from placebo to velmanase alfa

Outcome	Mean relative change from baseline value reported in placebo, double blind phase, % (SD)	
	Placebo double blind phase, month 12 (n=10)	Velmanase alfa only phase, last observation (n=9)
3-MSCT	-3.6 (13.5)	9.0 (25.1)
6-MWT	-0.8 (10.8)	2.2 (13.1)
Serum IgG	1.0 (16.9)	37.3 (16.1)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; SD, standard deviation.

Table 18: Reproduction of Table 29 form the CS[2]: Improvement in quality of life after switching from placebo to velmanase alfa

Outcome	Placebo double blind phase		Velmanase alfa only phase
	Baseline (n=9)	Month 12 (n=9)	Last observation (n=9)
CHAQ-DI, mean (SD)	1.56 (0.67)	1.71 (0.50)	1.43 (0.50)
CHAQ pain (VAS), mean (SD)	0.42 (0.59)	0.52 (0.66)	0.36 (0.51)

Abbreviations: CHAQ, childhood health assessment questionnaire; DI, disability index; SD, standard deviation; VAS, visual analogue scale.

Post hoc multi-domain responder analysis in rhLAMAN-05[10] and -10[1]

The results to the multi-domain responder analysis are provided in Table 19. Statistical significance was not reported. The ERG note that 30% of patients in the placebo arm of rhLAMAN-05[10] were classed as responders. A greater proportion of patients in the velmanase alfa arm were classified as responders (87%). More patients in the <18 years of age group in rhLAMAN-10[1] were classified as responders than in the ≥18 years of age group.

Table 19: Reproduction of Table 30 of the CS[2]: Results of multi-domain responder analysis

Responder	rhLAMAN-10[1] (N=33)			rhLAMAN-05[10] (N=25)	
	All (N=33)	<18 (n=19)	≥18 (n=14)	VA (n=15)	Placebo (n=10)
Responder (≥2 domains), n (%)	29 (87.9)	19 (100.0)	10 (71.4)	13 (86.6)	3 (30.0)
Three domains, n (%)	15 (45.5)	10 (52.6)	5 (35.7)	2 (13.3)	0
Two domains, n (%)	14 (42.4)	9 (47.4)	5 (35.7)	11 (73.3)	3 (30.0)
One domain, n (%)	3 (9.1)	0	3 (21.4)	2 (13.3)	3 (30.0)
No domains, n (%)	1 (3.0)	0	1 (7.1)	0	4 (40.0)

4.2.7 Critique of the analyses and results of rhLAMAN-05[10] and rhLAMAN-10[1]

Baseline characteristics of study participants

The clinical advisors to the ERG felt the spectrum of baseline characteristics were acceptable, given the inclusion/exclusion criteria. Given the heterogeneity of the disease, and the small numbers of patients with AM, the UK population probably does not reflect the full spectrum of disease possible.

As noted by the company, the patient groups in rhLAMAN-05[10] were not balanced for 3MSCT, 6MWT, FVC, BOT-2 or CHAQ disability, with a higher proportion of more compromised patients randomised to the velmanase alfa group (CSR, Table 11-1,[11] Appendix 4). It is unclear how this would affect estimates of efficacy, as more compromised patients may provide more scope for improvement, or alternatively may have irreversible deterioration due to the disease.

The ERG asked for clarification about whether patients were balanced for prognostic factors at baseline in rhLAMAN-05[10] (A9, clarification response).[11] The company stated there were no real prognostic factors known except age, for which patients were stratified at randomisation. The company described some of the classifications that have been used in AM, including the Malm classifications[4] based on phenotype (two versions) and classification by genetic mutations, but did not believe these to be prognostic, nor provide any data on whether patients were balanced at baseline for these classifications in rhLAMAN-05.[10]

Definition of efficacy not met in rhLAMAN-05[10]

The definition of efficacy in rhLAMAN-05[10] was:

- a statistically significant improvement in the two primary endpoints (at significance levels of 0.025 [serum oligosaccharides] and 0.05 [3-MSCT]) at the interim analysis (Month 6)).

Or

- a statistically significant reduction in serum oligosaccharides (at a significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis

Whilst a statistically significant improvement in serum oligosaccharides was observed, there is a lack of clarity in the statistical plan as to what should constitute a trend, and consequently it is unclear whether a 2.62 step/minute mean difference in absolute change from baseline (baseline mean: 54 metres) in 3-MSCT and a 7.35 metre mean difference in absolute change from baseline (baseline: 460 metres) in 6-MWT should be considered a trend for improvement. The ERG note that neither outcome met the MCID which was ≥7 steps for 3-MSCT, and ≥30 meters for 6-MWT (see Table 7).

Muti-domain responder analysis and minimal clinically important differences

The ERG and the clinical advisors to the ERG believe the multi-domain responder analysis to be problematic for a number of reasons:

- Dichotomising patients according to arbitrary cut-offs results in a loss of power relative to the original continuous data
- Dichotomising patients according to multiple domains assumes that the domains are equally important
- Serum oligosaccharides may not be clinically important
- Setting aside the fundamental problems with dichotomising continuous outcomes, clinical advisors to the ERG were of the opinion that infection rates and central nervous system effects should have been included in the responder analysis
- If serum oligosaccharides are excluded from the analysis, and only two domains are left [redacted], patients could potentially be considered a responder solely on the basis of improvements in any one of the tests included in the domains.
- Some of the MCIDs were defined after the trials results were un-blinded, and there is the potential for bias in their definition. This was, however, conducted in response to a request from the EMA, quoted in the clarification response to question A19[11] as:

""*The clinical relevance of the various changes compared to baseline or compared to placebo cannot be assessed for all endpoints due to the lack of predefined clinically important changes. Clinically relevant changes based on experience with comparable conditions for the various endpoints should be identified based on relevant literature. For example, 3MSCT and 6MWT might be related to the experience in patients with JIA. Responder analyses based on these clinically relevant differences should be submitted. Also the 3MSTC and 6MWT results should be presented as scatter plots of change (style shown in fig 11-6 in study report rhLAMAN-05[10]) in order to further appreciate the individual responses."*

- The ERG notes that, based on this quote, the EMA did not request a multi-domain responder analysis, only a responder analysis. In addition, the specifics of how the analysis was conducted were specified post-hoc and were not defined by the EMA. There is therefore a high risk of bias in these analyses in addition to concerns regarding the appropriateness of responder analyses.
- The methods used to define MCIDs comprised a literature review of values in conditions with similar clinical characteristics to AM. It appears only one clinical expert was asked to verify the domains selected: "*An expert was consulted and they concurred with the heterogeneity of AM and relevance of the domain response approach given the heterogeneity of disease manifestation and severity, and small patient numbers*." (CS Appendix 2, section 17.7.3.1.)[2]
- There are no MCIDs reported for motor function (BOT-2); hearing; Leiter-R; rates of infections; or EQ-5D.

Attrition in the trials

There is a lack of clarity around attrition in the later months of rhLAMAN-10.[1] Whilst some of attrition could be down to length of time enrolled, there are some clear examples of missing data secondary outcomes (see

Table 12). It is unclear what impact this may have, given no imputation was performed in rhLAMAN-10.[1]

Lack of adjustment for age and height

The ERG is satisfied that a lack of reference values for the 3-MSCT and assertion that it is not affected by age mean that the values can be interpreted as they stand. However, the change in rhLAMAN-05[10] was quite small (an absolute difference in change from baseline at 12 months of around 3 steps from a baseline of 53-56 steps), and the changes from baseline observed in rhLAMAN-10[1] were highly variable, possibly due to missing values and patients who had not been on treatment.

6-MWT % predicted for age, height and gender values were only supplied for rhLAMAN-10[1] as an exploratory analysis, and show that the last observation results are somewhat less favourable for the % predicted analysis (relative change from baseline 3.55 (SD 18.30, n=33)) than for the non-normalised analysis (relative change from baseline 7.1 (SD 22.0, p=0.071, n=33)).

Interaction with age

It was not clear if there is evidence of a difference in the effect of treatment depending on age so the ERG requested interaction tests. In response, the company replied that adding additional terms to the ANCOVA analysis in rhLAMAN-05[10] "*might have produced over-parameterisation issues*". Although, with only 25 observations, the test for an interaction lacks statistical power, there would be 1 degree-of-freedom for treatment, 1 degree-of-freedom for age, 1 degree-of-freedom for the interaction between treatment and age, and 21 degrees-of-freedom to estimate residual error. Hence, the ERG considers it reasonable to model the interaction between treatment and the variable continuous age in this trial. In rhLAMAN-05,[10] subgroup analyses were performed for patients aged <18 years of age and those aged ≥18 years. However, the ERG notes that the estimates of treatment effect presented in Tables 24 and 25 of the CS are derived differently.[2] For consistency with Table 24, the correct estimates of treatment effects on serum oligosaccharides are a 68.32% reduction for patients aged <18 years and a 70.42% reduction for patients aged ≥ 18 years. Although the ERG prefers not to perform subgroup analyses based on the dichotomisation of a continuous variable, these results suggest that if there is an interaction between age and treatment it may be small. Interaction tests were not provided for any other outcomes, so the statistical significance of the impact of age on treatment effect remains unknown. Observed differences in clinical outcomes between younger and older patients in both trials are generally greater in the younger patients.

In rhLAMAN-10,[1] the interaction between age (<18 years and ≥18 years) and time was significant for 3-MSCT, but not for serum oligosaccharides.

Long term effects

The duration of follow-up is not long enough to establish whether any treatment effects will be maintained in the long term. The company argue that effects seem to increase over time (see to clarification question A20[11]), based on the multi-domain responder analysis. The ERG notes length of follow-up varied a great deal in rhLAMAN-10,[1] with variable and smaller numbers, sometimes comprising different patients altogether, at the time points beyond 12 months. This difficult interpret data beyond 12 months, especially given the heterogeneity of disease and response, and the very small numbers in some analyses. The last observation analysis generally all patients and for the four main outcomes (serum oligosaccharides, 3-MSCT, 6-MWT, FVC % predicted) there was very little difference between the 12 month (n=31) and the last observation analyses (n=33). However, it is unclear what the mean follow-up length was for the last analysis, and it is possible that this is not much longer than 12 months. There were, however, differences in other secondary outcomes (

Table 12) including EQ-5D-5L and Leiter-R, thought the clinical significance of the size of the changes is unknown, and the lack of a comparator arm makes it difficult to draw conclusions regarding long term efficacy.

Patient status analysis

The patient status analysis was post-hoc and the cut off points defined were arbitrary. Many of the points raised concerning the multi-domain responder analysis apply to this analysis.

Missing data in rhLAMAN-10[1]

No imputation was used in the analysis which could be a problem if only patients who tolerated and responded to treatment continued to be followed up. An analysis of last observation was performed, but this did not always include all patients, and combined data across different times for example, FVC% predicted n=29/33; CHAQ pain VAS, n=21/33, see the final column in

Table 12. Analyses were also performed over time but these also did not always account for all patients.

Infection rates

Infection rates were not measured as an efficacy outcome. The company states "*at the time of designing the clinical trials for velmanase alfa the expected size of the trial population was considered too small to envisage the possibility to collect meaningful clinical data on the change of infection rate after treatment."* (response to clarification question A21).[11]

Infection rates were measured as an adverse event (AE) however, and rates appear higher in the velmanase alfa arm. The ERG asked for clarification of how AEs were reported, but the company response only concerned how the clinicians reported to the trial, not how patients reported to the clinicians, meaning the ERG cannot establish how well AEs were monitored, and therefore how reliable these event rates are.

In response to the ERGs request for clarification, the company provided additional data and analyses relating to infections and immune function. In summary these included:

- a post-hoc analysis of serum IgG in rhLAMAN-05,[10] where a statistically significant improvement was reported: adjusted mean difference vs placebo: 3.47 g/L; 95% confidence interval [CI]: 2.12, 4.81, $p<0.0001$
- a post-hoc analysis of changes in patients with low serum IgG: 9/25 pts had low serum IgG based on age and gender (5 velmanase alfa group, 4 placebo group). 3/5 (60%) of velmanase alfa patients achieved normal IgG levels and 2/5 improved; 0/4 improved/achieved normal levels in the placebo arm

An analysis of antibiotic use in the low serum IgG group demonstrated patients receiving velmanase velmanase alfa had fewer antibiotic uses than the placebo group after the first month (

- Table 16)
- An analysis of caregivers reports of infection rates supports a reduction in infections for patients in rhLAMAN-10[1]

The rationale for the importance of serum IgG appears reasonable (it being the standard therapy and a surrogate biomarker in hypogammaglobulinaemia). The ERG notes that the number of patients and events was extremely low and no statistical analysis was provided. Only patients with low IgG were included in the analysis, and it remains unclear what happened to the remaining patients, though the company state "*This sub-group of nine patients is the only group where a potential correlation between an increase in serum IgG due to treatment and improvement in rate and/or severity of infections could be formally demonstrated.*" which may indicate that infections were not improved for other patients. Given the responses presented from patient carers in the clarification response to question A20,[11] which state that infections are common and impact on social life, rates of 4 events for 10 patients over 12 months (in the placebo arm) suggest that not all impactful infections were captured and bring into question the relevance of the results reported.

The results of the analysis of data provided by caregivers are not analysed statistically but indicate that the majority of patients report fewer infections. However, the trial was open label and therefore the results are subject to bias. Also, the analysis relied on caregivers responding retrospectively, which is subject to recall bias. The ERG is also unclear if the questionnaire asked about both infections and social life problems; data presented relate to infection rates or social life problems, and it is unclear if the most favourable response has been selected for presentation. The questionnaire also only had a 69% response rate.

The observed infection rates reported as adverse events show more infections in the velmanase alfa arm than in the placebo arm, which does not match with the IgG analysis or the patient carer reports. It is therefore difficult to draw any firm conclusions as to the impact of velmanase alfa on infection rates.

Ceiling effect in 3-MSCT and 6-MWT

The company argue that baseline values for the 3-MSCT and 6-MWT are relatively high, difficult to detect an effect of treatment in such a small sample. The baseline value for the 6- around 460 meters in rhLAMAN-05[10] and 467 meters in rhLAMAN-10[1], equivalent to 69% for age, height and gender (see Table 11 and

Table 12). Given these values are similar, and these patients appear to have values 30% below the norm for their age, height and gender, there appears to be scope for improvement in these patients. The ERG was not able to identify comparative data for the 3-MSCT to assess whether a ceiling effect was likely. However, the company go on to note that the velmanase alfa arm had more severely disabled patients compared with the placebo arm for both 3-MSCT and 6-MWT, and that this may have confounded results; this appears to be at odds with the argument that ceiling effects may have reduced the ability of the trial to detect an effect, as the velmanase alfa arm would be less prone to ceiling effects in this instance.

Critique of trials identified and included in the indirect comparison and/or network meta-analysis
Not applicable

Critique of the indirect comparison and/or multiple treatment comparison
There was no indirect comparison or network meta-analysis (NMA) conducted. The ERG believes that HSCT could be considered a relevant comparator for a small proportion of patients, in which case an NMA could have been considered to generate a comparison between velmanase alfa and HSCT.

Additional work on clinical effectiveness undertaken by the ERG
No additional analysis of the clinical effectiveness data was undertaken by the ERG.

4.2.8 Safety data

AEs of any type or grade were frequent for patients receiving velmanase alfa. Only data from the rhLAMAN-05[10] phase III trial and the rhLAMAN-10[1] non-controlled study are presented here. These represent the most recent and extensive evidence in terms of numbers of patients and length of follow-up (the integrated data set of rhLAMAN-10[1] includes data from the earlier phase I/II trials rhLAMAN-02[13], -03[15], and -04[14], as well as the rhLAMAN-05[10] phase III trial). All patients in rhLAMAN-10[1] had been exposed to velmanase alfa for at least 12 months. All of the safety concerns raised in the earlier phase I/II trials were reflected in the more recent and more extensive data from the rhLAMAN-05[10] phase III trial and the rhLAMAN-10[1] study.

rhLAMAN-05[10]
In the rhLAMAN-05[10] trial, the patients received between 48 and 55 infusions (1 per week for 12 months), with a mean (SD) of 62.8 (44.2) (CSR[10], p.150). All patients in the treatment-arm of this trial reported at least one AE (Table 20), although nine out of 10 patients in the placebo arm also reported AEs. Approximately half of all patients in the treatment (46.7%) and placebo (50%) arms also reported 'treatment-related AEs'. The CS reported that one patient in the velmanase alfa study arm experienced 11 events categorised as Infusion Related Reactions (IRRs) (chills, nausea, hyperhidrosis and

vomiting),[2] but these were all considered to be mild or moderate in intensity (CS, page 155[2] and CSR[10], p121). As a result of five of these events, the drug was interrupted (n=4) or the infusion rate was reduced (n=1) (CSR[10], p121).

According to the CSR[10] (pages 58-59)[11] a Serious Adverse Event (SAE) was defined as any AE that resulted in one of the following outcomes: death; life-threatening experience; required or prolonged in-patient hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect; or any important medical events that jeopardised the patient or subject and might require medical or surgical intervention to prevent one of the outcomes listed above. Five patients (33.3%) reported experiencing a treatment-emergent SAE: knee deformity (genua valga both sites), joint swelling (swollen ankle), Sjogren's syndrome, sepsis and acute renal failure. Only one patient was considered to have a treatment-related SAE (acute renal failure, CS, p155[2]), although there was no reported SAE in the placebo arm. According to the CS[2] and CSR[10], no patients discontinued treatment due to any AE during the rhLAMAN-05[10] trial, and there was also no death in any arm during the trial. These data were confirmed by the company following a clarification request (clarification response to question A35).[11]

Table 20: Numbers of overall adverse events, severe and treatment-related adverse events, and events leading to treatment discontinuation (rhLAMAN-05[10]) (reproduced from CS, Table 32)

AE	VA (n=15)		Placebo (n=10)	
	n (%)	Events	n (%)	Events
Summary of AEs				
Any AE	15 (100.0)	157	9 (90.0)	113
Treatment-related AE	7 (46.7)	30	5 (50.0)	9
SAE	5 (33.3)	5	0	0
Treatment-related SAE	1 (6.7)	1	0	0
Severe AE*	1 (6.7)	1	0	0
Discontinuations due to AE	0	0	0	0

Abbreviations: AE, adverse event; VA, velmanase alfa. *No definition provided in CS or CSR.

The most frequent AEs experienced by two or more patients receiving velmanase alfa in the 12-month rhLAMAN-05[10] trial were: infections (86.7%), principally nasopharyngitis (66.7%); gastrointestinal disorders (60%), especially vomiting (20.0%); pyrexia (40.0%); headache (33.3%) and arthralgia (20.0%) (Table 21). The reported rates of many adverse events were similar between study arms, but some adverse events were reported more frequently in the velmanase alfa arm than the placebo arm: toothache, syncope, hypersensitivity and the infections of acute tonsillitis, influenza and gastroenteritis were reported in two patients (13.3%) in the velmanase alfa group compared with no patients (0%) in the placebo group. A number of AEs were also reported more frequently in the placebo arm than the velmanase alfa arm: vomiting (40.0% in the velmanase alfa group vs 20.0% in the placebo group

respectively), diarrhoea (30.0% vs 13.3%), pyrexia (50.0% vs 40.0%) and ear discomfort (20.0% vs 0%).

Table 21: Numbers of patients experiencing adverse events, >2 patients in any arm (rhLAMAN-05[10]) (reproduced in part from CS, Table 32 and CSR Table 12-2)

AE	VA (n=15)		Placebo (n=10)	
	n (%)	Events	n (%)	Events
Infections and infestations	13 (86.7)	48	7 (70.0)	23
Nasopharyngitis	10 (66.7)	30	7 (70.0)	16
Ear infection	2 (13.3)	2	1 (10.0)	1
Acute tonsillitis	2 (13.3)	2	0	0
Influenza	2 (13.3)	2	0	0
Gastroenteritis	2 (13.3)	2	0	0
Gastrointestinal disorders	9 (60.0)	18	8 (80.0)	24
Vomiting	3 (20.0)	5	4 (40.0)	6
Diarrhoea	2 (13.3)	2	3 (30.0)	3
Toothache	2 (13.3)	3	0	0
General disorders and administration site conditions	6 (40.0)	20	7 (70.0)	18
Pyrexia	6 (40.0)	11	5 (50.0)	11
Musculoskeletal and connective tissue disorders	7 (46.7)	11	5 (50.0)	16
Arthralgia	3 (20.0)	4	1 (10.0)	6
Back pain	2 (13.3)	2	1 (10.0)	1
Nervous system disorders	6 (40.0)	11	5 (50.0)	12
Headache	5 (33.3)	7	3 (30.0)	9
Dizziness	1 (6.7)	1	2 (20.0)	2
Syncope	2 (13.3)	2	0	0
Respiratory, thoracic and mediastinal disorders	4 (26.7)	7	2 (20.0)	4
Immune system disorders	2 (13.3)	5	2 (20.0)	2
Hypersensitivity	2 (13.3)	5	0	0
Ear and labyrinth disorders	0	0	3 (30.0)	3
Ear discomfort	0	0	2 (20.0)	2

Abbreviations: AE, adverse event; VA, velmanase alfa.

rhLAMAN-10[1]

The mean (SD) number of infusions reported in the CSR[1], p.150, for the rhLAMAN-10[1] study was 84.8 (63.1) overall (compared with 62.8 in the rhLAMAN-05 trial[10]), with a higher number reported in patients who participated in the rhLAMAN-02[13] study, and therefore in patients aged <18 years. In this study, the actual exposure of patients to velmanase alfa ranged from 357 to 1625 days, with greater exposure in patients who participated in the earliest phase I/II study, rhLAMAN-02[13] (mean exposure 1585.2 days), than in the more recent rhLAMAN-05[10] phase III study (mean exposure 630.0 days).

Almost all patients in the treatment-arm of the rhLAMAN-10[1] study reported at least one AE (Table 22). The proportions of patients in rhLAMAN-10[1] (n=33) being treated with velmanase alfa and experiencing AEs were similar to the proportions in the treatment arm of the rhLAMAN-05[10] trial (n=15): 17 patients (51.5%) reported 'treatment-related AEs'(weight increase, pyrexia and diarrhoea all affected three or more patients: CSR[1], page 156); 12 patients (36.4%) experienced a SAE; two (6.1%) experienced a treatment-related SAE (sepsis and loss of consciousness, CSR[1], p157-58) and three

(9.1%) a severe AE (pyrexia and tremor in one patient, loss of consciousness in one patient and sepsis in one patient: CSR[11], p156). Sepsis was the only SAE common to both rhLAMAN-05[10] and rhLAMAN-10.[1] The CS,[2] p158, reported that three patients in the velmanase alfa trial arm experienced 19 events categorised as IRRs (14 events for a single patient), but which were all considered to be mild or moderate in intensity.

Table 22: Numbers of adverse events, severe and treatment-related adverse events, and events leading to treatment discontinuation overall, and by age group (rhLAMAN-10[1]) (reproduced from CS, Table 34 and Table 62 from CSR, p.152)

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Any AE	29 (87.9)	546	17 (89.5)	423	12 (85.7)	123
Treatment-related AE†	17 (51.5)	84	12 (63.2)	69	5 (35.7)	15
SAE	12 (36.4)	14	7 (36.8)	9	5 (35.7)	5
Treatment-related SAE	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Severe AE*	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Discontinuations due to AE	0	0	0	0	0	0

Abbreviations: AE, adverse event; VA, velmanase alfa. *No definition provided in CS or CSR †Categorised as adverse drug reaction (ADR) in the CSR

As with the placebo-controlled, phase III trial rhLAMAN-05[10], according to the CS[2] and CSR[10], no patients discontinued treatment due to any AE during the rhLAMAN-10[1] study, and there was also no death during follow-up. These data were confirmed by the company following a clarification request (clarification response to question A35).[11] The proportion of patients experiencing AEs was generally similar across age groups, with the exception of treatment-related AEs and severe AEs. The percentage of patients affected by AEs was higher in the younger age group (<18 years of age) than in the older age group (>18 years of age): 63.2% of the younger patients reported treatment-related AEs compared to 35.7% of older patients; and 10.5% of the younger patients reported severe AEs compared to 7.1% of older patients (Table 21). These latter percentages represent the difference of only a single patient, but the ERG notes that the younger patients did have longer exposure to treatment than the older patients (CSR, p151).[1]

A broader range of AEs were reported as being experienced by two or more patients receiving velmanase alfa in the 12 to 48 month rhLAMAN-10[1] study (n=33) (Table 23). However, the most frequently-reported AEs were similar to the rhLAMAN-05[10] trial and also affected similar proportions patients, that is, nasopharyngitis (69.7% for rhLAMAN-10[1] vs 66.7% for rhLAMAN-05[10] respectively); gastrointestinal disorders (63.6% vs 60.0%), especially vomiting (30.3% vs 20.0%); pyrexia (33.3% vs 40.0%); headache (39.4% vs 33.3%) and arthralgia (21.2% vs 20.0%). Other specific AEs affecting five or more patients (>15%) were diarrhoea (27.3%), ear infections, gastroenteritis, weight increase, contusion and pain in extremity (18.2%), psychiatric disorders, excoriation and rash (15.2%). The ERG

notes that the frequency of patients reporting diarrhoea (13.3% compared with 27.3%) was much lower in the velmanase alfa arm in the rhLAMAN-05[10] trial.

The proportion of patients experiencing many AEs was higher in the younger age group (<18 years of age) (n=19) than in the older age group (≥18 years of age) (n=14) in the rhLAMAN-10[1] study. The AEs reported as being more frequently experienced in the younger age group included: most gastrointestinal disorders, especially vomiting (42.1% in the group aged <18 years vs 14.3% in the group aged ≥18 years); diarrhoea (31.6% vs 21.4%) and upper abdominal pain (21.1% vs 0%); pyrexia (47.4% vs 14.3%); headache (47.4% vs 28.6%); contusion (31.6% vs 0%); excoriation (26.3% vs 0%) and wound (31.6% vs 7.1%); weight increase (31.6% vs 0%); pain in extremity (26.3% vs 7.1%); dizziness (15.8% vs 0%); cough (42.1% vs 7.1%); and tooth extraction (21.1% vs 0%). Only peripheral oedema (5.3% in the group aged <18 years vs 14.3% in the group aged ≥18 years), pollakiuria (0% vs 14.3%), rash (10.5% vs 21.4%) and hypersensitivity (10.5% vs 14.3%) were higher in the older age group.

Although the rhLAMAN-10[1] integrated data set included safety data from the earlier Phase I/II trials (rhLAMAN-02[13], rhLAMAN-03[15], rhLAMAN-04[14]), these studies did report higher proportions of patients with the AEs of nasopharyngitis (90%-100% in the phase I/II trials vs 69.7% in rhLAMAN-10[1]), weight increase, headache and pyrexia (60% for each event in the Phase I/II trials vs 18.2%, 39.4% and 33.3% respectively in rhLAMAN-10).[1] These differences might be explained in part by differences in the trial populations: the participants in the earlier Phase I/II trials were aged 5-20 years (CS[2], Table 5, p80) and their higher reported rates of AEs are consistent with the higher reported rates of AEs in the <18 years age group of the rhLAMAN-10[1] study (Table 23), although this might also be due to increased exposure to velmanase alfa.

Table 23: Numbers of patients experiencing adverse events, >1* patients in any arm, overall and by age group (rhLAMAN-10[1]) (reproduced in part from CS, Table 34 and CSR Table 63)

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Blood and lymphatic system disorders	2 (6.1)	2	2 (10.5)	2	0	0
Lymphadenopathy	2 (6.1)	2	2 (10.5)	2	0	0
Ear and labyrinth disorders	4 (12.1)	8	3 (15.8)	7	1 (7.1)	1
Eye disorders	8 (24.2)	18	5 (26.3)	10	3 (21.4)	8
Conjunctival hyperaemia	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Eye infection	2 (6.1)	2	2 (10.5)	2	0	0
Eye pruritus	3 (9.1)	5	2 (10.5)	4	1 (7.1)	1
Gastrointestinal disorders	21 (63.6)	51	13 (68.4)	36	8 (57.1)	15
Abdominal pain	3 (9.1)	3	3 (15.8)	3	0	0
Abdominal pain upper	4 (12.1)	4	4 (21.1)	4	0	0
Diarrhoea	9 (27.3)	11	6 (31.6)	7	3 (21.4)	4
Nausea	3 (9.1)	3	3 (15.8)	3	0	0
Reflux gastritis	2 (6.1)	2	2 (10.5)	2	0	0
Toothache	2 (6.1)	3	2 (14.3)	3	0	0
Vomiting	10 (30.3)	14	8 (42.1)	12	2 (14.3)	2
General disorders and administration site conditions	17 (51.5)	59	11 (57.9)	46	6 (42.9)	13
Chills	2 (6.1)	9	2 (10.5)	9	0	0
Fatigue	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Malaise	2 (6.1)	3	2 (10.5)	3	0	0
Oedema peripheral	3 (9.1)	3	1 (5.3)	1	2 (14.3)	2
Pyrexia	11 (33.3)	26	9 (47.4)	23	2 (14.3)	3
Immune system disorders	4 (12.1)	10	2 (10.5)	5	2 (14.3)	5
Hypersensitivity	4 (12.1)	9	2 (10.5)	4	2 (14.3)	5
Infections and infestations	24 (72.7)	141	15 (78.9)	112	9 (64.3)	29
Acute tonsillitis	2 (6.1)	2	2 (10.5)	2	0	0
Ear infection	6 (18.2)	7	4 (21.1)	5	2 (14.3)	2
Gastroenteritis	6 (18.2)	7	5 (26.3)	6	1 (7.1)	1
Influenza	3 (9.1)	3	2 (10.5)	2	1 (7.1)	1
Laryngitis	2 (6.1)	2	2 (10.5)	2	0	0
Nasopharyngitis	23 (69.7)	89	14 (73.7)	71	9 (64.3)	18
Urinary tract infection	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Otitis media	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Injury, poisoning and procedural complications	15 (45.5)	65	13 (68.4)	63	2 (14.3)	2
Arthropod bite	3 (9.1)	4	3 (15.8)	4	0	0
Contusion	6 (18.2)	10	6 (31.6)	10	0	0
Excoriation	5 (15.2)	18	5 (26.3)	18	0	0
Ligament sprain	2 (6.1)	2	2 (10.5)	2	0	0
Post lumbar puncture syndrome	4 (12.1)	4	3 (15.8)	3	1 (7.1)	1
Wound	7 (21.2)	10	6 (31.6)	9	1 (7.1)	1
Investigations	11 (33.3)	14	10 (52.6)	13	1 (7.1)	1
Weight increased	6 (18.2)	7	6 (31.6)	7	0	0
Metabolism and nutrition disorders	4 (12.1)	4	2 (10.5)	2	2 (14.3)	2
Increased appetite	2 (6.1)	2	2 (10.5)	2	0	0
Musculoskeletal and connective tissue disorders	18 (54.5)	47	11 (57.9)	38	7 (50.0)	9
Arthralgia	7 (21.2)	14	5 (26.3)	10	2 (14.3)	4
Back pain	5 (15.2)	5	3 (15.8)	3	2 (14.3)	2
Myalgia	2 (6.1)	3	2 (10.5)	3	0	0

AE	Overall (n=33)		<18 years (n=19)		≥18 years (n=14)	
	n (%)	Events	n (%)	Events	n (%)	Events
Pain in extremity	6 (18.2)	14	5 (26.3)	13	1 (7.1)	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (6.1)	2	2 (10.5)	2	0	0
Skin papilloma	2 (6.1)	2	2 (10.5)	2	0	0
Nervous system disorders	16 (48.5)	43	10 (52.6)	34	6 (42.9)	9
Dizziness	3 (9.1)	4	3 (15.8)	4	0	0
Headache	13 (39.4)	27	9 (47.4)	22	4 (28.6)	5
Loss of consciousness	2 (6.1)	2	2 (10.5)	2	0	0
Syncope	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Psychiatric disorders	5 (15.2)	10	3 (15.8)	4	2 (14.3)	6
Renal and urinary disorders	4 (12.1)	5	1 (5.3)	1	3 (21.4)	4
Pollakiuria	2 (6.1)	2	0	0	2 (14.3)	2
Respiratory, thoracic and mediastinal disorders	15 (45.5)	28	11 (57.9)	20	4 (28.6)	8
Bronchitis	2 (6.1)	2	2 (10.5)	2	0	0
Cough	9 (27.3)	12	8 (42.1)	11	1 (7.1)	1
Rhinorrhoea	3 (9.1)	4	2 (10.5)	3	1 (7.1)	1
Skin and subcutaneous tissue disorders	14 (42.4)	23	9 (47.4)	13	5 (35.7)	10
Acne	2 (6.1)	2	0	0	2 (14.3)	2
Erythema	4 (12.1)	5	3 (15.8)	4	1 (7.1)	1
Rash	5 (15.2)	5	2 (10.5)	2	3 (21.4)	3
Scar pain	2 (6.1)	2	1 (5.3)	1	1 (7.1)	1
Surgical / medical procedures	8 (24.2)	11	8 (42.1)	11	0	0
Catheter removal	2 (6.1)	2	2 (10.5)	2	0	0
Ear tube insertion	2 (6.1)	2	2 (10.5)	2	0	0
Tooth extraction	4 (12.1)	4	4 (21.1)	4	0	0
Vascular disorders	3 (9.1)	3	2 (10.5)	2	1 (7.1)	1

Abbreviations: AE, adverse event; VA, velmanase alfa.
* reported as >1 in CSR[1] Table 63, or ≥1 in the CS.[2]

Summary

The proportion of patients receiving velmanase alfa and experiencing any AE is high (88%-100%); approximately one half experienced a treatment-related AE and one third a SAE. However, most AEs were reported as being mild or moderate. No patient in either of the rhLAMAN-05[10] or rhLAMAN-10[1] studies discontinued treatment due to AEs, although three patients in other studies did so: one from the Phase I/II trial rhLAMAN-03[15] but who entered the rhLAMAN-05[10] trial; one in the compassionate use programme, and one patient who ultimately chose not to re-enrol for the rhLAMAN-10[1] study (clarification response to question A35[11]). No deaths were reported. The safety data were well-reported and comprehensive and, for a small number of patients, represented follow-up of 24 months (n=19) and 48 months (n=9), respectively (CSR[1], pages 150-51). However, the number of patients is small, treatment would be received, in practice, for very many years (life-long), and there is possible correlation between increased exposure and higher rates of AEs.

4.3 Conclusions of the clinical effectiveness section

The ERG believes the CS[2] is complete with respect to evidence relating to velmanase alfa. The evidence base comprised one double-blind, placebo controlled RCT (rhLAMAN-05,[10] n=25) and one long-term, single arm, open label study (rhLAMAN-10,[1] n=33).

The patient spectrum of the evidence base is likely to be younger than the population in England due to the inclusion criteria (5 to 35 years old), and it may be easier to detect an effect in younger patients if disease progression is more rapid. It is unclear whether some of the patients included in the studies may have been eligible for HSCT in some clinical practices in England. The company provided draft start/stop criteria which, if applied in clinical practice, would be likely to exclude some patients who continued treatment in the trials. In clinical practice, therefore, fewer patients may be eligible for long term treatment, but for those who are, the studies are likely to have underestimated population-level efficacy.

The ERG were concerned about serum oligosaccharides being the co-primary outcome as this is a surrogate biomarker with pharmacokinetic relevance, but low clinical relevance and which has not been assessed as a surrogate using standard criteria. 3-MSCT, 6-MWT and FVC were the co-primary and prioritised (rhLAMAN-05)[10] secondary outcomes. Quality of life was measured using CHAQ and EQ-5D-5L. These are other secondary outcomes appeared relevant, but infections, which have a big impact on patients and which were listed in the NICE scope, were not measured.

rhLAMAN-05[10] appears reasonably well conducted, though some elements are at unclear risk of bias. The small numbers (n=25) are to be expected given the rarity of the condition. There was a statistically significant decrease in serum oligosaccharides, but no statistically significant decreases in the clinical co-primary and prioritised secondary outcomes or on the other secondary outcomes of motor function, cognition and hearing. It is unclear if the study met its definition for demonstrating efficacy. No comparative analyses of quality of life outcomes were provided. The observed differences for most outcomes did not meet MCIDs where these were provided. The lack of statistically significant results for the clinical outcomes means it is unclear whether the effect of velmanase alfa on the biomarker translates to an impact on clinical outcomes.

rhLAMAN-10[1] is a non-controlled, experimental study akin to a cohort study. The design has some risk of bias and due to the lack of a control arm the results are difficult to interpret. The length of follow-up varied a great deal for patients (12 months to 48 months), with variable and smaller numbers, sometimes comprising different patients altogether, at the time points beyond 12 months. The last observation analysis generally included all patients and for the four main outcomes (serum oligosaccharides, 3-

MSCT, 6-MWT, FVC % predicted) there was very little difference between the 12 month and the last observation analyses (though the mean length of follow-up in the last observation analysis is unclear).

Post-hoc analyses of the interaction between age groups in rhLAMAN-10[1] indicate that whilst there is no difference between younger (<18 years of age) and older (≥18 years of age) patients in serum oligosaccharides, there is in the clinical outcome of 3-MSCT. No other interaction tests were reported. Observed differences in clinical outcomes between younger and older patients in both trials are generally greater in the younger patients.

Adverse events were frequent in both studies, but mostly mild to moderate. The safety of treatment over a lifetime is unknown.

5 COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.[2]

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The CS[2] includes a review of cost-effectiveness evidence related to the decision problem, essentially based on the same broad searches as the review of clinical effectiveness with the addition of EconLit specifically for the purpose of identifying economic studies.

As noted in Section 4.1.1, these included all the databases usually recommended by NICE (Medline; EMBASE; Cochrane Library and EconLit); a selection of relevant conference proceedings and HTA reports; and an additional list of registers specifically designed to identify cost-effectiveness evidence (all detailed in CS Appendix 17.3.5.1).[2]

The search strategies (reproduced again in CS Appendix 3, Section 17.3)[2] were highly sensitive and designed to retrieved all published studies related to the disease area (AM), without applying any restrictive filters to limit the types of evidence retrieved. Results were then manually sifted for inclusion or exclusion in the parallel reviews looking at clinical effectiveness, cost-effectiveness, cost and resource use and health-related quality of life, with PRISMA flowcharts provided for each review.

The inclusion criteria for the economic and HRQoL reviews are provided in

Table 24, which is a reproduction of Table 46 from the CS.[2] The eligibility criteria for inclusion in the HRQoL review is provided in Table 25 which is a reproduction on Table 38 of the CS.[2]

Table 24: Inclusion criteria for health economic studies

Inclusion criteria	
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age).
Interventions	Not restricted (see Section 17.1.6 for details on treatments to include).

Outcomes	**Economic evaluation SR**
	• Main outcomes:
	  o ICERs: cost per QALY, cost per DALY, cost per event avoided
	• Additional outcomes:
	  o Range of ICERs as per sensitivity analyses
	  o Assumptions underpinning model structures
	  o Key cost drivers
	  o Sources of clinical, cost and quality of life inputs
	  o Discounting of costs and health outcomes
	  o Model summary and structure
	Cost of illness/resource use SR
	• Direct costs
	• Direct medical and pharmacy healthcare costs per patient per year (interventions, concomitant medications, treatment of AEs/co-morbidities)
	• Method of valuation
	• Indirect costs
	  o Productivity loss costs
	  o Presenteeism: at work productivity level (also from patients' viewpoint)
	  o Short- and long-term sick leave (absenteeism)
	  o Withdrawal from labour force
	  o Method of valuation (Human capital or friction cost approach or contingent valuation)
	  o Costs of special schooling for patients
	  o Costs of adapting home settings to account for progressive disability
	• Patient and family/caregiver costs
	  o Travel, co-payments
	  o Annual loss of income
	  o Formal and informal care
	• Caregiver burden

Study design	**Economic evaluation SR**
	• Cost-utility analyses
	• Cost-effectiveness analyses
	• Cost-benefit analyses
	• Cost-minimisation analyses
	Cost of illness/resource use SR
	• For studies to be eligible:
	  o Epidemiological approach should be specified for the design
	  o Perspective of the study should be clear
	  o Objectives of the study must include an assessment of costs of illness or an assessment of interventions in management of AM
	  o Studies reporting predictors of costs were considered for inclusion

Language restrictions	Unrestricted
Search dates	Unrestricted

Exclusion criteria	
Population	Patients aged <6 years with AM (all patients were included at first pass regardless of age).
Interventions	Unrestricted
Outcomes	Restricted to those stated in the eligibility criteria.
Study design	Restricted to those stated in the eligibility criteria.
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: AE, adverse events; AM, alpha- mannosidosis; CSF, cerebrospinal fluid; DALY, Disability-adjusted life year; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SR, systematic review.

Table 25: Eligibility criteria for inclusion in the HRQoL review

Criteria	Include
Population	Patients aged ≥6 years with AM (all patients were included at first pass regardless of age)
Treatments	No restriction
Outcomes	HSUV/QoL SR • Utilities values directly elicited using TTO/SG techniques • Utility values derived using generic preference-based instruments for relevant health states (e.g. EQ-5D, SF-6D, HUI3) • Mapping studies allowing generic or disease-specific measures to be mapped to preference-based utilities • Generic or disease-specific measures reporting the QoL associated with AM
Setting/study design	HSUV/QoL SR, no limitation and to include: • HSUV elicitation studies • Interventional studies • Observational studies e.g. cohort studies
Language of publication	No restriction. On completion of citation screening on the basis of title and abstract, a list of foreign-language publication was forwarded to Chiesi. A decision was then taken on whether the studies were conducted in a country of interest.
Date of publication	No restriction
Countries/global reach	No restrictions

Abbreviations: AM, alpha-mannosidosis; EQ-5D, EuroQol five dimensions questionnaire; HUI3, health utilities index Mark 3; HSUV, health-state utility value; QoL, quality of life; SG, standard gamble; SF-6D, short form 6D; SR, systematic review; TTO, time-trade-off.

5.1.2 Results produced from the company's systematic review of cost-effectiveness evidence

The company's initial search initially identified 1556 unique publications, which were reduced to 100 following screening of titles and abstracts. The full texts of these 100 studies were reviewed with the company determining that no studies reported an economic evaluation or cost/resource use. In the updated search, 65 unique records were identified; all of these were excluded following screening of title and abstract.

5.2 Description of the company's model

5.2.1 Model scope

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's economic analysis is summarised in Table 26. The ERG notes that this covers the outcomes contained in the final NICE scope.[9]

Incremental health gains, costs and cost-effectiveness of velmanase alfa are evaluated over a 100-year time horizon from the perspective of the UK NHS and Personal Social Services (PSS). All costs and health outcomes are discounted at a rate of 1.5% per annum. Unit costs are valued at 2016 prices.

Table 26: Summary of company's health economic model scope

Population	Patients aged six years and over with AM. This is subdivided into a paediatric cohort (6 to 11 years), an adolescent cohort (12 to 17 years) and an adult cohort (18 years and over)
Intervention	Once weekly treatment with velmanase alfa, administered intravenously, at a dose of 1mg/kg of body weight. Treatment is intended to be lifelong although the company propose both start and stop criteria that are described in this section.
Comparator	BSC†
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	100 years
Discount rate	1.5% per year
Price year	2016

BSC – Best Supportive Care; NHS – National Health Service; PSS – Personal Social Services; QALY – Quality-Adjusted Life Years.

† Note Haematopoietic Stem Cell Transplant was not included despite being in the final scope.

Population

The population considered within the company's economic analysis relates to patients aged six years and over with AM. These patients are divided into a 'paediatric cohort' (6 to 11 years of age), an 'adolescent cohort' (12 to 17 years of age) and an 'adult cohort' (aged 18 years and older). Within the company's clarification response[11] (question A9) it was stated that '*The European Medicines Agency (EMA) has adopted a positive opinion to velmanase alfa with a therapeutic indication not restricted by age, so as to no longer exclude patients aged under 6 years.*' However, the company also state that '*no clinical trial data concerning the efficacy and safety of velmanase alfa are available for patients aged 5 years and under; therefore, a clinical and economic case is put forward in this highly specialised technology (HST) evaluation for an AM population aged 6 years and older*.'

The company have proposed the following criteria, which if any are met, means that a patient would not be eligible for velmanase alfa treatment. Collectively these criteria have been termed the 'start criteria'.

- The patient does not have a confirmed diagnosis of AM; or

- The patient has experienced a severe allergic reaction to velmanase alfa or to any of the excipients (disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol and glycine); or
- The patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- The patient is unwilling or unable to comply with the associated monitoring criteria, i.e. that all patients are required to attend their appointed clinics two times per year for assessment

Intervention

The intervention under consideration is velmanase alfa (given alongside BSC). Velmanase alfa is assumed to be administered intravenously at a dose of 1mg/kg of body weight with the intended duration of treatment being lifelong.

The company have proposed the following set of criteria, which if any are met, would result in the cessation of velmanase alfa treatment. Collectively, these criteria are termed the 'stop criteria'.

- the patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 18-month period); or
- the patient fails to meet two of the three criteria as defined in multi-domain responder analysis at their Year 1 assessment (see Sections 9.4.1.4 and 9.6.1.3 of the CS[2])
- the patient is unable to tolerate infusions due to infusion related severe AEs that cannot be resolved; or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g. due to repeated recurrent chest infection or progressive and sustained lack of mobility; or
- the patient misses more than four infusions of velmanase alfa in any 12-month period, excluding medical reasons for missing dosages.

Comparator

The comparator included in the company's model is BSC. The company consulted key opinion leaders (KOLs) who stated that BSC was defined as a "*needs based approach to treatment, dealing with symptoms as they arise*" which may include the following treatments, amongst others.

- Provision of walking aids and wheelchairs, and home adaptations
- Aggressive management of infections

- Major surgical interventions (ventriculoperitoneal shunts, cervical spine decompression, joint replacement)
- Minor surgical intervention (tonsillectomy/adenoidectomy, grommet surgery [insertion and removal], umbilical/inguinal hernia repair, carpal tunnel release surgery, feeding tube insertion)
- Physiotherapy, including hydrotherapy
- Ventilation support
- General treatment of comorbidities
- Supportive measurements at home (hoists etc.)

In addition, monitoring and preventative measures would be necessary to detect or manage emerging problems which could include the following.

- MRI of brain and spine
- Skeletal surveys and respiratory function testing (routinely done in paediatric patients)
- Cardiac echo/ECG (typically done in older/adult patients)
- Prophylactic use of antibiotics

BSC is typically provided by a multidisciplinary team (MDT). In the UK, it is the metabolic consultant who is likely to be the primary physician.

The ERG notes that HSCT was not included in the model by the company despite being contained in the final scope.[9] Clinical advice received by the ERG and submitted to NICE suggests that HSCT may be an appropriate intervention for a small proportion patients. The clinical effectiveness and cost-effectiveness of velmanase alfa in patients who are suitable for HSCT are unknown.

5.2.2 Description of the company's health economic model structure and logic

Within this appraisal, the clarification process worked efficiently and many of the errors and/or limitations identified by the ERG in the initial two-week period were corrected by the company. See the clarification response by the company[11] and Table A in the revised results section presented after clarification,[30] for further details, Only the latest version of the model, and the revised results received by the ERG on the 23rd of February 2018 are discussed in this report unless it is imperative to detail those in a previous version. The net result of the amendments was to improve the cost-effectiveness of velmanase alfa compared with the company's reported base case.

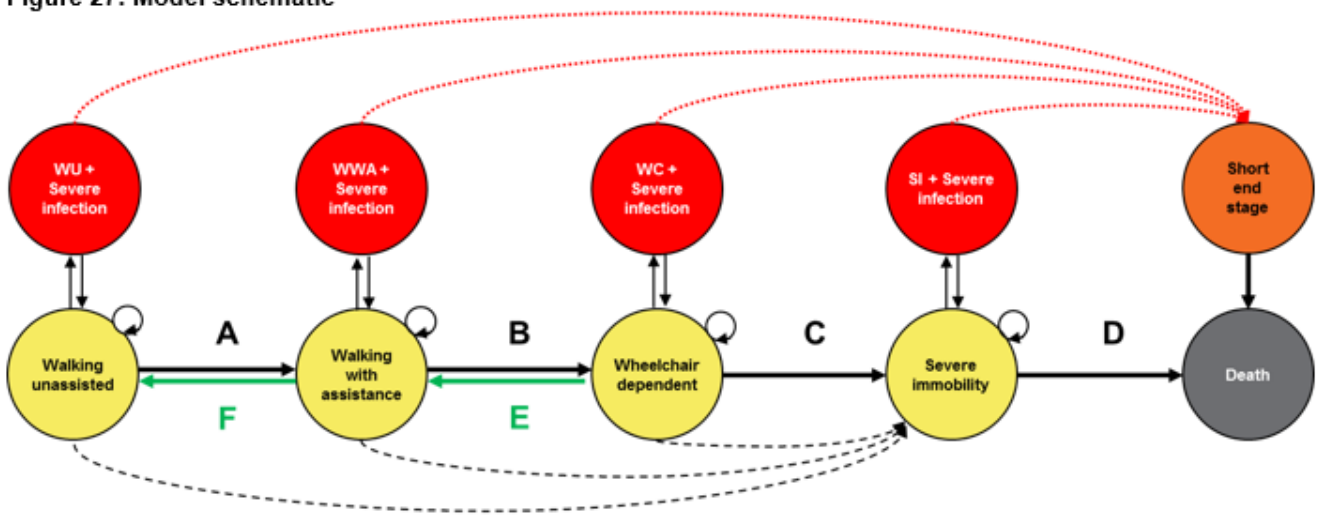
The general structure of the company's model is presented in Figure 3. The model is a state transition model with a time cycle of 1 year and a time horizon of 100 years.

The model has five primary health states: (i) walking unassisted; (ii) walking with assistance; (iii) wheelchair dependent; (iv) severe immobility and (v) dead. For patients on BSC, there is a probability that the condition will worsen and that the patient moves to the next most severe primary health state (equivalent to arrows A, B, C and D in Figure 3). These transitions are also relevant for patients on velmanase alfa treatment, although the company has assumed that it is possible for a patient on velmanase alfa treatment to improve health status (as shown with arrows E and F in Figure 3) but not for patients receiving BSC to improve.

In addition to the primary health states there are four tunnel states that patients enter when experiencing a severe infection. At the end of the time cycle a patient returns to the primary health state in which they were in before the severe infection, unless they are simulated to not recover from the severe infection, in which case they enter the short end stage health state. Once in the short end stage, the patient is assumed to die within four weeks.

Figure 3: Company's model structure (reproduced from CS, Figure 27)

Figure 27: Model schematic



Each health state accounts for the key drivers of disutility and costs due to the functional impairment, hearing impairment, cognitive impairment and pain experienced by patients with alpha mannosidosis

- Tunnel state: accounts for the cost, disutility and mortality risk associated with a severe infection
- Primary health state: patients start in the model in one of the four primary health states
- Short end stage: patients can only transition to short end stage from a severe infection tunnel state
- Death: patients can transition to death due to background mortality or surgery-related mortality from any health state
- Green arrow designates a disease improvement transition due to treatment with velmanase alfa
- Dashed arrow designates a transition to severe immobility as a result of a post-surgical complication
- Dashed arrow designates a transition to short end stage as a result of a severe infection that leads to death

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

Surgical complications can move a patient from any of the walking unassisted, walking with assistance, and wheelchair dependent states to the severe immobility state or to death. Death from causes unrelated to AM or the treatment of AM can occur at any time point, with the background rate of mortality taken from UK life tables.[31]

Each health state in the model has an associated cost per cycle and utility. These are detailed in Sections 5.2.3.8 and Sections 5.2.3.16 respectively.

The assumed functional status associated with the four living states is provided in Table 27.

Table 27: Clinical features of the primary health states defined by the company

State	Clinical features
Walking unassisted	• Patient is able to walk and go upstairs unassisted • Patient may have radiological skeletal abnormalities, but these may not present as clinical symptoms • Ataxia may be present but it does not greatly impact the patients' mobility
Walking with assistance	• The patient requires any form of assistance to walk (e.g. help from another person, footwear to support stability, a walking cane, wheelchair for long distances, hand rails etc.) • Patient may have radiological skeletal abnormalities presenting as clinical symptoms • Ataxia may be present and it may impact a patients' mobility
Wheelchair dependent	• Endurance is reduced; the patient is wheelchair-bound, but can still operate walking aids/use assistance to traverse short distances • Patient has some joint destruction that impacts mobility, however the patient can still transfer themselves without carer support (e.g. the patient can transfer from the wheelchair into bed independently) • Patient presents with some joint weakness and loss of joint flexibility
Severe immobility	• Patient requires a wheelchair/mobility device continuously and cannot transfer independently (i.e. requires hoists and other assistive equipment) • Joint destruction is present in weight-bearing joints (cervical spine, hips and/or knees), which severely restricts movement • Patient presents with poor muscle function and manual dexterity; for example, dressing unaided is impossible

5.2.3 Assumptions and evidence used to inform the model parameters

The parameters are detailed in the forthcoming sections. For ease of reference, Section 5.2.3.21 provides a summary of the sources used for parameters to which the ICER is particularly sensitive. The majority of these parameters are populated either through data obtained in an elicitation session or interviews with UK KOLs and are not informed by data observed in clinical studies. Details of the elicitation session and interviews are provided in Sections 5.2.3.1 and 5.2.3.2.

5.2.3.1 Details of the elicitation exercise.

The company described the elicitation process in Section 12.2.5 of the CS.[2] Additionally the company provided a 174 document extensively detailing the elicitation process. In brief, five clinical experts (out of ten contacted) participated, representing four LSD centres in the UK. The Sheffield Elicitation Framework (SHELF) methodology was followed which is appropriate. All experts received honoraria (funded by Chiesi) to cover the time required to prepare for the elicitation exercise (pre-reading of the evidence dossier) and attendance at a one-day elicitation panel.

5.2.3.2 Details of the interviews with KOLs.

The company described the elicitation process in Section 12.2.5 of the CS.[2] In brief, the interview process had three stages. The company stated that the first (18 questions) supported the early scoping / design stages of developing the model, the second (29 questions) generated and validated key assumptions in the model, and the third (36 questions) generated and validated key model parameters for which published data in AM patients did not exist. Ten KOLs were contacted of which five participated in at least one stage of the interview process. All five KOLS had experience of treating AM with BSC, although only one had experience of treating AM with an ERT. However, all five had experience of using an ERT in LSD. Pre-reading was supplied to KOLs before each interview. In each interview, questions and data were displayed to KOLs via teleconference and a WebEX link. Each KOL had to confirm in writing that the minutes and summary were an accurate reflection of the discussions and their responses provided during the interview.

Each KOL received honoraria (funded by Chiesi) to cover the time required to prepare for the interviews (pre-reading of the interview brief and questions) and time to attend at each interview.

5.2.3.3 The population being modelled

The company designated three cohorts: (i) a paediatric cohort; (ii) an adolescent cohort and (iii) an adult cohort.

The starting age of patients within each cohort and the assumed distribution between primary health states assumed by the company are reproduced in

Table 28. The company assumed that all patients were at the lowest age within each age band, and the distribution of patients' functional status across primary health states was taken from rhLAMAN-10.[1]

Table 28: Characteristics of the modelled population assumed by the company

Parameter	Age (years)	WU	WWA	WC	SI
Paediatric	6	78%	22%	0%	0%
WWA to WC	12	73%	27%	0%	0%
WC to SI	18	62%	38%	0%	0%

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

Paediatric and adolescent patients on model entry were assumed to incur the costs associated with adult patients once they became 17 years of age.

5.2.3.4 Disease progression whilst treated with BSC

The company undertook a UK Expert Elicitation Panel to provide information regarding the number of years it was expected that a patient would reside in each of the primary health states before progressing to the next more severe health state when treated with BSC. These disease progression data, which are marked as academic in confidence (AIC) are reproduced with slight amendments in Table 29.

Table 29: Assumed time to disease progression whilst treated with best supportive care

Parameter	Value	95% Credible Interval
Years in State: Best Supportive Care		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

5.2.3.5 Disease progression whilst treated with velmanase alfa

Three further elicitation exercises were undertaken assessing the additional years in each health state that treatment with velmanase alfa would provide divided into results for the paediatric cohort, the adolescent cohort and the adult cohort. For the adult cohort, the company also state that the rhLAMAN-10[1] responder analysis was used, although the ERG did not know how. These disease progression data, which are marked as AIC are reproduced with slight amendments in

Table 30.

Table 30: Assumed time to disease progression whilst treated with velmanase alfa

Variable	Value	95% Credible Interval
Additional years in state associated with velmanase alfa treatment: Paediatric cohort		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]
Additional years in state associated with velmanase alfa treatment: Adolescent cohort		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]
Additional years in state associated with velmanase alfa treatment: Adult cohort		
WU to WWA	[redacted]	[redacted]
WWA to WC	[redacted]	[redacted]
WC to SI	[redacted]	[redacted]
SI to death	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

The ERG notes that the company stated in response to clarification question A44[11] that of those patients in the walking unassisted health state in rhLAMAN-05[10] that 20% (2/10) of people in the velmanase alfa arm deteriorated to the walking with assistance health state whilst 40% (4/10) of people in the placebo arm deteriorated to the walking with assistance health state. Thus, a relative reduction in deterioration was observed for velmanase alfa treatment compared with BSC.

5.2.3.6 Disease improvement

The company assumed that disease improvement, in terms of primary health states was not possible for patients receiving BSC alone. In contrast, for those patients receiving velmanase alfa in the Walking With Assistance and Wheelchair Dependent health states, the company assumed that improvement was possible. These values were informed by the interviews with UK KOL, who were aware of the results from rhLAMAN-10.[1] The assumed yearly transition probabilities are shown in Table 31. The ERG comments that as this is a cohort model that on average, one in 25 patients would move from Wheelchair Dependent to Walking Unassisted in the initial two years. The plausibility of this value is not known.

Table 31: Assumed probability of disease improvements when treated with velmanase alfa

Variable	Value	95% Credible Interval
Transition Probabilities associated with velmanase alfa in years 1 and 2		
WWA to WU	20%	0% to 70%
WC to WWA	20%	0% to 70%
Transition Probabilities associated with velmanase alfa in years 3 and beyond		
WWA to WU	2.5%	0% to 5%
WC to WWA	2.5%	0% to 5%

WC – Wheelchair dependent; WU – Walking unassisted; WWA – Walking With Assistance

The ERG notes that the company stated in response to clarification question A44[11] that of those patients in the walking with assistance health state in rhLAMAN-05[10] that 40% (2/5) of people in both the velmanase alfa and the placebo arm improved to the walking unassisted state. Thus, no relative gain in improvement was observed for velmanase alfa treatment compared with BSC.

5.2.3.7 Velmanase alfa treatment discontinuation

The company assumed that patients would be assessed at the end of 12 months of velmanase alfa treatment and those that did not have an adequate response would have treatment discontinued. Adequate response for a patient was defined as the response criteria being reached in at least two of the three domains, with a patient considered a responder in a domain '*if they showed a response for at least one efficacy parameter within that domain by achieving the adopted MCID for that outcome.*' Based on data from rhLAMAN-05,[10] it was assumed that 86.67% of patients would be classified as responders, and that 13.33% would discontinue at one year. This value was assumed for all age groups and primary health states, with an arbitrary credible interval (CrI) of 10.0% to 16.7%, which was assumed to follow a Beta distribution. The model assumed that there would be no further discontinuation based on response criteria in future years.

The model assumed an underlying discontinuation rate, for reasons including infusion-related reactions, non-compliance, patient preferences and/or occurrence of life limiting conditions (e.g. cancer) of 10% based on interviews with UK KOL with an arbitrary CrI of 7.5% to 12.5%, which was assumed to follow a Beta distribution.

Furthermore, the company state that treatment with velmanase alfa would be discontinued after one year when a patient enters the severe immobility state '*This is to reflect that once a person moves into the severe immobility state, there will be a period where their health status in confirmed by their specialist consultant, and the decision is made in collaboration with the patient and their carer to withdraw active treatment.*' (clarification response,[11] question B1). Treatment with velmanase alfa would be discontinued once a patient entered the short end stage health state.

5.2.3.8 The underlying costs associated with each health state

In Table 65 of the CS,[2] the company provide a summary of the assumed annual costs by health state for patients receiving BSC. These are comprised of costs associated with consultations and costs associated with surgery. The type and frequency of consultations were summarised in Table 66 of the CS, and the unit costs of consultations and surgery were summarised in Table 67 of the CS.[2] For reasons of brevity, neither table is reproduced. The company assumed that the costs reported in

Table 32 are applicable independent of whether the patient was receiving velmanase alfa or whether the patient was receiving BSC. It should be noted that the values reported in the CS do not match those used in the model although the numbers were similar[2]
Table 32 reports the values used in the model.

Table 32: Assumed annual costs by health state

	Year 1		Year 2 and beyond	
Health State	**Paediatric**	**Adult**	**Paediatric**	**Adult**
WU	£4395	£4361	£4108	£4042
WWA	£4089	£4069	£3802	£3750
WC	£3739	£3720	£3453	£3400
SI	£2156	£2145	£1888	£1875
WU + S Inf	£13,040	£16,038	£12,753	£15,718
WWA + S Inf	£12,957	£15,968	£12,670	£15,649
WC + S Inf	£13,029	£16,040	£12,742	£15,721
SI + S Inf	£13,244	£16,264	£12,977	£15,994
SES*	£46.782	£36.603	£46.782	£36.603

SI – Severe Immobility; S Inf – Severe Infection; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
* four weeks' cost only.

5.2.3.9 The additional costs associated with velmanase alfa treatment

The largest cost component of velmanase alfa treatment is that associated with purchasing the intervention, which has a list price of £886.61 (excluding VAT) per 10mg vial. The company have applied for a PAS which will take the form of a simple discount on the price per vial resulting in a cost of [redacted] (excluding VAT) per 10mg vial. Dosing is weight-based with one vial required for patients weighing up to 10kg, two vials required for patients weighing between 10kg and 20kg and so on. For information, this would result in patients weighing between 60 and 70kg having an annual drug acquisition cost of [redacted] (excluding VAT).

The company assumed that the drug would be initiated in a LSD centre for the first three infusions, before the patient moves on to having an infusion in the home setting (98%) or at a local hospital (2%). These proportions were stated by the company to '*capture the minority of patients that may revert to hospital briefly for the management of Infusion-Related Reactions (IRRs), before returning to homecare once the IRRs are resolved.*' Costs associated with infusions at either an LSD centre or a local hospital were assumed to be £213 based on the Outpatient procedure tariff for vascular access except for renal replacement therapy without complication and comorbidity based on NHS National prices and national tariff 2015-16.[32] Home infusions were assumed to be associated with no additional costs. The number of infusions before leaving the care of the LSD centre, and the proportion of patients receiving home infusions were estimated through interviews with UK KOLs.

The weights for each age group were assumed to be fixed by the company as 'clinical data were not available to derive a population distribution from which to estimate an expected number of vials.' The

use of fixed weights is likely to produce inaccurate answers, but it is not clear whether this would favour or disadvantage velmanase alfa.

5.2.3.10 The probability of undergoing major surgery and associated risks and costs

The company assumed that the annual probability of major surgery for patients with AM were as detailed in

Table **33**. These data, which are marked as AIC, were informed by the elicitation exercise undertaken with UK experts. It was assumed that these rates were applicable irrespective of whether the patient was treated with BSC or with velmanase alfa.

Table 33: Assumed yearly probability of major surgery

Health State	Value	95% Credible Interval
WU	[redacted]	[redacted]
WWA	[redacted]	[redacted]
WC	[redacted]	[redacted]
SI	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking unassisted; WWA – Walking With Assistance

Major surgery is associated with potential mortality and potential complications, which the company assumed would leave the patient in the severe immobility health state. Data on the probability of these events were obtained through interviews with UK KOLs (Table 34); each parameter had an assumed CrI that was +/- 50% of the base case value, which was characterised by a Beta distribution. Based on interviews with UK KOLs, the company further assumed that treatment with velmanase alfa would reduce the risk surgery mortality by 50%, reduce the risk of surgical complications by 50% and reduce the recovery time required after surgery by 50%. All of these values had an arbitrary CrI relating to the reduction of 37.5% to 62.5%, which was assumed to follow a Beta distribution.

Table 34: Assumed probability of surgical-related mortality and surgical-related complications

Health State	Surgical-related mortality	Surgical-related complications†
WU	5.00%	10.00%
WWA	5.00%	10.00%
WC	10.00%	20.00%
SI	10.00%	20.00%

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

† Assumed independent of mortality rate.

The costs related to major surgery were assumed by the company to be the mean costs associated with: ventriculoperitoneal shunt; cervical fusion, complex; cervical fusion, very complex; hip replacement;

and knee replacement using NHS Reference costs 2015-2016. This resulted in a value of £11,097 per major surgery. More details are provided in Table 67 of the CS.[2]

5.2.3.11 The probability of minor surgery and associated costs

The probabilities of a patient undergoing minor surgery in a year assumed by the company was informed by the interviews with UK KOLs. The values were: 100% (95% CrI: 75% - 100%) for the Walking Unassisted state, 50% (95% CrI: 37.5% - 62.5%) for both the Walking With Assistance and the Wheelchair dependent state, and 0%, with no allowance for uncertainty for the Severely Immobile state.

The costs related to minor surgery were assumed by the company to be the average costs associated with: tonsillectomy; carpal tunnel surgery; and grommet surgery using NHS Reference costs from 2015-2016. This resulted in a value of £1711 per minor surgery. More details are provided in Table 67 of the CS.[2]

5.2.3.12 The probability of severe infection and associated risks and costs

In the elicitation session with UK experts previously described elicitation was undertaken to form probability distributions related to the annual probability of severe infection for patients receiving BSC. These data, which were marked as AIC, are shown in Table 35. Based on interviews with UK KOLs, the company assumed that treatment with velmanase alfa would reduce the risk of severe infection by 50%.

Table 35: Assumed yearly risks of severe infection

Health State	Value	95% Credible Interval
WU	[redacted]	[redacted]
WWA	[redacted]	[redacted]
WC	[redacted]	[redacted]
SI	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

It was assumed that severe infection was associated with a risk of mortality where the patient spent four weeks in the short end stage health state. The probability of this was elicited from UK experts with the data, that is marked as AIC, reproduced in

Table 36. Based on interviews with UK KOLs, the company assumed that treatment with velmanase alfa would reduce the risk of mortality following a severe infection by 50%; this value was arbitrarily assumed to have a 95% CrI ranging from a 37.5% reduction to a 62.5% reduction, characterised by a Beta distribution. Finally, also based on KOL interviews, the company assumed that a patient receiving velmanase alfa would recover in 50% of the time that it takes a person treated with BSC to recover; this value was arbitrarily assumed to have a 95% CrI ranging from a 37.5% reduction to a 62.5% reduction, characterised by a Beta distribution.

Table 36: Assumed probability of mortality following a severe infection

Health State	Value	95% Credible Interval
WU	[redacted]	[redacted]
WWA	[redacted]	[redacted]
WC	[redacted]	[redacted]
SI	[redacted]	[redacted]

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

The costs associated with severe infections were estimated based on the time spent required in an intensive care unit and a general ward multiplied by their respective unit costs per day. This calculation was undertaken separately for paediatrics and adults (see Table 37). The duration of hospital stay was assumed equal to that required for patients with sepsis, with the values for children being those reported in Paul *et al*.[33] and those for adults being taken from Levy *et al*.[34] The costs per intensive care unit (ICU) stay were a weighted average of multiple NHS Reference costs for paediatrics and multiple NHS Reference costs for adults. Further details are provided in Table 67 of the CS.[2]

Table 37: The costs associated with severe infection

Health State	Patients aged 16 years or younger	Patients aged 17 years or older
ICU length of stay	6.25	7.80
Unit cost per day in ICU	£1671	£1307
General ward length of stay	2.98	15.00
Unit cost per day in a general ward	£273	£273
Total costs	£11,255	£14,286

ICU – Intensive Care Unit

5.2.3.13The requirement for, and the costs of ventilation

The company report the UK KOLs indicated that patient with AM typically require ventilator support as their disease severity worsens. The KOLS also '*suggested that velmanase alfa may help to reduce the need for ventilatory support, due to the positive effects of treatment on lung function*'. The company also reported that '[redacted]' The company assumed that patients on velmanase alfa had 50% of the ventilation requirements associated with BSC, with no allowance for uncertainty. The ventilation costs associated with BSC are provided in

Table 38.

Table 38: Assumed costs of ventilation by health state for patients on best supportive care

Health State	Overnight ventilation	24-hour care ventilation at home	24-hour care ventilation at institution	Total ventilation cost per year
Annual Cost *	£95,448	£285,176	£358,930	-
WU	0%	0%	0%	£0
WWA	0%	0%	0%	£0
WC	20%	0%	0%	£19,090
SI	50%	25%	25%	£208,751

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
* Taken from Noyes *et al.*[35] and inflated to 2016 prices

5.2.3.14 The requirement for caregiver time and associated costs

The company assumed that data included in Hendriksz et al.[36] relating to the hours of caregiver time required per day in patients with Morquio A syndrome were appropriate for patients with AM. An assumption (without further explanation), was used to estimate the proportion of care delivered by professionals in each primary health state. The estimated carer cost per year was calculated by multiplying the proportion of professional carer time by the anticipated hours of care provided by year. These calculations are reproduced in Table 39.

Table 39: Assumed annual costs of professional care by health state

Health State	Hours of Care required per day (95% Credible Interval) [36]	Proportion of care provided by professionals (95% Credible Interval) †	Cost per Year *
WU	1.3 (0.98 – 1.63)	10% (7.5% - 12.5%)	£1139
WWA	3.9 (2.93 – 4.88)	20% (15% - 25%)	£6833
WC	13.8 (10.35 – 17.25)	50% (37.5%- 62.5%)	£60,444
SI	13.8(10.35 – 17.25)	80% (60% - 100%)	£96,710

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
† Assumption (no further details provided).
* Assuming a cost per hour of £24.00 for professional care[37]

During the clarification period, the company commissioned a survey that assessed the caregiver requirements for patients with AM.[38] This report was marked as AIC in its entirety. [redacted] The data obtained within the survey were not used in the cost-effectiveness modelling.

5.2.3.15 The frequency of adverse events and associated costs

The only adverse event included in the model was IRRs. The rate of IRRs reported in rhLAMAN-10[1] (9.1% per annum 95%CrI 6.82% to 11.36%) were assumed by the company to be generalisable were velmanase alfa used in UK practice. The company assumed that IRRs were associated with zero costs. The company state that this is based on White et al. that reports that '*that IRRs in patients with LSDs receiving ERT requires minimal intervention*'.[39] On examination of the reference provided, the ERG did not find the sentence quoted, but believes that the inclusion of the costs of the treatments received, intravenous hydrocortisone only (2%) and combination intramuscular adrenaline, intravenous hydrocortisone and intravenous antihistamine (3%), are unlikely to influence the incremental cost-effectiveness ratio (ICER).

5.2.3.16 The utility assumed in each health state

In the CS,[2] the utility associated with each health state was estimated using clinicians as a proxy using the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire. The estimated values (which are marked as AIC) are shown in Table 40. Disutilities associated with caregivers were estimated by expert clinicians 'mapping' each primary health state onto an expanded disability status scale and using published data relating to patients with multiple sclerosis.[40] The disutilities assumed for a caregiver is apparently for only one person, and were assumed fixed. It was assumed that the utilities associated with the Short End State were equal to those who were severely immobile.

Table 40: Assumed utility associated with each health state

Health State	Utility of the patient – original submission	Utility of the patient – revised submission	Disutility of the caregiver	Cost per year *
WU	[redacted]	0.906	0.01	£1139
WWA	[redacted]	[redacted]	0.02	£6833
WC	[redacted]	0.100	0.05	£60,444
SI / SES	[redacted]	-0.011	0.14	£96,710

SES – Short End State; SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

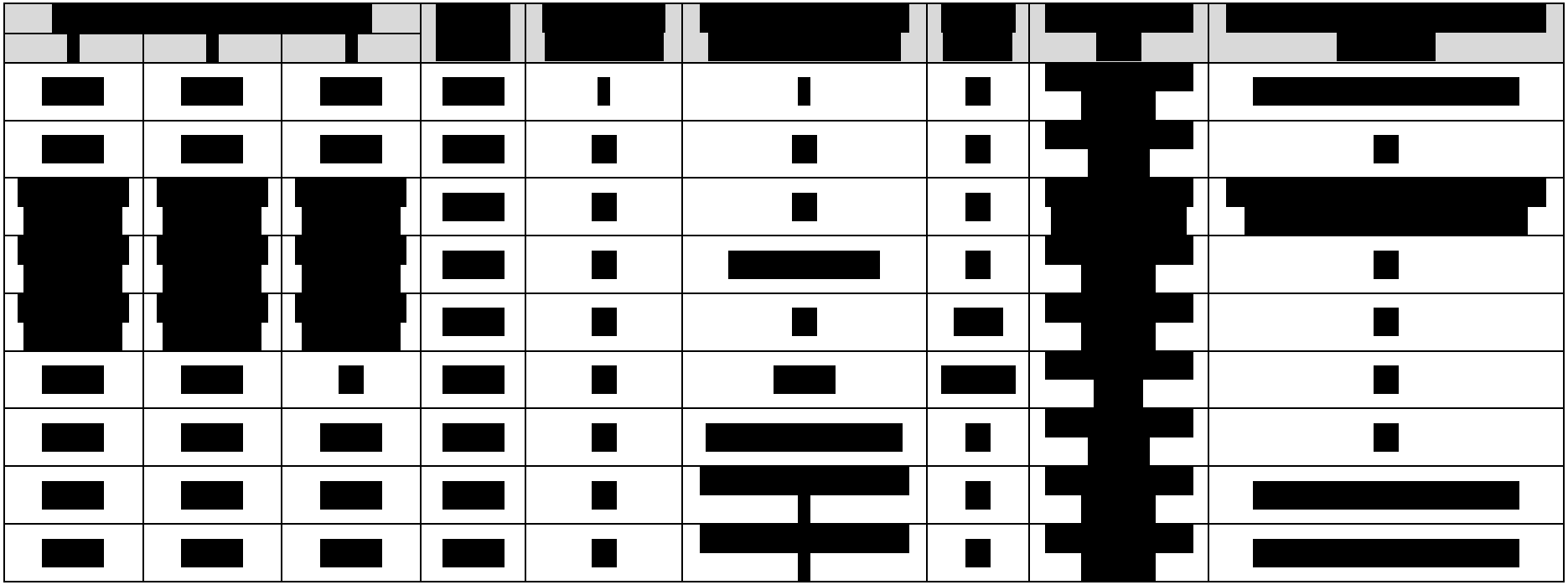
During the clarification process, the ERG commented that these values lacked face validity with respect to the ordering of the values, and the absolute value of one health state ([redacted]) in particular. To address these concerns, the company commissioned a survey with the objective of providing additional data on the utility within each health state. Mucopolysaccharidosis (MPS) Commercial (a wholly owned, not for profit subsidiary of the UK MPS Society) was commissioned to design the survey questionnaires and to conduct the survey. The company provided the results in a full report, which was marked as AIC in its entirity.[38]

[redacted]

[redacted]

Whilst it was not stated clearly in the documentation, the ERG believes that the values presented are EQ-5D-5L values crosswalked to the EQ-5D-3L values using the method detailed by van Hout et al.[41]

Table 41: Patient characteristics of those patients responding to the survey regarding utility



Abbreviations: AM, alpha-mannosidosis; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis; NR, non-response; UK, United Kingdom.
†At time of survey completion; ‡Responses taken from phase 3 of the survey responses, as they are the most up to date data, except for CH006 who did not consent to completing the phase 3 survey; §Treatment described as bone marrow transplant in survey responses; §The patient-reported age at diagnosis of CH004; ¶The carer-reported age at diagnosis of CH004

The base case and the scenario analyses are detailed below. [redacted]Base case: Patient utility as reported by the carer (by proxy) regardless of prior treatment

Scenario 1: Comparison of patient utility reported by the carer (by proxy) and by the patient (by self-report). This analysis is only applicable for the three patients with both carer-reported and patient-reported patient utilities.

Scenario 2: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC, i.e. patients who had received stem cell transplant or velmanase alfa were excluded from the pooled analyses. A resulting missing data point for the 'walking with assistance' health state was imputed using the EQ-5D-5L utility for this health state as in the CS^2 by use of KOL input.

Scenario 3: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC. A resulting missing data point for the 'walking with assistance' health state was imputed using the mean of the utility values calculated for the 'walking unassisted' and 'wheelchair dependent' states.

Scenario 4: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC. A resulting missing data point for the 'walking with assistance' health state was imputed using a ratio of utility for 'walking with assistance' relative to 'walking unassisted' determined through KOL input.

[redacted]

[redacted]

Table 42: Utility estimates (standard deviation) by primary health state produced by the company

Health State	n	WU	WWA	WC	SI
Base case	9	0.794 (0.200)	0.758 (N/A)	0.100 (N/A)	-0.011 (0.053)
Scenario 1	3	0.794 (0.000)	0.758 (N/A)	N/A	N/A
Scenario 2†	5†	0.906 (0.000)	[redacted]	0.100 (N/A)	-0.011 (0.053)
Scenario 3	4†	0.906 (0.000)	0.503 (N/A)	0.100 (N/A)	-0.011 (0.053)
Scenario 4	4†	0.906 (0.000)	0.345 (N/A)	0.100 (N/A)	-0.011 (0.053)
rhLAMAN-10[1] baseline	15	0.652 (0.149)	0.577 (0.200)	N/A	N/A
rhLAMAN-10[1] Last observation	25	0.702 (0.171)	0.635 (0.085)	N/A	N/A

N/A – Not Available; SES – Short End State; SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

† Plus one value in the WWA state estimated from UK KOL estimates

† Used in the model

5.2.3.17 The assumed utility benefit associated with velmanase alfa treatment

Of note, the company has assumed that any patient treated with velmanase alfa would receive a utility gain of 0.1. This value was stated to have been validated with UK KOLs, with the company further stating in the clarification response[11] (question B15) that there were many aspects of AM that were not completely accounted for in the model including: 'reducing rates of minor infections; reducing rates of psychiatric problems with investigators noticing that in '[redacted]'; reduced ventilator dependency; providing intra-ambulatory health state improvements', for example, moving from multiple aids/assistance for walking to only requiring one minimal aid for walking (e.g. footwear for stability); and the provision of a structured homecare visit programme with regular (weekly) nurse visits [redacted]. Four UK KOLs confirmed that '*applying an 'on-treatment utility increment' was appropriate, to account for these additional benefits that treatment with velmanase alfa may incur, which are not formally accounted for in the model by other existing parameters.*' The company report that a value of 0.1 was chosen with reference to the improvements of 0.05 and 0.058 in the Walking Unassisted and Walking With Assistance states that had been seen in the EQ-5D analyses using data from the rhLAMAN-10[1] trial and the possibility that some benefits of velmanase alfa '*will only be apparent after a number of years of treatment*.'

5.2.3.18 The assumed disutility associated with severe infection

The disutility associated with severe infection for patients receiving BSC was assumed to be approximated by that reported for patients with sepsis by Drabinski et al.[43] which was a value of 0.18 for a period of six months. This resulted in an undiscounted quality-adjusted life year (QALY) loss of 0.09 per severe infection. The company assumed that this disutility would be halved for patients

receiving velmanase alfa based on interviews with UK clinical experts with an arbitrary CrI relating to the reduction of 37.5% to 62.5%, which was assumed to follow a Beta distribution.

5.2.3.19 The assumed disutility associated with major surgery

For the disutility associated with major surgery the company chose to use a value previously reported by BioMarin in a Highly Specialised Technology Appraisal and which was said to be accepted by NICE in a related mucopolysaccharidosis condition.[44] This disutility was 0.25 and was applied for a period of 6 months resulting in an undiscounted QALY loss of 0.125 per patient receiving major surgery. The company assumed that this disutility would be halved for patients receiving velmanase alfa based on interviews with UK clinical experts with an arbitrary CrI relating to the reduction of 37.5% to 62.5%, which was assumed to follow a Beta distribution.

5.2.3.20 The assumed disutility associated with minor surgery and adverse events

No disutility was assumed for either minor surgery or IRRs.

5.2.3.21 Summary of the evidence sources used for key parameters within the model.

A summary of the sources associated with parameters to which the ICER is particularly sensitive is provided in

Table 43. This allows the committee to distinguish which values are populated with observed data, which are populated with data from elicitation sessions with clinical experts and which are populated via interviews with KOLs. For conciseness, the values assumed are not repeated in

Table 44.

Table 43: The data sources for key parameters within the company model

Parameter	Source for company base case analysis
Age of population	Assumption
Starting health state of population	Taken from data observed in rhLAMAN-10[1]
Time to disease progression when treated with BSC	UK Expert Elicitation Panel
Additional time to disease progression when treated with velmanase alfa	UK Expert Elicitation Panel
Improvement in health state associated with velmanase alfa treatment	Interviews with UK KOLs
Treatment discontinuation due to lack of efficacy	Data from the multi-domain responder analysis conducted in rhLAMAN-05[10]
Treatment discontinuation due to other reasons	Interviews with UK KOLs
Probability of major surgery conditional on health state	UK Expert Elicitation Panel
Probability of mortality and complications associated with major surgery	UK Expert Elicitation Panel
Reduction in the risks of mortality and complications associated with surgery due to velmanase alfa treatment	Interviews with UK KOLs
Probability of severe infection conditional on health state	Interviews with UK KOLs
Probability of mortality associated with severe infection	UK Expert Elicitation Panel
Reduction in the risks of mortality and complications associated with severe infections due to velmanase alfa treatment	Interviews with UK KOLs
Requirement for ventilation conditional on health state	Interviews with UK KOLs
Reduction in the requirement for velmanase alfa due to the use of velmanase alfa	Interviews with UK KOLs
Utility in each health state	Survey conducted by the UK MPS Society.
Utility gain associated with being on velmanase alfa	Assumption

BSC – Best Supportive Care; KOLs – Key Opinion Leaders; MPS - mucopolysaccharidosis

5.2.4 Model evaluation methods

The CS presents the results of the economic analysis in terms of the incremental cost per QALY gained for velmanase alfa versus BSC.[2] The base case results are presented deterministically using the base case estimate for each parameters. The CS[2] also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSA) and scenario analyses. The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The results of the DSA are presented in tabular form with an additional tornado diagram which is limited to the ten most influential model parameters. The distributions applied in the company's PSA are summarised in Table 63. These values have been provided in the relevant sub-section of Section 5.2.3.

5.2.5 Company's model results

Table 44 presents the estimates of cost-effectiveness derived from the company's revised model following the clarification process. Based on the probabilistic versions of the model, in the paediatric cohort velmanase alfa is expected to generate an additional 2.50 QALYs at an additional cost of [redacted] per patient: the ICER is [redacted] per QALY gained. In the adolescent cohort these values were an additional 2.64 QALYs at an additional cost of [redacted] per patient: the ICER is [redacted] per QALY gained. In the adult cohort, these values were an additional 2.61 QALYs at an additional cost of [redacted] per patient: the ICER is [redacted] per QALY gained.

The deterministic version of the model produces similar ICERs of: [redacted] per QALY gained for velmanase alfa versus BSC in the paediatric cohort; [redacted] per QALY gained for velmanase alfa versus BSC in the adolescent cohort; and [redacted] per QALY gained for velmanase alfa versus BSC in the adult cohort. The undiscounted incremental QALY gain for the paediatric cohort was stated by the company to be 3.13 with the discounted value being 2.53. According to the Methods Guide for Highly Specialised Technology Appraisals[45] a value below ten QALYs would have a weight of 1 with respect to a £100,000 cost per QALY gained threshold. As such, all the base case ICERs reported by the company, using the list price of velmanase alfa, are in excess of the appropriate threshold.

The ERG comments that the ICERs are more favourable to velmanase alfa in the paediatric group due to the smaller doses of interventions required as the treatment has weight-based dosing.

Table 44: Company's estimates of cost-effectiveness – velmanase alfa versus BSC

Paediatric cohort					
Probabilistic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	9.90	[redacted]	2.50	[redacted]
BSC	[redacted]	7.40	-	-	-
Deterministic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	10.32	[redacted]	2.53	[redacted]
BSC	[redacted]	7.79	-	-	-
Adolescent cohort					
Probabilistic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	9.65	[redacted]	2.64	[redacted]
BSC	[redacted]	7.02	-	-	-
Deterministic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	10.04	[redacted]	2.66	[redacted]
BSC	[redacted]	7.39	-	-	-
Adult cohort					
Probabilistic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	8.82	[redacted]	2.61	[redacted]
BSC	[redacted]	6.21	-	-	-
Deterministic model					
	Costs	**QALYs**	**Inc. costs**	**Inc. QALYs**	**Cost per QALY gained**
VA	[redacted]	9.17	[redacted]	2.67	[redacted]
BSC	[redacted]	6.51	-	-	-

BSC – best supportive care; inc – incremental; QALY - quality-adjusted life years;
VA – velmanase alfa

CEACs and scatterplots are presented in the CS[2] but, for brevity are not reproduced here. The ERG notes that by inspection the CEACs the ICERs did not appear to be below £[redacted] per QALY gained for any of the three cohorts in any of the PSA iterations conducted by the company. Therefore the probability of the ICER being below [redacted] per QALY gained was estimated to be [redacted]%.

Table 45 presents the results of the company's DSAs for the paediatric cohort, with the corresponding results for the adolescent and adult cohorts shown in Table 46 and Table 47, respectively. Across all analyses, the ICER for velmanase alfa versus BSC remains greater than [redacted] per QALY gained, with this value marked as commercial-in-confidence (CIC) by the company as it relates to the cost of a vial of velmanase alfa. The ERG comments that the price of velmanase alfa is directly under the control of the company and should not be entered into the DSA. Excluding this variable, the lowest ICER is greater than £[redacted] per QALY gained.

Table 45: The company's deterministic sensitivity analyses – velmanase alfa versus BSC in the paediatric cohort

Parameter	Value			Cost per QALY gained		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10%	8%	13%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Progression (added years in state) – VA – Paediatric – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

Table 46: The company's deterministic sensitivity analyses – velmanase alfa versus BSC in the adolescent cohort

Parameter	Value			Outcome		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10%	8%	13%	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	[redacted]	[redacted]	23.23	[redacted]	[redacted]	[redacted]
Progression (added years in state) – VA – Adolescent – WU to WWA	[redacted]	[redacted]	2.59	[redacted]	[redacted]	[redacted]

Abbreviations: VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

Table 47: The company's deterministic sensitivity analyses – velmanase alfa versus BSC in the adult cohort

Parameter	Value			Outcome		
	Base case	Min	Max	Min	Max	Difference
Cost – VA vial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y1 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Progression (years in state) – BSC – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – outcomes	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y2 – WWA to WU	20.0%	0.0%	70.0%	[redacted]	[redacted]	[redacted]
Discount rate – costs	1.5%	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Backwards transition (probability) – VA – Y3+ – WWA to WU	2.5%	0.0%	5.0%	[redacted]	[redacted]	[redacted]
Utility – VA on-treatment increment (post discontinuation)	0.00	0.00	0.05	[redacted]	[redacted]	[redacted]
Discontinuation – Annual probability of withdrawal	10%	8%	13%	[redacted]	[redacted]	[redacted]
Progression (added years in state) – VA – Adult – WU to WWA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; TE, treatment effect; VA, velmanase alfa; WWA, walking with assistance; WU, walking unassisted; Y, year.

The company performed extensive scenario analyses that were reported in Table 111 of the appendix submitted post clarification response.[11] This table is reproduced in Table 48.

Table 48: Company's scenario analyses – velmanase alfa vs best supportive care (adapted from CS Table 111)

Model parameter (base case)	Scenario analysis	Results (£) ICER (incremental cost, incremental QALYs)		
		Paediatric cohort	Adolescent cohort	Adult cohort
Base case results	-	[redacted]	[redacted]	[redacted]
Utilities (UK MPS Society Survey)	Morquio A proxy utility values adjusted for complications using minimum method and age-adjusted	[redacted]	[redacted]	[redacted]
	rhLAMAN-10[1] trial data for WU and WWA states	[redacted]	[redacted]	[redacted]
	rhLAMAN-10[1] trial data for WWA state only	[redacted]	[redacted]	[redacted]
Time horizon (Lifetime)	10 years	[redacted]	[redacted]	[redacted]
	20 years	[redacted]	[redacted]	[redacted]
	30 years	[redacted]	[redacted]	[redacted]
	50 years	[redacted]	[redacted]	[redacted]
Patient age (lowest cohort age (6, 12, 18))	rhLAMAN-10[1] average age (8, 15, 25)	[redacted]	[redacted]	[redacted]
Discount rates for costs and QALYs (1.5%)	0.00%	[redacted]	[redacted]	[redacted]
	3.50%	[redacted]	[redacted]	[redacted]
Discontinuation (13.3% at year 1, 10% annual, and discontinue at severe immobility	No discontinuation at all	[redacted]	[redacted]	[redacted]
	Annual discontinuation of 20%	[redacted]	[redacted]	[redacted]
	Discontinue once in wheelchair	[redacted]	[redacted]	[redacted]

Caregiver disutility (Gani et al, 2008 (109)). SES state has full year disutility	Acaster et al, 2013 (110)	[redacted]	[redacted]	[redacted]
	No caregiver disutility	[redacted]	[redacted]	[redacted]
	Caregiver disutility in SES applied for 4 weeks	[redacted]	[redacted]	[redacted]
VA on-treatment utility increment (0.1)	0	[redacted]	[redacted]	[redacted]
	0.2	[redacted]	[redacted]	[redacted]
VA on-treatment utility increment post discontinuation (0.0)	0.01	[redacted]	[redacted]	[redacted]
	0.05	[redacted]	[redacted]	[redacted]
Reduction in probability of major surgery in patients on VA (0.0%)	50%	[redacted]	[redacted]	[redacted]
VA monitoring (included in routine BSC specialist appointment	Monitoring not part of BSC	[redacted]	[redacted]	[redacted]
Societal costs (not included)	Include personal & caregiver expenditure	[redacted]	[redacted]	[redacted]
	Include caregiver productivity loss	[redacted]	[redacted]	[redacted]

	Include both personal & caregiver expenditure and productivity loss	[redacted]	[redacted]	[redacted]
Ventilation costs from Noyes (2006) study and VA patients assumed to have 50% lower rate of ventilation/ 24-hour ventilation in WC and SI health states	Double the costs of ventilation	[redacted]	[redacted]	[redacted]
	Remove the cost of ventilation	[redacted]	[redacted]	[redacted]
	VA ventilation equal to BSC ventilation	[redacted]	[redacted]	[redacted]
	No 24-hour care ventilation required for VA patients	[redacted]	[redacted]	[redacted]

Abbreviations: AM, alpha-mannosidosis; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; VA, velmanase alfa; WC, wheelchair; WWA, walking with assistance; WU, walking unassisted.

5.2.6 Budget impact analyses

The company report a budget impact analysis, should velmanase alfa be recommended for use by NICE, in Table 21 of the CS.[2] This predicts a total cumulative budget impact of £8.93 million over a five-year period, increasing from £1.48 million in year 1 to £2.16 million in year 5. The ERG has no reason to believe these values are likely to be significantly inaccurate.

5.3 Critique of the company's model and exploratory and sensitivity analyses undertaken by the ERG

The ERG has endeavoured to produce an ERG base case ICER subject to the constraints of the model submitted by the company, detailed at the end of this section. Within the ERG base case changes are only made to the company's base case where the ERG has a strong preference for a different assumption to the one made by the company. Where the ERG believes that the means of the parameters values are open to debate, but the ERG does not have a preferred value scenario analyses have been undertaken.

The ERG reiterates that many parameters are not populated with observed data but are instead populated by using distributions elicited from experts or estimated from interviews. The values from the interviews and arbitrary distributions used by the company do not benefit from using a formal elicitation process. The ERG is concerned that the parameter estimates may not reflect genuine beliefs which leads to questions regarding the appropriateness of both the company's and the ERG's base case analysis.

Five changes were made to the company's base case ICER:

1) Using the utility values for the Walking Unaided and Walking With Assistance states that were reported at baseline in the rhLAMAN-10[1] study.

   Fifteen patients recruited to rhLAMAN-10[1] provided baseline utility values for the Walking Unaided and the Walking With Assistance health states. This is greater than the number ([redacted]) that responded to the MPS Survey used in the company base case. The baseline value has been chosen rather than the last observation value as [redacted]

2) Using a discount rate value of 3.5% per annum rather than 1.5% per annum

   In their clarification response[11] (Question B30) the company stated that '*NICE recommends that a discount rate of 1.5% can be used for costs and QALYs in treatments where patients would otherwise not survive, patients suffer from severely impaired life conditions or when the condition is sustained for over 30 years.*' The ERG notes that in the latest methods guide to highly specialised technology appraisals[45] it is stated that '*In line with the Guide to the Methods of Technology Appraisal, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered.*' The ERG does not think that velmanase alfa meets these criteria as the intervention does not restore a patient to full or near full health.

3) Using a utility increase associated with velmanase alfa treatment of 0.00 rather than 0.10

   The company's rationale for using a utility increase of 0.10 associated with velmanase alfa treatment is reported in Section 5.2.3.15. The ERG comments that the gain shown between the baseline and the last observation n rhLAMAN-10[1] is non-comparative (as no patient received BSC) and that the values could be confounded by different patient numbers, with different disease severities. The ERG comments that utility gains would be double-counted if a patient improved health state as there would be an increase related to the health state and also a utility increase

associated with being on velmanase alfa treatment. Further double-counting would exist when patients have been maintained in the same health state rather than progressing due to velmanase alfa treatment. The ERG comments that the additional years in each state elicited from the clinical experts (

Table 30) are not sufficiently high to support evidence of clear ongoing utility gain for patients receiving velmanase alfa.

4) Amending an implementation error in the model relating to transition probabilities

After the clarification period, the ERG identified an error in that patients who had received velmanase alfa treatment but had discontinued and were receiving BSC, did not have the same transition probabilities as those patients who were on BSC. This discrepancy was amended by the ERG setting these probabilities equal to the values for patients in the comparator arm.

5) Amending an implementation error in the model relating to costs post discontinuation of velmanase alfa

After the clarification period, the ERG identified an error in that patients who had received velmanase alfa treatment but had discontinued and were receiving BSC, did not have the same ventilation costs as patients on BSC. The model has been amended so that patients who have discontinued treatment have the ventilation costs associated with BSC.

The following scenario analyses were run adapting the ERG's base case. These have been run to provide additional potentially informative data to the committee. These are ordered in terms of the headings in Section 5.2.3 and not in order of perceived importance.

1) Assessing the cost-effectiveness of velmanase alfa in each of the primary health states

The ERG explored whether the ICER was sensitive to the distribution of patients in each starting health state by setting 100% of patients to each of the primary health states in turn.

2) Using the mean age of patients in the three age groups observed in rhLAMAN-10[1] rather than setting this to the lowest age

The company set the starting age of patients to be the lowest age for each age band. In response to clarification question[11] B31 the company stated that '*The lowest age of each band was selected to reflect UK KOLs comments that the earlier the intervention with an ERT (such as velmanase alfa), the more potential for a treatment benefit to be realised, and to reflect the reality that future patients with AM are likely to be diagnosed as an incident population in childhood, rather than the rhLAMAN clinical programme which identified patients from a prevalent cohort of patients with AM*' Whilst a case could be made for setting the youngest age to 6 years, there seems no reason to believe that had a patient with AM not been diagnosed at early childhood then they would be diagnosed at 12 rather than at 11 or 13. As such, the average values from rhLAMAN-10[1] were used in an exploratory analysis.

3) Assuming that improvements in health state were only possible in the first 12 months

The company used values from UK KOLs to assume that there was a 20% chance of improvement from the Wheelchair Dependent health state to the Walking With Assistance Health state, and a 20% chance of improving from the Walking With Assistance health state to the Walking Unassisted state for the initial 2-year period. For each year thereafter, the company assumed a probability of 2.5% for both improvements. The ERG has explored the impact on the ICER if it was assumed that there were no improvements after the initial year, which is the duration of the randomised rhLAMAN-5[10] study.[46] The ERG highlights that the transition probabilities for patients on velmanase alfa are still preferable to those of BSC, and that only improvements in health states beyond 12 months are prohibited. The impacts on surgical and severe infection remain as in the base case.

4) Assuming that velmanase alfa had no beneficial effect on the risks, and the recovery times, associated with surgery

The company assumed that treatment with velmanase alfa would reduce the risk of surgery mortality by 50%, reduce the risk of surgical complications by 50% and reduce the recovery time required after surgery by 50%. These values were produced based on interviews with UK KOLs and could have some element of double-counting as patients also have reduced risks in better health states. Given that there are very few data to populate these parameters, the ERG has performed exploratory analyses to assess the impact of removing these benefits on the ICER.

5) Assuming that velmanase alfa had no beneficial effect on the risks, and the recovery times, associated with severe infection

The company assumed that treatment with velmanase alfa would reduce the risk of severe infection by 50%, reduce the risk of mortality given a severe infection by 50% and reduce the recovery time required after severe infection by 50%. These values were produced based on interviews with UK KOLs and could have some element of double-counting as patients also have reduced risks in better health states. Given that there are very few data to populate these parameters, the ERG has performed exploratory analyses to assess the impact of removing these benefits on the ICER.

6) Assuming that the costs of severe infections were set to £2742

The company used published literature to estimate the costs associated with severe infection, using severe sepsis as a proxy, resulting in costs of £11,255 for a paediatric patient and £14,286 for an adult population. Based on NHS Reference costs (using non-elective long stay codes WJ05A, WJ05B, WJ06A, WJ06B, WJ06C, WJ06D, WJ06E, WJ06F, WJ06G, WJ06H, WJ06J[32])

weighted by the number of finished consultant episodes the ERG estimated that the cost was £2742 which has been used in the exploratory analyses.

7) Assuming that velmanase alfa had no beneficial effect on the costs associated with ventilation

The company assumed, based on interviews with UK KOLs, that the ventilation requirements for patients treated with velmanase alfa would be reduced by 50%. The model could have some element of double-counting as patients also have reduced ventilation requirements in better health states. Given that there are very few data to populate these parameters, the ERG has performed exploratory analyses to assess the impact of removing these benefits on the ICER. It should be noted that a minor coding error in the company's model was amended in order that the company's functionality to select this option could be used.

8) Assuming the values on caregiver time reported in the UK MPS survey

The UK MPS survey produced alternative estimates for the amount of caregiver time required in each health state. The ERG explored the impact on the ICER if it were assumed that [redacted]

9) Removing the impact on caregiver utility from the model

The ERG explored the impact on the ICER of removing caregiver disutility from the model to ascertain the sensitivity of the ICER to this parameter.

10) Including personal expenditure by the family within the model

The ERG explored the impact on the ICER of including personal expenditure by the family within the model.

11) Including the loss of caregiver productivity within the model

The ERG explored the impact on the ICER of including the loss of caregiver productivity within the model.

12) Assuming the chronic utility gain associated with velmanase alfa treatment was 0.05

For reasons previously described, the ERG has set the chronic gain associated with being on velmanase alfa treatment to zero. However, noting that UK KOLs expect a utility increase with velmanase alfa treatment the ERG has performed a scenario analysis using a utility increase of 0.05 based on the improvements seen in rhLAMAN-10[1] ([redacted] for the Walking Unaided state and [redacted] for the Walking With Assistance state).

Combinations of the scenario analyses have not been performed due to the large number of permutations, but specific scenarios can be provided quickly at the Appraisal Committee meeting if desired.

The following limitations in the model were also noted, although no formal changes were made by the ERG as these were not possible within the time frame of the HST.

1) The prohibition of improvement in the BSC arm

The company do not allow any improvement in health state for those patients modelled to have BSC alone. In their clarification response[11] (question B3), the company described this as a simplifying assumption and for the velmanase alfa arm used the level of improvement associated with velmanase alfa over and above BSC. The ERG comments that this simplification is likely to change the ICER, although the direction is not known. A more accurate ICER would be obtained by using the absolute values of improvement for both velmanase alfa and for BSC rather than setting BSC to zero and velmanase alfa to the difference between the treatments.

2) The model output will fail to match the input data elicited from clinicians
   The elicitation with clinicians asked the additional time in each health state a person would be in were they provided with velmanase alfa treatment. These values are used directly in the model. However, logically the model will not produce the answers elicited from the expert clinicians for two reasons: (i) where patients improve health states in the velmanase alfa arm, they would have to progress from the improved state to the original state and then would have a further additional time in the original health state, and (ii) events such as reaching the Short End Stage through infection or the severe immobility state through surgical complications will change the life expectancy of each patients. While a formal analysis of this has not been conducted, the ERG believes that the actual increase in life expectancy will be higher than that predicted by the clinicians.

3) Using fixed weights rather than a distribution of weights may not provide an accurate answer or reflect the true uncertainty
   The use of fixed weight within a model can produce inaccurate answers.[47] In the company's model, it is assumed that all 1-year old females have a weight of 10.27kg, and all 5-year-old females have a weight of 19.91kg. As one vial of velmanase alfa is required for every 10kg, both 1 year old and 5-year-old females will require 2 vials per week. In reality, many 1-year old females will only require one vial, whereas many 5-year olds females will require 3 vials. It is not clear whether the limitations associated with using fixed weights will be favourable or unfavourable to velmanase alfa.

4) Patients who discontinue treatment due to lack of efficacy are assumed to do so at the midpoint of the first year rather than at 12 months
   This is an implementation issue which will be marginally unfavourable to velmanase alfa as the full 12 months' benefit relating to surgery, or severe infection would not be captured, and any assumed utility increase due to velmanase alfa treatment would not be fully realised.

Despite observed data in rhLAMAN-05[10] showing no relative improvement in health state for velmanase alfa treatment compared with BSC, see response to clarification question A44,[11] this was not removed within the ERG base case as the value used in the company base case had been elicited from five clinical experts.

Finally, the ERG did not perform any analyses with HSCT as a comparator. As such, the clinical effectiveness and cost-effectiveness of velmanase alfa in patients who are suitable for HSCT are unknown.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has presented ICERs for a most plausible ERG base case ICER, subject to the caveats that some limitations relating to the model could not be fixed within the time frames of the appraisal.

Table 49 details the differences between the components of the company's base case ICER and that of the ERG. This table also provides the deterministic ICER associated with each individual change in the base case. Deterministic ICERs were calculated for computational time reasons given that the model has been shown in

Table 44 to be relatively linear, and because the ERG base case ICER was significantly above the thresholds reported in the HST Methods guide.[45] Additional scenario analyses relating to key uncertainties have been undertaken on the ERG base case ICER and are presented in Table 50.

In the ERG base case the undiscounted QALY gains were 1.89 for paediatric patients, 2.00 for adolescent patients and 2.00 for adult patients; the discounted QALYs gained were 1.08 for paediatric patients, 1.14 for adolescent patients 1.17 for adult patients. In the scenario analysis where an ongoing 0.05 utility gain associated with velmanase alfa treatment was assumed the undiscounted (discounted) QALY gains were 2.24 (1.36) for paediatric patients, 2.35 (1.43) for adolescent patients and 2.35 (1.45) for adult patients, which was the scenario analysis with the highest QALY gains associated with velmanase alfa treatment.

Table 49: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case [redacted])**	**Adolescent (CS base case £[redacted])**	**Adult (CS base case [redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906; [redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; CS – company submission; WU – Walking Unassisted; WWA – Walking With Assistance

It is seen that the changes made within the ERG base case result in considerable increases in the ICERs. The increase observed when removing an ongoing utility gain for receiving velmanase alfa treatment, over and above any changes in health state, show the results are particularly sensitive to this parameter. As previously detailed, the ICERs are more favourable in paediatric patients due to the smaller doses of velmanase alfa required.

Table 50: Scenario analyses run on the ERG's base case

	CPQ given individual change		
Analyses	**Paediatric (ERG base case £[redacted])**	**Adolescent (ERG base case £[redacted])**	**Adult (ERG base case [redacted])**
Assuming 100% in the WU health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WWA health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WC health state	[redacted]	[redacted]	[redacted]
Assuming the average age per age band observed in rhLAMAN-10[1]	[redacted]	[redacted]	[redacted]
Assuming no improvements in health state after 12 months	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to surgery.	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to serious infection.	[redacted]	[redacted]	[redacted]
Assuming the costs of a severe infection are set to £2742	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to ventilation costs.	[redacted]	[redacted]	[redacted]
Assuming the UK MPS survey as the source for caregiver requirements.	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility	[redacted]	[redacted]	[redacted]
Including personal expenditure by the family	[redacted]	[redacted]	[redacted]
Including caregiver productivity losses	[redacted]	[redacted]	[redacted]
Assuming that patients treated with velmanase alfa have a utility gain of 0.05	[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; MPS – Mucopolysaccharidosis; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

7 OVERALL CONCLUSIONS

The clinical evidence base comprised one double-blind, placebo controlled RCT (rhLAMAN-05[10], n=25) and one long-term, single arm, open label study (rhLAMAN-10[1], n=33). The patient spectrum was largely representative mild to moderate disease, though likely with a higher proportion of young patients than in England. The ERG noted that some patients included in these studies may have been eligible for HSCT in England. Some patient in the studies may have had their treatment halted if the draft start/stop criteria produced by the company had been applied; for those who would have continue treatment, the studies are likely to have underestimated population-level efficacy.

The ERG had concerns about the use of serum oligosaccharides as the primary outcome. This outcome has low clinical relevance and has not been assessed as a surrogate using standard criteria.[29] Other outcomes, including 3-MSCT, 6-MWT, FVC, cognition, hearing and quality of life, appeared relevant, but infections, which have a big impact on patients and which were listed in the NICE final scope[9], were not measured.

rhLAMAN-05[10] reported a statistically significant decrease in serum oligosaccharides, but no statistically significant decreases in other outcomes (where statistical tests were conducted). The ERG was unclear if the study met its definition for demonstrating efficacy. The observed differences for most outcomes did not meet MCIDs where these were provided. It is unclear to the ERG whether the effect of velmanase alfa on the biomarker translates to a useful impact on clinical outcomes. rhLAMAN-10[1] provided longer term data, but the ERG noted variable and smaller numbers, sometimes comprising different patients altogether, at time points beyond 12 months making results difficult to interpret. Further, there was often little difference between 12 month and last observation data, though the mean length of follow-up at last observation was not reported. Interaction tests showed a difference in effect based on patient age (<18 years of age compared with ≥18 years of age) in 3-MSCT in rhLAMAN-10[1], but not for serum oligosaccharides. No other interaction tests were reported in either study, though observed differences between age groups were generally more favourable in those ages <18 years. Adverse events were frequent, but mostly mild to moderate. The safety of treatment over a lifetime is unknown.

The ERG comments that key clinical parameters of the model that were assumed to be influenced by velmanase alfa treatment were informed largely through elicitation of experts' beliefs with, or interviews with, clinical experts. There were large differences in the base cases ICERs produced by the company and those produced by the ERG, with the values produced by the ERG approximately double that of the company estimates. The cause of the differences were five changes made by the ERG to the company model. These were: (1) the use of utility data collected in the rhLAMAN-10[1] study ([redacted]) in preference to data taken from the MPS survey ([redacted]); (2) changing the discount rate from 1.5% per annum to 3.5% per annum; (3) removing the utility gain of 0.10 that was assumed by the company to be gained when being on velmanase alfa treatment; (4) the correction of a model implementation error

where the transition rates between those patients receiving BSC were different dependent on whether the patient had received velmanase alfa initially; and (5) the correction of a model implementation error where the incorrect costs post discontinuation of velmanase alfa were used. The ERG's base case ICERs were greater than [redacted] per QALY for the paediatric group, the adolescent group and the adult group.

In addition, the ERG performed multiple sensitivity analyses which indicated that the ICER was sensitive to the following assumptions relating to velmanase alfa treatment: the duration of potential improvement of health state; the benefit associated with surgical outcome; the benefit associated with serious infection; and any underlying utility gain that may be conferred by velmanase alfa. There are limited data on these parameters and thus the estimated ICER is uncertain. It was also noted that the ICER was sensitive to assumptions made regarding which health state patients were in when receiving velmanase alfa and also the assumed average ages of patients.

The ERG noted four structural assumptions that it could not amend within the timescales of the HST appraisal relating to: the prohibition of patients receiving BSC improving (and the rate of velmanase alfa also improving by the same amount); that the model output would not predict the elicited input data regarding time in health state; that the number of vials required were not based on a distribution; and that patients discontinuing velmanase alfa treatment were assumed to do so at six months rather than 1 year. It is not known how amending the model to accommodate these changes would change the ICER.

The ERG highlights that all ICERs contained in the main text of this document are using the list price of velmanase alfa. The results when the PAS is incorporated are provided in Appendix 5.

7.1 Implications for research

In order to estimate the ICER accurately additional evidence, with multiple years follow up, are needed on

- The improvement in health states associated with velmanase alfa compared to BSC
- The benefit of velmanase alfa compared to BSC in relation to surgical outcomes
- The benefit of velmanase alfa compared to BSC in relation to serious infection and outcomes after serious infection
- The benefit of velmanase alfa compared to BSC in relation to ventilation requirements
- Any gain in utility associated with velmanase alfa that are not captured by the health state, surgical outcomes and serious infection outcomes.

8 REFERENCES

1. Chiesi Farmaceutici. Clinical Study Report – rhLAMAN-10. A single center, open label clinical trial investigating the long-term efficacy of rhLAMAN-(recombinant human alpha-mannosidase or Lamazym) treatment in subjects with alpha-mannosidosis who previously participated in Lamazym trials. . 2016.
2. Chiesi. Velmanase alfa for treating alpha mannosidosis (ID800). Specification for company submission of evidence. 2018.
3. 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.
4. Malm D, Nilssen O. Alpha-mannosidosis. *Orphanet J Rare Dis* 2008;3:21.
5. Wall D, Grange D, Goulding P, Daines M, Luisiri A, Kotagal S. Bone marrow transplantation for the treatment of alpha mannosidosis. *The Journal of Pediatrics* 1998;133:282-5.
6. Malm D, Halvorsen D, Tranebjaerg L, Sjursen H. Immunodeficiency in alpha-mannosidosis: a matched case-control study on immunoglobulins, complement factors, receptor density, phagocytosis and intracellular killing in leucocytes. *Eur J Pediatr* 2000;159:699-703.
7. NHS England. 2013/14 NHS Standard contract for lysosomal storage disorders service (children). Particulars, schedule 2 – the services, a – service specification. 2013:1-39.
8. Grewal S, EG. S, Krivit W, Charnas LR, Lockman L, Delaney K*, et al.* Effective treatment of a-mannosidosis by allogeneic hematopoietic stem cell transplantation. *The Journal of Pediatrics* 2004;144:569-73.
9. National Institute for Health and Care Excellence. Velmanase alfa for treating alpha-mannosidosis. Final scope. 2017.
10. Chiesi Farmaceutici. Clinical Study Report – rhLAMAN-05. A multi-centre, double-blind, randomized, placebo-controlled, parallel group trial, investigating the efficacy and safety of repeated Lamazym treatment of subjects with alpha-mannosidosis. 2016.
11. Chiesi. Highly Specialised Technologies Evaluation Programme. Velmanase alfa for treating alpha mannosidosis (ID800). Clarification Response. 2018.
12. ClinicalTrials.gov. A Placebo-Controlled Phase 3 Trial of Repeated Lamazym Treatment of Subjects With Alpha-Mannosidosis. 2012, https://clinicaltrials.gov/ct2/show/record/NCT01681953 [Accessed 23.03.18].
13. Chiesi Farmaceutici. Clinical Study Report – rhLAMAN-02. A single center, open-label, dose escalation study of the safety and pharmacokinetics of rhLAMAN (recombinant human alpha-mannosidase or Lamazym) for the treatment of patients with alpha-mannosidosis. . 2015.
14. Chiesi Farmaceutici. Clinical Study Report – rhLAMAN-04. A multi-center, open-label trial of the long-term efficacy and safety of Lamazym for the treatment of patients with alpha-Mannosidosis. . 2014.
15. Chiesi Farmaceutici. Clinical Study Report – rhLAMAN-03. A single center, randomized, open-label, multiple-dose study of the efficacy and long-term safety of rhLAMAN (recombinant human alpha-mannosidase or Lamazym) for the treatment of patients with alpha-mannosidosis. . 2015.
16. Borgwardt L, Dali CI, Fogh J, Mansson JE, Olsen KJ, Beck HC*, et al.* Enzyme replacement therapy for alpha-mannosidosis: 12 months follow-up of a single centre, randomised, multiple dose study. *J Inherit Metab Dis* 2013;36:1015-24.
17. Borgwardt L, Dali C, Fogh J, Mansson J-E, Olsen K, Beck H*, et al.* Enzyme Replacement Therapy in Children and Adolescents With a-Mannosidosis: An 18-Month Follow-Up. *Journal of Inborn Errors of Metabolism & Screening* 2014:93-4.
18. Guffon N, Amraoui Y, Cattaneo F, Ardigo D, Geraci S, Gil-Campos M*, et al.* Improvements in Endurance, Serum Immunoglobulin G Levels and Quality of Life in Alpha-Mannosidosis Patients Switching from Placebo to Velmanase Alfa Long-Term Enzyme Replacement Therapy. 2017.
19. Harmatz P, Cattaneo F, Ardigo D, Geraci S, Lund AM, Borgwardt L. Towards Establishment of a Minimal Clinically Important Difference in the Treatment of Alpha-Mannosidosis: First Results from Velmanase Alfa (Human Recombinant Alpha-Mannosidase) Development Programme 2017.

20. Borgwardt L, Lund AM, Amraoui Y, Andersen O, De Meirleir L, Dolhem P*, et al.* Improvement in fine and gross motor proficiency after long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha mannosidase) in alpha-mannosidosis patients. *Molecular Genetics and Metabolism* 2017c;120:S29-S30.
21. Lund AM, Borgwardt L, Amraoui Y, Andersen O, De Meirleir L, Dolhem P*, et al.* Long-term enzyme replacement therapy with velmanase alfa (human recombinant aplpha-mannosidase) improves mobility in alpha-mannosidosis patients. *Mol Genet Metab* 2015;120:S88-S9.
22. Borgwardt L, Guffon N, Amraoui Y, De Meirleir L, Gil-Campos M, Fogh J*, et al.* Impact of Anti-Drug Antibodies (ADA) on Safety and Efficacy of Velmanase Alfa (Human Recombinant Alpha-Mannosidase) Long-Term Enzyme Replacement Therapy in Patients with Alpha-Mannosidosis. 2017d.
23. Cattaneo F, Borgwardt L, Dali CI, Tylki-Szymanska A, Wijburg F, Van den Hout JM*, et al.* Quality of Life and Activities of Daily Living in Alpha-Mannosidosis: Long-Term Data of Enzyme Replacement Therapy With Velmanase Alfa (Human Recombinant Alpha Mannosidase). *Journal of Inborn Errors of Metabolism & Screening* 2016:60-1.
24. Ardigo D, Borgwardt L, Dali CI, Gil-Campos M, Guffon N, Jameson E*, et al.* Enzyme Replacement Therapy for Alpha-Mannosidosis: Long-Term Safety Data in Patients Treated With Velmanase Alfa (Recombinant Human Alpha Mannosidase). *Journal of Inborn Errors of Metabolism & Screening* 2016:47-8.
25. Borgwardt L, Cattaneo F, Dali CI, Amraoui Y, Andersen O, Beck M*, et al.* Long-Term Follow-Up of Patients Treated With Velmanase Alfa (Recombinant Human Alpha-Mannosidase): A Comprehensive Evaluation of Efficacy of Enzyme Replacement Therapy in Alpha Mannosidosis. *Journal of Inborn Errors of Metabolism & Screening* 2016:48-9.
26. Hughes D. Clinical expert statement. Velmanase alfa for treating alpha-mannosidosis [ID800]. 2018.
27. Broomfield A. Clinical expert statement. Velmanase alfa for treating alpha-mannosidosis [ID800]. 2018.
28. MPS society. Data on file: UK MPS Society Survey. 2018.
29. Sargent D, Mandrekar S. Statistical issues in the validation of prognostic, predictive, and surrogate biomarkers. *Clinical Trials* 2013;10:647-52.
30. Chiesi. Appendix D – Updated patient access scheme template. Patient Access Scheme submission template. 2018.
31. Office for National Statistics. National life tables, UK Statistical bulletins. 2018, https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/previousReleases.
32. Department of Health. NHS reference costs 2015-16. 2017, https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 (Accessed: August 2017).
33. Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. *Pediatrics* 2012;130:e273-80.
34. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T*, et al.* Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. *The Lancet Infectious Diseases* 2012;12:919-24.
35. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. *Health Soc Care Community* 2006;14:508-22.
36. Hendriksz CJ, Lavery C, Coker M, Ucar SK, Jain M, Bell L*, et al.* The Burden Endured by Caregivers of Patients With Morquio A Syndrome. *Journal of Inborn Errors of Metabolism and Screening* 2014;2.
37. Curtis L, Burns A. Unit Costs of Health & Social Care 2016. *PSSRU* 2016.
38. UK MPS Society. Velmanase alfa for treating alpha mannosidosis (ID800). UK MPS Society Survey Report. 2018.
39. White MK, Davison JE, Gan C, Mnkandla S, Camero I, Batzios S*, et al.* G388(P) Enzyme replacement therapy infusion related reactions: a large single-centre review of children with lysosomal storage disorders. Paper presented at: British Inherited Metabolic Disease Group and British Paediatric Neurology Association.

40. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-Effectiveness Analyses of Natalizumab (Tysabri®) Compared with Other Disease-Modifying Therapies for People with Highly Active Relapsing-Remitting Multiple Sclerosis in the UK. *Pharmacoeconomics* 2008;26:617-27.
41. van Hout B, Janssen M, Feng Y, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. . *Value Health* 2012;15:708-15.
42. Chen G, Khan M, Iezzi A, Ratcliffe J, Richardson J. Mapping between 6 Multiattribute Utility Instruments. . *Med Decis Making* 2016;36:160-75.
43. Drabinski A, Williams G, Formica C. Observational Evaluation of Health State Utilities among a Cohort of Sepsis Patients., abstract no. 17, p. 130.
44. Limited BE. Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA [ID744]: Natioanal Institute for Health and Care Excellence. Highly Specialiased Technologies Evaluation Programme.
45. National Institute for Health and Care Excellence. Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. 2017, https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf. [Accessed 1st March 2018].
46. Chiesi Farmaceutici. A single center, open label clinical trial investigating the long-term efficacy of rhLAMAN-(recombinant human alpha-mannosidase or Lamazym) treatment in subjects with alpha-mannosidosis who previously participated in Lamazym trials. no. EUDRACT No. / IND No : 2014-003950-15; 2016.
47. Hatswell A, Porter J, Lee D, Hertel N, NR. L. The Cost of Costing Treatments Incorrectly: Errors in the Application of Drug Prices in Economic Evaluation Due to Failing to Account for the Distribution of Patient Weight. . *Value in Health* 2016;19:1055-8.

9 APPENDICES

Appendix 1: Eligibility for velmanase alfa and start/stop criteria

Reproduction of section 10.1.16 of the CS.[2]

10.1.16.1 Eligibility

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

Patients will not be eligible to receive treatment with velmanase alfa if any of the following apply:

- the patient does not have a confirmed diagnosis of alpha-mannosidosis; or
- the patient has experienced a severe allergic reaction to velmanase alfa or to any of the excipients (disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol and glycine); or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or
- the patient is unwilling or unable to comply with the associated monitoring criteria, i.e. that all patients are required to attend their appointed clinics two times per year for assessment

10.1.16.2 Start criteria

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

- Patient eligibility criteria must be met as defined in Section 10.1.16.1
- A full set of baseline biochemical, functional and QoL assessments have been obtained

10.1.16.3 Stop criteria

Patients will cease treatment with velmanase alfa if any of the following apply:

- the patient is non-compliant with assessments for continued therapy (noncompliance is defined as fewer than two attendances for assessment in any 18-month period); or
- the patient fails to meet two of the three criteria as defined in multi-domain responder analysis at their Year 1 assessment (Section 9.4.1.4 and 9.6.1.3)
- the patient is unable to tolerate infusions due to infusion related severe AEs that cannot be resolved; or
- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit; or

- the patient's condition has deteriorated such that they are unable to comply with the monitoring criteria, e.g. due to repeated recurrent chest infection or progressive and sustained lack of mobility; or
- the patient misses more than four infusions of velmanase alfa in any 12-month period, excluding medical reasons for missing dosages.

Patients whose treatment with velmanase alfa is discontinued due to stop criteria will continue to be monitored for disease progression and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

Appendix 2: Study Flow Charts

Reproduction of Figures from the CS relating to patient flow through the trial.

Figure 4: reproduction of Figure 6 from the CS:[2] rhLAMAN-02[13] patient disposition

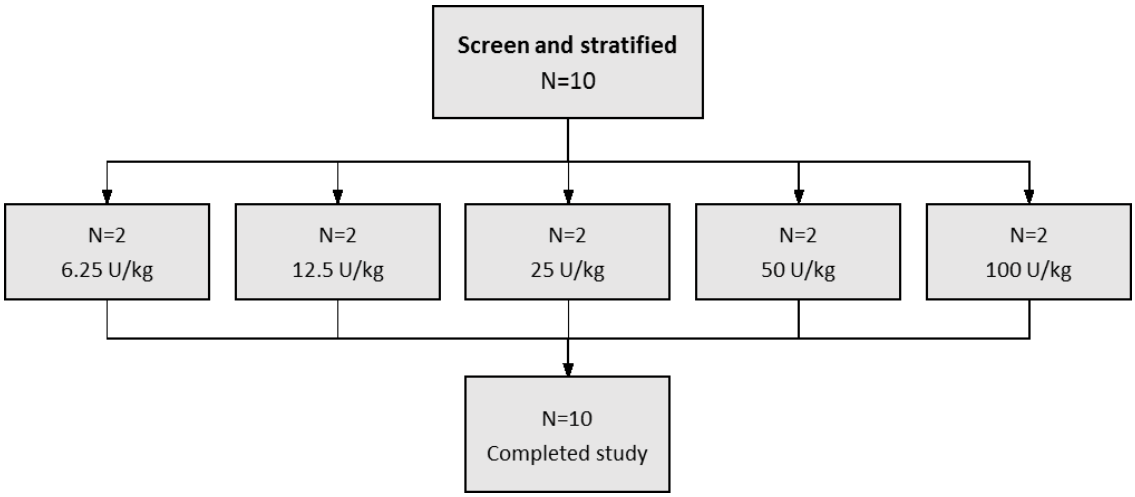
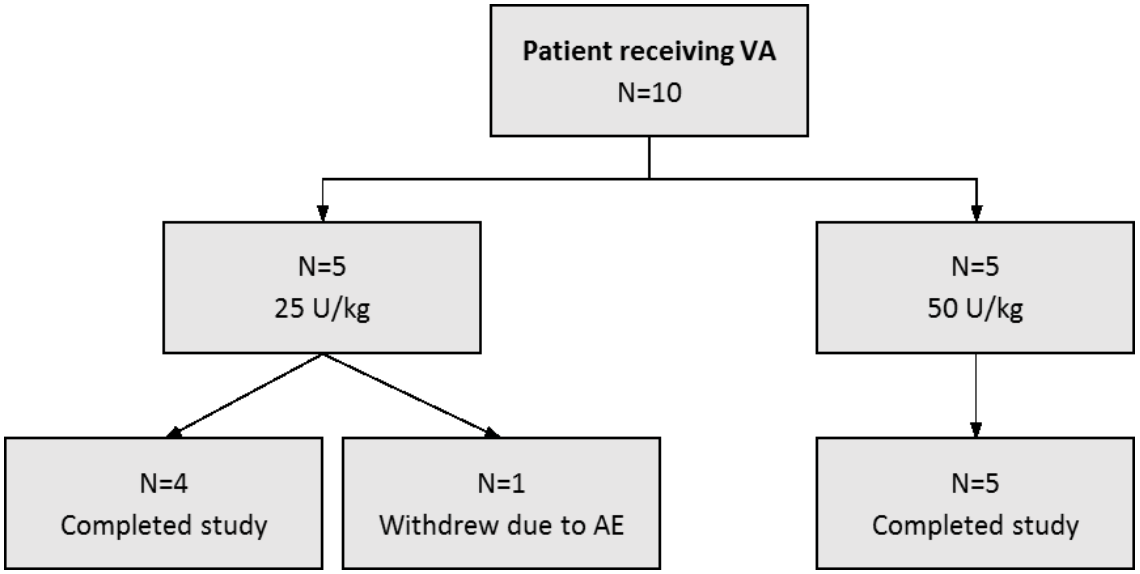
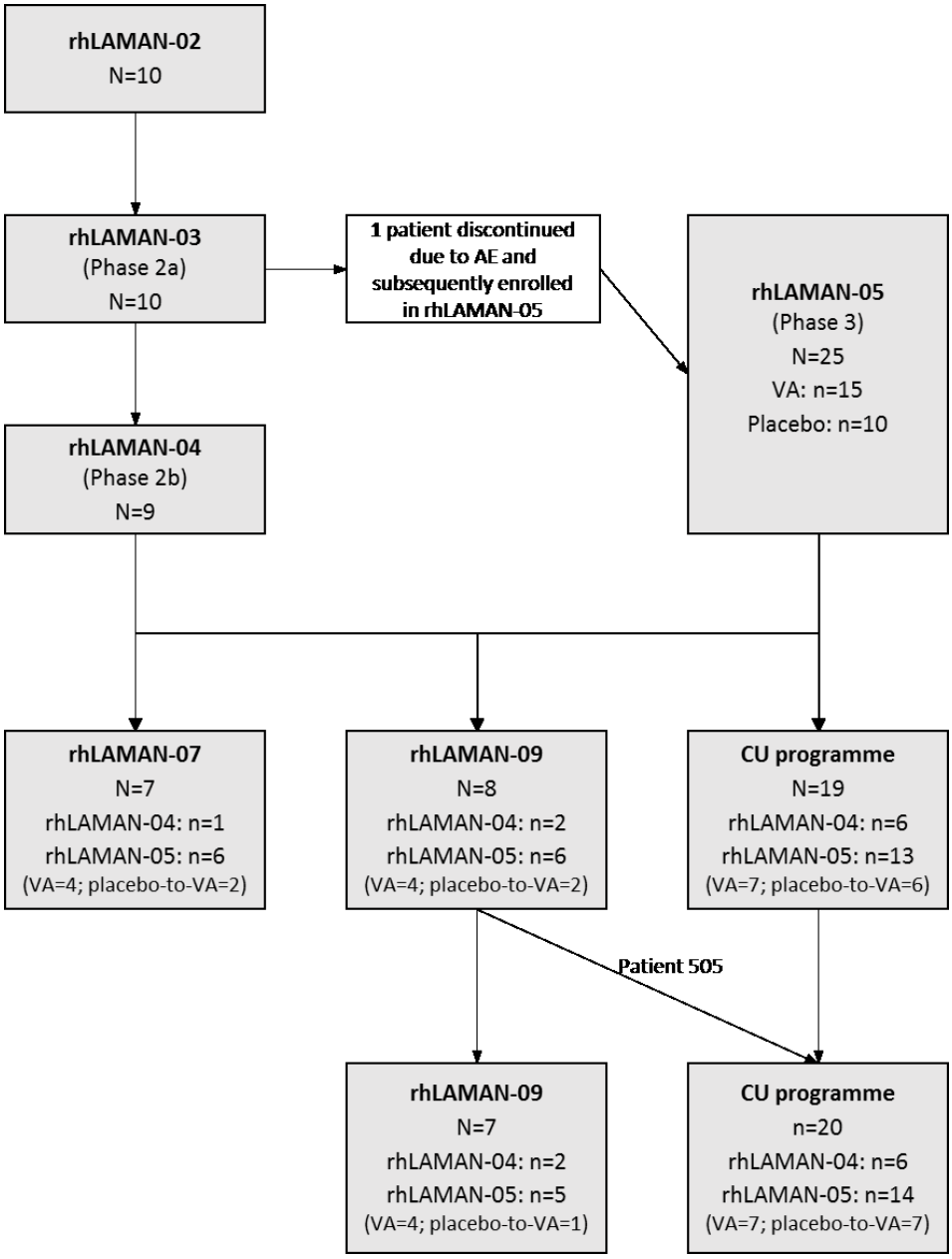


Figure 5: reproduction of Figure 7 from the CS:[2] rhLAMAN-03[15] patient disposition



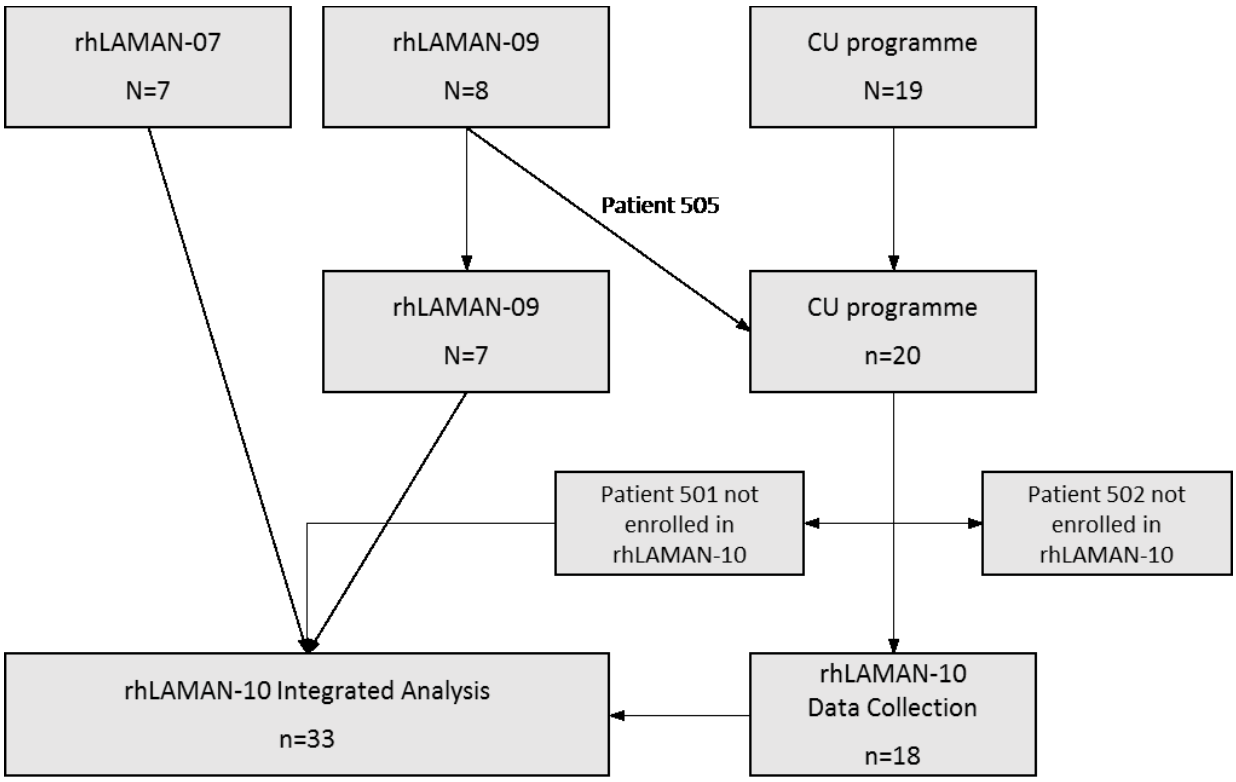
Abbreviations: AE, adverse event; VA, velmanase alfa.

Figure 6: reproduction of Figure 8 from the CS:[2] Patient disposition from Phase I to after-trial studies and compassionate use programme



Abbreviations: AE, adverse event; CU, compassionate use.

Figure 7: reproduction of Figure 9 from the CS:[2] Patient disposition from after-trial studies and compassionate use programme to rhLAMAN-10[1] data collection (CEV) and integrated data set analysis



Abbreviations: CU, compassionate use.
Note: See text for description.

Appendix 3: Patient status analysis: cut off points

Table 51: Reproduction of Table 18 from the CS[2]: Criteria for level of impairment per outcome

Outcome	Not/slightly impaired	Impaired	Seriously impaired
Serum oligosaccharide, µmol/L	0–1.5	>1.5–4.9	≥5
CSF oligosaccharides, µmol/L	0–2	2–7	≥7
Serum IgG, mg/mL	Reference range according to reference range in Cassidy (1974) (98)	4 to normal range	<4
3-MSCT, steps/min	>55	45–55	<45
6-MWT, % of predicted	>80–120	>50–80	≤50
FVC, % of predicted	>80–120	>50–80	≤50
FEV_1, % of predicted	>80–120	>50–80	≤50
PTA air conduction left ear, dBHL	≤25	26–55	≥56
PTA air conduction right ear, dBHL	≤25	26–55	≥56
PTA bone conduction best ear, dBHL	≤25	26–55	≥56
CHAQ disability index, score	0–1	>1–2	>2–3
CHAQ pain (VAS), score	0–1	>1–2	>2–3

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PTA, pure tone audiometry.

Appendix 4: Baseline characteristics of rhLAMAN-05[10] and rhLAMAN-10[1]

Table 52: reproduction of Table 16 from the CS[2]: Baseline characteristics of rhLAMAN-05[10]

Characteristic	VA (N=15)	Placebo (N=10)
Age, n (%)		
<12	4 (26.7)	2 (20.0)
12–<18	3 (20.0)	3 (30.0)
≥18	8 (53.3)	5 (50.0)
Female, n (%)	6 (40.0)	5 (50.0)
Male, n (%)	9 (60.0)	5 (50.0)
Race (white)	15 (100.0)	10 (100.0)
Weight, kg		
Mean (SD)	60.2 (21.5)	64.2 (12.2)
Height, metres		
Mean (SD)	1.51 (0.19)	1.61 (0.14)
BMI, kg/m^2		
Mean (SD)	25.1 (4.9)	24.7 (2.7)
3-MSCT, steps/min		
Mean (SD)	52.9 (11.2)	55.5 (16.0)
35–45, n (%)	1 (6.7)	3 (30.0)
45–55, n (%)	9 (60.0)	2 (20.0)
55–65, n (%)	3 (20.0)	1 (10.0)
≥65, n (%)	2 (13.3)	4 (40.0)
6-MWT, metres		
Mean (SD)	460 (72.3)	466 (140)
200–400, n (%)	2 (13.3)	3 (30.0)
400–500, n (%)	11 (73.3)	3 (30.0)
≥500, n (%)	2 (13.3)	2 (40.0)
FVC		
% of predicted, mean (SD)	81.7 (20.7)	90.4 (10.4)
L, mean (SD)	2.5 (1.1)	3.3 (0.9)
FEV_1		
% of predicted, mean (SD)	80.3 (19.6)	85.9 (18.2)
L, mean (SD)	2.3 (1.0)	2.9 (0.9)
PEF, L/s		
Mean (SD)	4.6 (2.2)	5.7 (1.6)
Leiter-R, years		
TEA-AME mean (SD)	6.3 (2.6)	6.6 (1.8)
TEA-VR mean (SD)	5.7 (1.7)	6.1 (1.6)
Serum oligosaccharides, µmol/L		
Mean (SD)	6.8 (1.2)	6.6 (1.9)
CSF oligosaccharides, µmol/L		
Mean (SD)	11.4 (3.0)	10.3 (2.9)
BOT-2 Total Score, points		
Mean (SD)	94.93 (41.68)	109.2 (51.84)
CHAQ disability index, score		
Mean (SD)	1.37 (0.82)	1.59 (0.64)
EQ-5D index, score		
Mean (SD)	0.61 (0.19)	0.61 (0.18)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five-dimension questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation; TEA-AME, total equivalence age for attention and memory; TEA-VR, total equivalence age for visualisation and reasoning; VA, velmanase alfa.

Table 53: reproduction of Table 17 from the CS[2]: Baseline characteristics of patients included in the rhLAMAN-10[1] integrated data set, overall, by age and by parental study

Characteristic	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)	Phase I/II trial (N=9)	rhLAMAN-05[10] (N=24)
Age of starting treatment, years Mean (SD)	17.1 (7.8)	11.6 (3.7)	24.6 (5.3)	12.4 (3.8)	18.9 (8.3)
Female, n (%)	13 (39.4)	6 (31.6)	7 (50.0)	2 (22.2)	11 (45.8)
Male, n (%)	20 (60.6)	13 (68.4)	7 (50.0)	7 (77.8)	13 (54.2)
Race (white)	33 (100.0)	19 (100.0)	14 (100.0)	9 (100.0)	24 (100.0)
Weight, kg Mean (SD)	58.8 (18.6)	49.8 (19.7)	70.9 (6.2)	49.5 (17.5)	62.3 (18.1)
Height, metres Mean (SD)	1.53 (0.18)	1.46 (0.20)	1.63 (0.08)	1.46 (0.19)	1.55 (0.17)
BMI, kg/m^2 Mean (SD)	24.3 (4.3)	22.4 (4.2)	26.9 (2.9)	22.2 (3.9)	25.1 (4.3)
3-MSCT, steps/min Mean (SD)	53.60 (12.53)	54.04 (13.34)	53.00 (11.82)	52.63 (14.25)	53.96 (12.14)
6-MWT, metres Mean (SD)	466.6 (90.1)	454.2 (86.3)	483.4 (95.6)	452.8 (106.7)	471.8 (85.0)
FVC n % of predicted, mean (SD) L, mean (SD)	 29 84.9 (18.6) 2.65 (1.08)	 17 79.6 (16.4) 2.24 (0.93)	 12 92.5 (19.4) 3.23 (1.05)	 9 81.7 (14.1) 2.20 (0.87)	 20 86.4 (20.4) 2.86 (1.13)
FEV_1 n % of predicted, mean (SD) L, mean (SD)	 29 83.8 (17.6) 2.44 (1.00)	 17 79.0 (15.0) 2.06 (0.83)	 12 90.5 (19.3) 2.98 (1.00)	 9 82.2 (12.8) 2.05 (0.79)	 20 84.5 (19.6) 2.62 (1.05)
PEF, L/s n Mean (SD)	 29 4.85 (2.04)	 17 3.90 (1.58)	 12 6.20 (1.90)	 9 3.89 (1.50)	 20 5.29 (2.14)
Leiter-R TEA-VR, years Mean (SD)	5.88 (1.57)	5.40 (1.40)	6.53 (1.59)	5.69 (1.29)	5.95 (1.68)
Leiter-R TEA-AME, years n Mean (SD)	 24 6.51 (2.18)	 10 5.93 (2.11)	 14 7.03 (1.92)	 - -	 24 6.514
Serum oligosaccharides, µmol/L Mean (SD)	6.90 (2.30)	7.63 (2.52)	5.91 (1.54)	9.00 (2.74)	6.11 (1.53)

Characteristic	Overall (N=33)	<18 years (N=19)	≥18 years (N=14)	Phase I/II trial (N=9)	rhLAMAN-05[10] (N=24)
CSF oligosaccharides, µmol/L Mean (SD)	10.64 (3.53)	10.65 (3.84)	10.62 (3.20)	10.33 (4.66)	10.75 (3.11)
BOT-2 total score, points Mean (SD)	107.0 (47.6)	101.9 (53.8)	113.9 (38.6)	120.7 (54.1)	101.9 (45.1)
CHAQ disability index, score Mean (SD)	1.36 (0.77)	1.22 (0.89)	1.55 (0.55)	0.97 (0.80)	1.51 (0.73)
EQ-5D index, score n Mean (SD)	24 0.62 (0.17)	10 0.70 (0.18)	14 0.57 (0.14)	- -	24 0.62 (0.17)

Abbreviations: 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BMI, body mass index; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; EQ-5D, EuroQol five dimension; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, litres; PEF, peak expiratory flow; SD, standard deviation; TEA-AME, total equivalence age for attention and memory; TEA-VR, total equivalence age for visualisation and reasoning.

Appendix 5: PAS Results

Within the main document all cost-effectiveness analyses were undertaken using the list price of velmanase alfa. The company have agreed a patient access scheme (PAS) which takes the form of a simple discount, which reduces the list price from £886.61 (excluding VAT) per 10mg vial to [redacted] (excluding VAT) per 10mg vial.

This document contains the analyses conducted by the ERG using the PAS price of velmanase alfa.

Table 49 contains the ERG's base case, subject to caveats described in the main report. Table 50 contains the scenario analyses performed.

Table 54: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case [redacted])**	**Adolescent (CS base case_[redacted])**	**Adult (CS base case [redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906;_[redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa			[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; WU – Walking Unassisted; WWA – Walking With Assistance

Table 55: Scenario Analyses run on the ERG's base case

	CPQ given individual change		
Analyses	**Paediatric (base case [redacted])**	**Adolescent (base case [redacted])**	**Adult (base case [redacted])**
Assuming 100% in the WU health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WWA health state	[redacted]	[redacted]	[redacted]
Assuming 100% in the WC health state	[redacted]	[redacted]	[redacted]
Assuming the average age per age band observed in rhLAMAN-10[1]	[redacted]	[redacted]	[redacted]
Assuming no improvements in health state after 12 months	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to surgery.	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to serious infection.	[redacted]	[redacted]	[redacted]
Assuming the costs of a severe infection are set to £2742	[redacted]	[redacted]	[redacted]
Assuming velmanase alfa confers no benefit in relation to ventilation costs.	[redacted]	[redacted]	[redacted]
Assuming the UK MPS survey as the source for caregiver requirements.	[redacted]	[redacted]	[redacted]
Excluding caregiver disutility	[redacted]	[redacted]	[redacted]
Including personal expenditure by the family	[redacted]	[redacted]	[redacted]
Including caregiver productivity losses	[redacted]	[redacted]	[redacted]
Assuming that patients treated with velmanase alfa have a utility gain of 0.05	[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; MPS – Mucopolysaccharidosis; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
Dominant refers to producing more health at fewer costs.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Velmanase alfa for treating alpha-mannosidosis [ID800]

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **12noon** on **Wednesday 4 April 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Patient numbers contributing to health state utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 13 and 14, the ERG report states: *'the use of utility data taken from a UK Society for Mucopolysaccharide Diseases survey ([redacted]) rather than those from rhLAMAN-10[1] ([redacted]);'* The use of patient numbers (n) in this statement is unclear, as the sentence does not describe which health state the ERG are referring to. For example, a greater number of patients are provided by both data sources (MPS survey and rhLAMAN-10), when looking across all model health states.	The ERG should either include which health state they are referring to (e.g. walking unassisted), or use total patient numbers across all health states in the model for which the two data sources provide.	Unclear reporting of patient numbers (n)	These have been amended to *([redacted]) and ([redacted])*
On page 120, the ERG states: *"Fifteen patients recruited to rhLAMAN-10 provided baseline utility values for the Walking Unaided and the Walking With Assistance health states"* This is incorrect. A total of 24 patients recruited provided baseline utility values for the 'Walking Unassisted' (n=15) and the 'Walking with Assistance' (n=9) from rhLAMAN-10.	Amend the sentence to reflect the correct patient numbers.	Incorrect reporting	The change has been made

<table>
<tr>
<td>On page 110, Table 42 the ERG assigns the following patient numbers (n) to each utility estimate scenario:

<table>
<tr><th>Health State</th><th>n</th></tr>
<tr><td>Base case</td><td>9</td></tr>
<tr><td>Scenario 1</td><td>3</td></tr>
<tr><td>Scenario 2†</td><td>5†</td></tr>
<tr><td>Scenario 3</td><td>4†</td></tr>
<tr><td>Scenario 4</td><td>4†</td></tr>
<tr><td>rhLAMAN-101 baseline</td><td>15</td></tr>
<tr><td>rhLAMAN-10[1] Last observation</td><td>25</td></tr>
</table>
† Plus one value in the WWA state estimated from UK KOL estimates

† Used in the model

The patient numbers for Scenario 3, Scenario 4, rhLAMAN-10 baseline and rhLAMAN-10 last observation are incorrect.</td>
<td>Amend as outlined in the table below:

<table>
<tr><th>Health State</th><th>n</th></tr>
<tr><td>Base case</td><td>9</td></tr>
<tr><td>Scenario 1</td><td>3</td></tr>
<tr><td>Scenario 2†</td><td>5†</td></tr>
<tr><td>Scenario 3</td><td>5†</td></tr>
<tr><td>Scenario 4</td><td>5†</td></tr>
<tr><td>rhLAMAN-10[1] baseline</td><td>24</td></tr>
<tr><td>rhLAMAN-10[1] Last observation</td><td>31</td></tr>
</table>
† Plus one value in the WWA state estimated from UK KOL estimates

† Used in the model

For rhLAMAN-10, the numbers now account for the patients contributing to the ‘walking with assistance’ health state (n=9 at baseline and n=6 at last observation).</td>
<td>Incorrect reporting</td>
<td>We have made these changes</td>
</tr>
</table>

Issue 2 Company value base case for utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Table 1 and Table 49, the ERG states that the Company’s base case utility value for the ‘walking with assistance’ health state is [redacted]. This statement is incorrect – the base	Revise the base case value for the ‘walking with assistance’ health state to [redacted].	Incorrect reporting	Amendment made

case utility value for the 'walking with assistance' health state in the Company's submission is [redacted].			

Issue 3 Justification for utility choices

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 109, the ERG states: *"Scenario 2 was used in the revised modelling. The company provided no justification of why this was preferred to the base case values, or data collected from within the rhLAMAN-10 study"* A justification was provided in the ERG clarification question response (B47) as follows: Scenario 2 has been chosen on the grounds of: • It is more appropriate to include patients on BSC only to derive patient utility data as: ○ Including patients with prior treatment means there is a potential for 'double counting' the on-treatment utility benefit of velmanase alfa ○ The AM patient population who have received (or who are clinically indicated to receive) allogeneic	Remove statement saying that no justification was provided.	Incorrect reporting of data provided by the Company.	Statement removed

HSCT do not overlap with the patient population suitable to receive velmanase alfa; hence why the three patients who have received allogeneic HSCT should also be removed from the data set • Scenario 2 uses a UK KOL validated utility value for patients who are 'walking with assistance', whereas scenario 3 and 4 are mathematical approaches to impute the data gap			

Issue 4 UK MPS Society Survey response rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 105, when referring to the UK MPS Society Survey, the ERG states: *"The potential selection bias associated with the 33% response rate is unknown"* This is factually incorrect. The response rate was 9/24 = 38%	Amend to a 38% response rate.	Incorrect reporting	Amendment made, in addition we have changed eight to nine within the text.

Issue 5 Data sources for key parameters within the company model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 112, Table 43, the ERG describes one of the model parameters as: *"Reduction in the requirement for velmanase alfa due to the use of velmanase alfa"* This statement needs correcting.	Please correct parameter description.	Incorrect reporting	Change has been made, the first velmanase alfa has been changed to ventilation
On page 112, Table 43, the source of 'Probability of mortality and complications associated with major surgery' is incorrectly described as 'the UK Expert Elicitation Panel'.	The correct source is 'Interviews with UK KOLs'.	Incorrect reporting	Change made
On page 112, Table 43, the source of 'Probability of severe infection conditional on health state' is incorrectly described as 'Interviews with UK KOLs'.	The correct source is 'UK Expert Elicitation Panel'.	Incorrect reporting	Change made

Issue 6 Interpretation of formal clinical expert interviews

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 120, the ERG report states: *"The values from the interviews and arbitrary*	Please include a statement to clarify the reasoning and/or evidence behind	Unclear reporting	We have included the word 'therefore' before 'concerned' to

distributions used by the company do not benefit from using a formal elicitation process. The ERG is concerned that the parameter estimates may not reflect genuine beliefs which leads to questions regarding the appropriateness of both the company's and the ERG's base case analysis." It is unclear as to why the ERG has concluded that '*the parameter estimates may not reflect genuine beliefs'*. For example, is it because the ERG would have liked to see formal elicitation conducted for all unknown parameters and/or concerns with the methods used to conduct the UK KOL interviews?	the ERG's conclusions.		link this more clearly with the lack of a formal elicitation process.
On page 14, the ERG report states: *"The rationale for some of the assumptions used within the company's model were unclear or contentious"* The Company has provided full details of the methods/approaches (e.g. UK KOL interviews and UK expert elicitation) to develop and validate the economic model assumptions, which use UK clinical expert opinion. The Company considers the conclusion that the justifications provided are '*unclear*' or '*contentious*' as factually incorrect and that this conclusion is not supported by the evidence described in the Company Submission and the responses to the ERG clarification questions.	Please include a statement to clarify the reasoning and/or evidence behind the ERG's conclusions.	Unclear reporting	We have removed 'unclear', but maintain that some assumptions are contentious, but have qualified this by stating that this is in the view of the ERG.

Issue 7 Costs post discontinuation of velmanase alfa

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 121, the ERG state: *"After the clarification period, the ERG identified an error in that patients who had received velmanase alfa treatment but had discontinued and were receiving BSC, did not have the same ventilation costs as patients on BSC. The model has been amended so that patients who have discontinued treatment have the ventilation costs associated with BSC."* This is not an implementation error but an assumption within the model. The model assumes that patients who receive velmanase alfa and then discontinue may continue to have improved lung functioning, which may reduce the need/intensity of future ventilation. We apologise that the assumption was not clearly stated in the original submission or response to clarification questions; this assumption is supported by feedback/evidence provided in the stage 3 UK KOL interviews.	Please amend 'error' to 'assumption'. This may also require an amendment to the ERG's preferred base case analysis depending on their view regarding this assumption.	Incorrect reporting	We have changed the text. We note the company's acknowledgement that this assumption had not be stated but have not put this in the report.

Issue 8 Health state utility values

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>On page 110, Table 42 the ERG describes the following health state utility values for ‘scenario 1’ i.e. a comparison of patient utility values reported by the carer (by proxy) and by the patient (by self-report) for the n=3 patients which have both a self-reported and carer-reported values.
<table>
<tr><th>Health State</th><th>n</th><th>WU</th><th>WWA</th><th>WC</th><th>SI</th></tr>
<tr><td>Scenario 1</td><td>3</td><td>0.794 (0.000)</td><td>0.758 (N/A)</td><td>N/A</td><td>N/A</td></tr>
</table>
The stated values are incorrect.</td>
<td>Please consult the supporting data on file (Excel file) supplied at the ERG clarification stage for the full details of the UK MPS Society Survey data. For completion, the health state utility values for the n=3 patients that have both self-reported and carer-reported utility values are shown below:
<table>
<tr><th>Health State</th><th>n</th><th>WU</th><th>WWA</th><th>WC</th><th>SI</th></tr>
<tr><td>Scenario 1 – carer-reported</td><td>3</td><td>0.906 (0.000)</td><td>0.758 (N/A)</td><td>N/A</td><td>N/A</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>N/A</td><td>N/A</td></tr>
</table></td>
<td>Incorrect reporting</td>
<td>This change has been made.</td>
</tr>
<tr>
<td>On page 120, the ERG describes their rationale for using the utility values derived from rhLAMAN-10 (at baseline) for the ‘Walking Unassisted’ and ‘Walking with Assistance’ states in the economic base case, as opposed to using the UK MPS Society Survey data:

“Fifteen patients recruited to rhLAMAN-10 provided baseline utility values for the Walking Unaided and the Walking With Assistance health states. This is greater than the number (2) that responded to the MPS Survey used in the company base case. The baseline value</td>
<td>Further consideration of the different health state utility datasets, their plausibility and appropriateness of being used in the economic base case, is required.</td>
<td>Incomplete reporting</td>
<td>Additional text has been added to provide more balance.</td>
</tr>
</table>

has been chosen rather than the last observation value as (1) the company suggest that treatment with velmanase alfa may improve utility which would confound the results, and (2) the difference between the two reported sets of values are not very large." When comparing the two datasets (rhLAMAN-10 baseline data vs the UK MPS Society Survey data), the ERG report does not mention several other important attributes of the datasets: • The utility data derived from the UK MPS Society Survey were collected using health state definitions that match the economic model exactly. In other words, patients were stratified into health states (e.g. 'walking unassisted') using the definitions of the economic model. This is not the case for the rhLAMAN-10 dataset, which is based on a stratification according to the CHAQ 'Helps and Aids' questions relating to 'walking'. ○ This discrepancy in definitions used to stratify patients is important. For example, based on the definition used in the UK MPS Society Survey and economic model, to be classed as a patient who was 'walking unassisted', the patient required no assistive means for walking. However, using the CHAQ stratification method from rhLAMAN-10, patients could be classed as 'walking unassisted' (as they didn't require help from a cane,			

walker, crutches, wheelchair or help from another person), but could still have been using other assistive means (e.g. bath rail, handrail, etc.) • The UK MPS Society Survey data provides real-world data for a UK-specific patient cohort aligned to the NICE decision problem			

Issue 9 On treatment utility benefit with velmanase alfa

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 121, the ERG report states: *"The ERG comments that the additional years in each state elicited from the clinical experts (Table 30) are not sufficiently high to support evidence of clear ongoing utility gain for patients receiving velmanase alfa."* The Company considers that on treatment utility benefit and the additional time (years) spent in health states due to treatment with velmanase alfa are two separate model parameters. In this aforementioned statement the ERG remarks that, by some unexplained means, the additional time (years) spent in each health state is related to the on treatment utility benefit with velmanase alfa, and suggests that the additional time (years) is *'not sufficiently high'* to support the assumed on treatment utility benefit (0.1). The ERG does not provide evidence and/or thresholds to support this association between additional time (years) spent in health states and expected on treatment utility benefit with velmanase alfa.	Please provide rationale and/or evidence to support this conclusion, or remove the statement.	Incomplete reporting	The text has been changed to show that this is a matter of judgment rather than a fact

Issue 10 Reference to central nervous system outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 23 and 44 the ERG report states: *"The clinical advisors were further surprised that psychiatric problems such as acute psychosis were missing both from the NICE scope and from the trials, as this is also a problem for many patients.* In addition, on page 74 the ERG report states: *"Clinical advisors to the ERG were of the opinion that infection rates and central nervous system effects should have been included in the responder analysis"* The Company considers the request to include central nervous system outcomes in the responder analysis as inappropriate given the licenced indication of velmanase alfa, which is as an enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis. In addition, the responder analysis is based on the identification of variables and biochemical/clinical domains that are expected to be improved by the use of velmanase alfa. Velmanase alfa does not	Amendment of the request, given that neurological manifestations fall outside of the licenced indication of velmanase alfa.	Inappropriate request given the licenced indication for velmanase alfa. Incorrect interpretation of the approach used in the responder analysis (i.e. parameters that are expected to be improved by the treatment on the basis of its mechanism of action).	The ERG understand that velmanase alfa does not cross the blood-brain barrier and therefore cannot be expected to impact on CNS outcomes. However, the point that these symptoms of the disease are not treated by velmanase alfa, and are considered by clinicians to be an important outcome, is still an important point to be made. The fact that the clinical advisors made this point is not factually inaccurate. However, we agree that the statement was incomplete, and have amended to: "*The clinical advisors were further surprised that psychiatric problems such as acute psychosis were missing both from the NICE scope*[9] *and from the trials, as this is also a problem for many patients. The ERG note that the omission of psychiatric outcomes is because velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on these outcomes for patients, even though they are an important symptom of*

cross the blood-brain barrier; therefore, central nervous system effects cannot be expected and thus there is no rationale to include the corresponding outcome measures in the responder analysis.			*the disease." (pg 23)* "*The clinicians were further surprised that psychiatric problems such as acute psychosis were missing as this is also a problem for many patients. The NICE scope[9] listed language as an outcome, but this was not measured in any trial. The ERG note that the omission of psychiatric, language and other central nervous system outcomes is because velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on these outcomes for patients, even though they are an important symptom of the disease."* (pg 44 of the ERG report) And "…*clinical advisors to the ERG were of the opinion that infection rates and central nervous system effects should have been included in the responder analysis. The ERG note that velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on CNS outcomes for patients, even*

			though they are an important symptom of the disease." (pg 73 of the ERG report)

Issue 11 Reference to the velmanase alfa licenced indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 22 and 23 the ERG report states: *"However, the CS (pages 21 and 33) states that the anticipated licence is now for velmanase alfa as an enzyme replacement therapy (ERT) for the treatment of non-neurological manifestations in patients of any age with mild to moderate AM, who are not clinically indicated for HSCT"* This is factually incorrect. The licenced indication for velmanase alfa is as an enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis. The Company has chosen, within the above stated licenced indication, to position velmanase alfa in the UK in patients with alpha-mannosidosis alongside best supportive care for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible.	Amendment of the wording to reflect the licenced indication for velmanase alfa vs the Company's proposed UK positioning.	Incorrect reporting	The ERG have amended this to: *"The technology was granted a licence in March 2018 as "an enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis".* *The ERG notes that the final NICE scope[9] specified patients aged 6 years or older and that the CS provides clinical trial data on patients aged 5 years or older (CS,[2] Section 9) who are not clinically indicated for HSCT. The company has chosen to restrict their positioning of the drug in the treatment pathway to children aged 6 years or older who are not clinically indicated for HSCT. However, it should be noted*

			*that the licence does not restrict by age or by indication for HSCT..”(*pg 22 of the ERG report) And *“The final NICE scope[9] indicated that the only comparators are BSC or HSCT, where clinically indicated. However, the CS[2] (pages 21 and 33) states that the positioning of the treatment in the pathway in the UK is for patients for whom HSCT is not indicated, and therefore this therapy does not represent a valid comparator.”* (pg 23 of the ERG report)

On pages 22, 23 and 40 the ERG reports refers to the licenced indication for velmanase alfa as "*anticipated".* Marketing authorisation has now been granted for velmanase alfa (March 2018), therefore the licenced indication is confirmed and finalised.	Removal of the word 'anticipated' in relation to the licenced indication for velmanase alfa.	Incorrect reporting	See previous response for pg 22 and 23 Pg 40 changed to: "*The intervention appears to match the licenced posology and dose."* And "*It should be noted that the licence does not restrict treatment by age, as the EMA recognises that early treatment could be beneficial."*

Issue 12 Allogenic HSCT as a suitable comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 23 the ERG report states: *"Clinical advice received by the ERG and submitted to NICE within expert statements suggests that HSCT could present a valid comparator for a minority of these patients, including those aged 5 years or more."* The Company has chosen, within the licenced indication, to position velmanase alfa in the UK in patients with alpha-mannosidosis alongside best supportive care for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and/or not possible. Therefore, HSCT cannot be considered as a suitable comparator when taking into account this proposed UK positioning.	Amendment of the wording to reflect the Company's proposed UK positioning.	Incorrect interpretation of the Company's proposed UK positioning of velmanase alfa.	The ERG understand the point the company makes, however, the quoted text should have read (and has now been amended to) "*However, clinical advice received by the ERG and submitted to NICE within expert statements suggests that HSCT could present a valid comparator for a minority of the patients included in the trials, including those aged 5 years or more*." (Pg 23)

Issue 13 Use of dichotomised variables in the response model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 74, the ERG states: "*Dichotomising patients according to arbitrary cut-offs results in a loss of power relative to the original continuous data*". Although this statement is correct when referring to the definition of the primary endpoint of a trial, it is not applicable in the context of the proposed MCID analysis, as any response analysis is in fact based on the creation of a justifiable threshold to define a relevant change.	Remove the statement from the list of comments regarding the MCID-based response analysis.	Not applicable in the context of an MCID-based response analysis.	The ERG does not consider that there is any circumstance when it is acceptable to dichotomise a continuous variable: http://www.methodsappraisal.com/education-dichotomania/.

Issue 14 Use of serum oligosaccharides in the responder analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 74, the ERG states: "*Serum oligosaccharides may not be clinically important"* The scope of the model is to	Please include a statement to clarify that the variable is used in the context of a patient's response to treatment, without claiming specific clinical relevance, but rather as a biomarker of a pharmacodynamic response to treatment.	Misleading comment regarding the context in which the variable has been used within the responder analysis.	The ERG does not agree that the statement is misleading or factually incorrect. Serum Oligosaccharides are a surrogate endpoint, and their

investigate the presence of a treatment response in the context of the variables collected in the rhLAMAN-05 and -10 trials; the co-primary endpoints in both trials were a decrease in serum oligosaccharides and an increase in the clinically relevant variable, the 3-MSCT. In this context, a similar response is a minimum requirement in order to define a responder in the model (i.e. at least the biochemical domain and one clinical domain). No specific claim regarding the clinical relevance of oligosaccharides has been put forward in the model.			inclusion in an analysis which aims to identify clinical response is questionable. The company describes the analysis as a "*multi-domain responder analysis combining multiple endpoints into single domains representing clinically important effects*" (pg 24 of the Company Submission) It is therefore entirely reasonable for the ERG to question the clinical relevance of this surrogate endpoint.

Issue 15 Inclusion of outcome measures in the responder analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 75, the ERG states: "*There are no MCIDs reported for motor function (BOT-2); hearing; Leiter-R; rates of infections; or EQ-5D.*". The way this statement is expressed suggests that the Company has not been able to or has decided not to identify MCIDs	Please remove the statement for what concerns hearing and Leiter-R and clarify that some secondary clinical variables were not included in the model due to the way the outcome measure was collected (infections) or because it was collected only in a sub-group of patients (EQ-5D).	The statement may mislead the reading regarding the choice of variables for the model.	The section of the report that this quote is taken from is entitled "*Multi-domain responder analysis and minimal clinically important differences;* i.e. it relates to both the multi-domain responder analysis and minimal clinically important

for all the enlisted variables, giving the impression that the model is missing a number of otherwise appropriate outcome measures. This is misleading in terms of the responder analysis, as these variables were not included in the response model for various reasons not related to the identification of an MCID. In particular: • BOT-2 test does not have a recognised reference MCID for the global score. In addition, the test was not completed in all its parts in the rhLAMAN patients due to the length and complexity of the test for the patient • Although many factors can affect hearing impairment in alpha-mannosidosis (including ENT infections), the neurological component of the hypoacusia plays a major role. As velmanase alfa does not cross the blood-brain barrier (as reflected by its therapeutic indication in the SPC), an effect on these variables cannot be expected. Therefore, there is no rationale to include it in the responder analysis • Leiter R is a psychometric test			differences, as many of the points listed apply to both, as the MCIDs were used in the responder analysis. The bullet point quoted by the company relates to minimal clinically important differences, and it remains correct. However, we agree that it is misleading that the bullet point is not separated out as relating to the MCIDs rather than the responder analysis also. We have amended by adding a new paragraph "*In addition, in relation to MCIDs and the interpretation of the trial outcomes:"* followed by the bullet point.

assessing cognitive function. As the product does not cross the blood-brain barrier, an effect on these variables cannot be expected. Therefore, there is no rationale to include it into the responder analysis • Rates of infections were not collected as an efficacy endpoint in the rhLAMAN studies and therefore could not qualify as an efficacy outcome measure to be included in the model • EQ-5D was only collected in the phase III trial, rhLAMAN-05; therefore, results were not available for 9 out of 33 patients. For this reason, it has been excluded from the responder analysis. However, an MCID for this variable has been identified as described in the 'data on file – response to clinical question 137D' provided to NICE as part of the Company submission and ERG clarification question response.			

Issue 16 Generation of the randomisation sequence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 28, Table 4, the ERG states: "*It is not clear how the randomisation sequence was generated*". An SAS program was used for the creation of the randomisation list. The program was generated by a statistician and validated according to internal procedures (reported in CRO's SOP 502, available upon request). However, "*Compared to other double blind clinical trials rhLAMAN-05 was special with regards to the patient population: all potential patients were known to the investigators before the start of the trial. At the same time, it was important to balance treatment allocations with regards to age of patients. On this background it was chosen to stratify all patients according to age. The randomization numbers were allocated as the rank after an age wise sorting of patients; the youngest patient was allocated the lowest number and*	Please remove the statement from the comments regarding the absence of clarity on the generation of the randomisation sequence or substitute it with a new one based on the updated information provided here.	Comment generated by lack of specific information in the submitted documentation, which is now provided.	It is unfortunate that the company did not provide this information with their submission: it is a fundamental aspect of critical appraisal of RCTs. We have amended the report Table 4, and our critical appraisal of the study on pg 27 of the ERG report: "Overall, the ERG initially judged rhLAMAN-05[10] to be of reasonable quality, with some faults. The ERG judged rhLAMAN-05[10] to be at low risk of bias in three domains, compared to six domains judged at low risk by the company. The ERG judged there to be a lack of clarity about randomisation procedure (i.e. how the random sequence was

the oldest was allocated the highest number. This process was not blinded to trial staff. The randomization of treatment (velmanase alfa or placebo) was handled in a fully blinded manner." (quotation from an internal memo on file, available upon request).			generated), allocation concealment (even after the company's clarification response to A4)[11] and blinding of outcome assessors, whereas the company judged these to be at low risk of bias (see **Error! Reference source not found.**). However, after information provided during the Fact Check by the company, two of these items were scored positively, and whilst the third (allocation concealment) remains somewhat unclear, it is likely allocation concealment was maintained. The ERG concluded that rhLAMAN-05 was at generally low risk of bias." And on pg 11: "The ERG believes the CS is complete with respect to evidence relating to velmanase alfa. The ERG

			judged rhLAMAN-05 to be at generally low risk of bias and rhLAMAN-10 to be at some or unknown risk of bias." And on pg 14: "Given the rarity of the disease, the availability of RCT evidence is commendable. rhLAMAN-05 was at generally low risk of bias, though somewhat small." And on pg 85 "rhLAMAN-05[10] appears to be at generally low risk of bias."

Issue 17 Blinding of outcome assessors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 29, Table 4, the ERG states: "*it is not specified if all outcome assessors (e.g. 3MSCT) are blinded."* Patients, investigators and staff (sponsor and clinical CRO) were	Please remove the statement from the comments regarding the absence of clarity regarding blinding of outcome assessors or substitute it with a new one based on the updated information provided here.	Comment generated by lack of specific information in the submitted documentation, which is now provided.	See previous response

blinded to treatment allocation (excluding the randomisation statistician who performed the randomisation and the programmer responsible for printing the sealed envelopes at the CRO). The “investigators” were also the “assessors” and were all personnel of the coordinating site (Copenhagen) and not external staff.			

Issue 18 Additional typographical/cross referencing errors

Description of problem	Description of proposed amendment			Justification for amendment	ERG Response
Typographical/cross referencing errors	**Section, page**	**Error**	**Correction**	For accuracy and clarity	
	1.2, 10	*'6-minute walk test (6-MWT) and functional vital capacity (FVC) were prioritised secondary outcomes..'*	'*and forced vital capacity (FVC)..*		corrected
	1.2, 10	*'other outcomes measured in both trials…'*	Missed 'CSF oligosaccharides and CSF biopmarkers (tau, NFLp and GFAp)' from the list of other outcomes measured in both trials.		These have been listed with an amendment: "Outcomes not listed in the NICE scope but measured in both trials included CSF oligosaccharides and CSF biopmarkers (tau, NFLp and GFAp)."
	1.2, 10	*'adjusted mean difference in relative change and adjusted mean difference in absolute change results respectively..'*	'adjusted mean difference in relative change and adjusted mean difference in absolute change between velmanase alfa and placebo results respectively..'		corrected
	1.2, 10	'*for 3-MWT, estimates were..*	6-MWT		corrected

	2.2, 21	*'allogeneic HSCT is only clinically indicated for patients aged five years or less'*	allogeneic HSCT is typically only clinically indicated for patients aged five years or less		Change made
	3.2, 23	List price is incorrectly reported	The list price of velmanase alfa is £886.61		Change made
	3.3, 23	*…'(CS[2], pages 23 and 68)'*	The reference to page 68 should be revised to page 67		Change made
	4.2, 34	"*Flow charts of patients through the trials rhLAMAN-02[13], -0315, -04[14], -07, -09 and -10[1] are provided in Appendix 1".*	The cross reference should be to Appendix 2		Change made
	4.2, 36 Table 6	*rhLAMAN-05.* **Efficacy (primary):** Serum OGS; 3-MWT *rhLAMAN-10 integrated dataset:* **Efficacy (primary):** Serum OGS; 3MWT	3-MSCT		corrected
	4.2.5.1, 46	*'the co-primary endpoints were serum oligosaccharides and the 3-MWT'* *'…in serum oligosaccharides with a trend for*	3-MSCT		corrected

		improvement in the 3-MWT and one prioritised secondary outcome..'			
	4.2.5.2, 46	*'The co-primary endpoint were serum oligosaccharides and the 3-MWT'*	3-MSCT		corrected
	4.2.6, 55, Table 11	FVC% predicted normal value Adjusted mean absolute change (95%CI): – 8.21 (1.79, 14.63)	8.20 (1.79, 14.63)		corrected
	4.2.6, 56, Table 11	Leiter R- cognition TEA-VR (years) Relative (%) change from baseline (SD): 1.73 (12.24) 6.16 (	1.73 (12.24) ~~6.16 (~~		corrected
	4.2.6, 59–63, Table 12	Bolding of p-values appears to denote significance. However, bolding is inconsistent – for example, significant p-values for 3-MSCT (e.g. 18 months) are not in bold	Revise so all p-vales ≤0.05 are in bold		All statistically significant p values made bold.
	4.2.6, 60,	FVC % predicted	93.1 (21.7)		corrected

	Table 12	Actual value (SD) Last observation 93.121.7)			
	4.2.6, 60, Table 12	CHAQ disability index Absolute change from baseline (SD) Last observation -0.13 (0.440	-0.13 (0.44)		corrected
	4.2.6, 60, Table 12	CHAQ disability index Relative (%) change from baseline (SD) 48 months 13.13 (72.270	13.13 (72.27)		corrected
	4.2.6, 63, Table 12	It appears that the data for serum IgG from baseline through to Month 48 may have been erroneously omitted	These data are available in Table 14.2.14.1 (Summary of serum-Immunoglobulin G (g/L) - by timepoint – FAS) of the rhLAMAN-10 CSR; also available in the Data on file supplied in response to clarification question A39		corrected
	4.2.6, 66	The value from the CHAQ pain (VAS) has been incorrectly applied in the following sentence: *"The change in CHAQ*	The sentence should be revised to: *"The change in CHAQ disability achieved the MCID of ≥0.13 at -0.13 (SD*		corrected

		disability exceeded the MCID of ≥0.13 at -0.17 (SD 0.65)"	*0.44)"*		
	4.2.8, 80	*"40.0% in the velmanase alfa group vs 20.0% in the placebo group respectively"*	*"40.0% in the placebo group vs 20.0% in the velmanase alfa group respectively"*		corrected
	5.2.3.1, 97	*"Additionally the company provided a 174 document extensively…"*	*"Additionally the company provided a 174-page document extensively…"*		corrected
	5.2.3.2, 97	*"The company described the elicitation process in Section 12.2.5 of the CS"*	*"The company described the KOL interview process in Section 12.2.5 of the CS"*		Change made
	5.2.3.9, 100	*"The company have applied for a PAS which will take the form of a simple discount on the price per vial…"*	*"The company have applied for a PAS, [redacted] which will take the form of a simple discount on the price per vial…"*		Change made, although the ERG had not been formally made aware of this at the time of writing.

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

ERRATUM

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1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) adequately describes the decision problem. The CS assesses the clinical effectiveness of velmanase alfa within its licensed indication for the treatment of patients with alpha-mannosidosis and the cost-effectiveness of velmanase alfa for patients aged six years and older. The comparator of best supportive care (BSC) was appropriate although the company did not include haematopoietic stem cell transplant as a comparator; clinical advice to the ERG suggested that it could be a comparator in some cases. Evidence relating to all outcomes listed in the final scope produced by the National Institute for Health and Care Excellence (NICE) was included within the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence base comprised one 12 month, double-blind, placebo controlled RCT (rhLAMAN-05, n=25) and one long-term, single arm, open label study (rhLAMAN-10, n=33). Some patients were enrolled in both studies. In rhLAMAN-05 participants were treated with velmanase alfa 1mg/kg or placebo infusions once per week.

Both studies used the biomarker serum oligosaccharides as a co-primary outcome, with the clinical outcomes 3-minute stair climb test (3-MSCT) as the second co-primary outcome. 6-minute walk test (6-MWT) and forced vital capacity (FVC) were prioritised secondary outcomes in rhLAMAN-05 and secondary outcomes in rhLAMAN-10. Other outcomes measured in both trials were other pulmonary function tests (PFTs), Bruininks-Oseretsky test of motor proficiency, 2nd edition (BOT-2), Leiter-R (cognition), Pure Tone Audiometry (PTA), Childhood Health Assessment Questionnaire (CHAQ), and the EuroQol five-dimension-five-levels (EQ-5D-5L) quality of life questionnaire. Infections and psychiatric outcomes were not measured as efficacy outcomes. Outcomes not listed in the NICE scope but measured in both trials included CSF oligosaccharides and CSF biopmarkers (tau, NFLp and GFAp).

In rhLAMAN-05, there was a statistically significant decrease in serum oligosaccharides (adjusted mean difference in relative change between velmanase alfa and placebo group −70.47% (95% confidence interval (CI): −78.35, −59.72), p<0.001; adjusted mean difference in absolute change -3.50 µmol/L (95% CI: -4.37; -2.62), p< 0.001). However, there were no statistically significant decreases in the clinical co-primary and prioritised secondary outcomes or on the other secondary outcomes relating to motor function, cognition and hearing. The adjusted mean difference in relative change and adjusted mean difference in absolute change between velmanase alfa and placebo results respectively were: 3-MSCT: 3.01% (95% CI: −9.86, 17.72), p=0.648 and 2.62 steps/min (95% CI: -3.81, 9.05), p=0.406; For 6-MWT estimates were: 1.86% (95% CI: −6.63, 11.12), p=0.664 and 7.35 meters (95% CI: -30.76; 45.46), p=0.692; FVC% 8.40% (95% CI −6.06, 25.08), p=0.269 and 5.91% predicted (95% CI −4.78,

16.60), p=0.278. The company stated that the trial met the endpoint of "*a statistically significant reduction in serum oligosaccharides (at a significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis*".

In rhLAMAN-10, the relative change from baseline results (SD) at last observation were: serum oligosaccharides -62.8% (33.61), p<0.001; 3-MSCT 13.77% (25.83), p=0.004; 6-MWT 7.1% (22.0), p=0.071; FVC% predicted 10.5% (20.9), p=0.011. Other statistically significant results at last observation were: EQ-5D-5L Index (11.2% (24.7218), p=0.036); BOT-2 total (13.0% (33.9), p=0.035; Leiter-R (visualisation and reasoning) (5.338 (10.45) p= 0.006), and serum IgG levels, a surrogate for infections, 44.07% 95% CI (32.58, 55.57), p=<0.001.

The company also provided pre-planned analyses in rhLAMAN-10 including age subgroups (<18 years vs ≥18 years) and a patient status analysis. Post-hoc analyses included a multi-domain responder analysis in both studies and an evaluation by age (<18 years vs ≥18 years). The multi-domain responder analysis showed more patients were responders in the velmanase alfa arm of rhLAMAN-05 than the placebo arm (87% vs 30% respectively), and more patients <18years were responders than ≥18 years in rhLAMAN-10 (100% vs 71%). The age subgroup analyses showed observed differences between groups, but interaction tests were not performed in rhLAMAN-05 and were only performed for serum oligosaccharides (non-significant interaction) and 3-MSCT (a significant interaction) in rhLAMAN-10.

To address ERG concerns about the omission of infection rates from the trials, the company provided additional post-hoc analyses of serum IgG, use of antibiotics and a questionnaire provided to caregivers. These data were interpreted by the company as indicating improvements in infection rates were likely.

The proportion of patients receiving velmanase alfa and experiencing any AE is high (88%-100%); approximately one half experienced a treatment-related AE and one third a SAE. However, most AEs were reported as being mild or moderate.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG believes the CS is complete with respect to evidence relating to velmanase alfa. The ERG judged rhLAMAN-05 to be at generally low risk of bias and rhLAMAN-10 to be at some or unknown risk of bias. The clinical advice provided to the ERG suggested that serum oligosaccharides are a surrogate with pharmacokinetic relevance, but low clinical relevance. They also considered infection rates and psychiatric outcomes (not measured as efficacy outcomes in the studies) as clinically relevant outcomes.

The ERG was concerned that the data relating to infection rates was not ideal. In rhLAMAN-05 there was a higher observed adverse event rate of infections and infestations in the velmanase alfa arm than in the placebo arm in rhLAMAN-05(48 events (87% of patients), versus 23 events (70% of patients) respectively).

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a health model constructed in Microsoft Excel® that compared treatment with velmanase alfa to treatment with BSC. The primary outcome measure was cost per quality-adjusted life year (QALY) gained using an NHS and personal social services perspective. The model uses a state transition approach with one-hundred yearly time cycles. There are five primary health states: (i) walking unassisted; (ii) walking with assistance; (iii) wheelchair dependent; (iv) severe immobility and (v) death. In addition, patients can experience severe infection, which can result in transition to a short end stage where death occurs four weeks' later, and patients can also undergo surgery, which can result in either death or transitioning to severe immobility health state. Key clinical parameters of the model that were assumed to be influenced by velmanase alfa treatment were informed largely through elicitation of experts' beliefs with, or interviews with, clinical experts. These included: improvement in health state; the additional time in a health state before progression; the reduction in the probability of major surgery; the reduction in surgical-mortality and surgical complications; the reduction in mortality and complications associated with severe infections; and the reduced requirement for ventilation. Resource use and unit costs were populated from published literature. Based on the deterministic version of the company's revised model, post clarification, the incremental cost-effectiveness ratio (ICER) for velmanase alfa versus BSC was estimated to be: £[redacted] per QALY gained for a paediatric cohort; £[redacted] per QALY gained for an adolescent cohort; and £[redacted] per QALY gained for an adult cohort. Probabilistic estimates were similar to the deterministic estimates.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent of these include: (i) the use of utility data taken from a UK Society for Mucopolysaccharide Diseases survey (***) rather than those from rhLAMAN-10[1] (***); (ii) the use of an inappropriate discount rate of 1.5% per annum rather than one of 3.5% per annum; (iii) the assumption of a utility increase of 0.10 for those patients receiving velmanase alfa; (iv) a model implementation error relating to the transition probabilities after treatment discontinuation; and (v) a model implementation error relating to the expected costs after discontinuation of velmanase alfa treatment. In addition to the five issues previously described, there is considerable uncertainty in many key parameters relating to the effectiveness of velmanase alfa.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Given the rarity of the disease, the availability of RCT evidence is commendable. rhLAMAN-05 was at generally low risk of bias, though somewhat small.

The ERG considers the general model structure adopted by the company to be appropriate. The company fixed errors identified by the ERG in the clarification process.

1.6.2 Weaknesses and areas of uncertainty

The small number of patients in the studies and the relatively short (for a treatment that will be given life-long) length of follow-up leads to uncertainty around the estimates of efficacy. The lack of statistical significance is perhaps not surprising in some instances given the small sample size, though the small observed differences between treatment arms is still a concern. The company assert that improvements over the natural course of the disease are likely over time, and the biological rationale for this is plausible. However, the available evidence is difficult to interpret because of the small number of patients followed-up for longer than 12 months, and the inclusion of different patients at different time points.

The rationale for some of the assumptions used within the company's model were, in the opinion of the ERG, contentious. Many of these assumptions could be seen as being favourable to velmanase alfa. In addition, two programming errors were identified by the ERG after the clarification process. Clinical advice received by the ERG suggested that haematopoietic stem cell transplant may be an appropriate treatment for some patients; however, this was not included in the company model as a comparator.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made five changes to the company model. These were: (1) the use of utility data collected in the rhLAMAN-10[1] study ([redacted]) in preference to data taken from the MPS survey ([redacted]); (2) changing the discount rate from 1.5% per annum to 3.5% per annum; (3) removing the company's assumption that patients receiving velmanase alfa treatment have a gain in utility of 0.10; (4) the correction of a model implementation error whereby the transition rates between those patients receiving BSC were different dependent on whether the patient had received velmanase alfa previously; and (5) the correction of a model implementation error whereby the incorrect costs were used after the

Table 1: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case [redacted])**	**Adolescent (CS base case [redacted])**	**Adult (CS base case [redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906; [redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; WU – Walking Unassisted; WWA – Walking With Assistance

Bone marrow transplant (BMT) and allogeneic Haematopoietic Stem Cell Transplant (HSCT) represent the only treatment options for some patients, but there is substantial morbidity and mortality associated with these procedures.[4, 5, 8] The CS[2] (page 23) states that in the UK, allogeneic HSCT is typically only clinically indicated for patients aged five years or less, without additional comorbidities/recurrent infections, and who have a matched sibling or umbilical cord donor. However, the CS[2] (Section 8.3.3, pages 67-68) also states that broader clinical criteria might be applied in practice.

Given the lack of treatment options, current service provision principally consists of symptom management for the pain and impairments associated with the disorder. This is represented by best supportive care (BSC) and includes walking aids, physiotherapy, infection management and, where appropriate, surgical intervention (CS, Section 8.2.4 and pages 64-65).[2] Given the highly heterogeneous nature of the disorder, and the highly individual nature of its presentation, patients must be managed on a case-by-case basis.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The remit detailed in the final scope issue by the National Institute for Health and Care Excellence (NICE)[9] is to appraise the clinical and cost-effectiveness of velmanase alfa within its licensed indication for AM. The technology was granted a licence in March 2018 as "an enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis".

The ERG notes that the final NICE scope[9] specified patients aged 6 years or older and that the CS provides clinical trial data on patients aged 5 years or older (CS,[2] Section 9) who are not clinically indicated for HSCT. The company has chosen to restrict their positioning of the drug in the treatment pathway to children aged 6 years or older who are not clinically indicated for HSCT. However, it should be noted that the licence does not restrict by age or by indication for HSCT.

Therefore, there is uncertainty regarding the generalisability of the results to child patients aged less than 5 years, who were excluded from the trials (rhLAMAN-05[10] and rhLAMAN-10[1]) presented in the CS.[2] Given the absence of discrete diagnostic criteria for severe, moderate and mild forms of the disorder, there might also be an issue distinguishing between patients with 'severe' AM and patients with 'moderate or mild AM'. Clinical advice to the ERG suggested that patients diagnosed under 5 years of age tend to be classified as having a 'severe' form of the disorder, with those diagnosed at 5 years or older being considered to have moderate or mild form, which ultimately progresses to 'severe' in later life. Clinical advice received by the ERG also confirmed that the clinical evidence relates to trials of patients with 'moderate or mild' AM.

3.2 Intervention

The intervention evaluated by the company is velmanase alfa (Lamzede®). Velmanase alfa is a white powder that is reconstituted to provide a final concentration of 10 mg/5 ml (2 mg/ml) per vial. The recommended dose of velmanase alfa is 1 mg/kg of body weight, once every week, to be administered by intravenous (IV) infusion at a controlled speed. As velmanase alfa is dosed by weight, (1mg/kg of body weight) dose adjustments are required as/if the patient's weight changes. Velmanase alfa is intended to be used continuously throughout a patient's lifetime, subject to the 'start' and 'stop'

criteria described in the CS[2] (pages 182-83). A patient is excluded from treatment if they do not have a confirmed diagnosis of AM; has experienced a severe allergic reaction to velmanase alfa or to any of its excipients; if they are diagnosed with an additional progressive life-limiting condition where treatment would not provide a long-term benefit; or if the patient is unable to comply with the associated monitoring criteria. Treatment may be stopped due to reasons of non-compliance, non-response and/or deterioration of functional capacity. The list price for velmanase alfa is £886.61 per vial with the number of vials required per week dependent on the patient's weight.

3.3 Comparators

The final NICE scope[9] indicated that the only comparators are BSC or HSCT, where clinically indicated. However, the CS[2] (pages 21 and 33) states that the positioning of the treatment in the pathway in the UK is for patients for whom HSCT is not indicated, and therefore this therapy does not represent a valid comparator. If this position is accepted, the ERG believes that the rhLAMAN-05[10] and rhLAMAN-10[1] trials, which compared velmanase alfa (plus BSC) with placebo (plus BSC), are appropriate to address the decision problem. For brevity, velmanase alfa in combination with BSC intervention has henceforth been abbreviated to velmanase alfa, and placebo in combination with BSC has been termed BSC.

However, clinical advice received by the ERG and submitted to NICE within expert statements suggests that HSCT could present a valid comparator for a minority of the patients included in the trials, including those aged 5 years or more. The ERG also notes that there are no universally-accepted criteria regarding patients for whom 'allogeneic HSCT is not suitable and/or not possible' (CS[2], pages 23 and 67). The CS[2] (page 23) states that, '*allogeneic HSCT is typically only reserved for AM patients with extensive disease presenting in early infancy (≤5 years), and who do not have additional comorbidities/recurrent infections, and where a matched sibling or matched umbilical cord donor is available … Additionally, the risk of allogeneic HSCT-associated morbidity and mortality increases with age … Therefore, patients over the age of 6 are less likely to have any treatment options'*. The ERG notes that the clinical evidence is drawn from trials of AM patients aged 5 years or older who have never been exposed to allogeneic HSCT (CS[2], pages 97 and 100). There is therefore no comparison of clinical effectiveness or cost-effectiveness of velmanase alfa for patients who are suitable for HSCT.

3.4 Outcomes

Nearly all clinical outcomes listed in the final NICE scope[9] were addressed in the clinical section of the CS;[2] however, infections were only reported as adverse events and language was not measured. The ERG received clinical advice that infections are an important outcome as they are a source of mortality and morbidity and should have been included as an efficacy outcome. The potential status of

oligosaccharides as a surrogate outcome for patients' functional outcomes[3] was not demonstrated by the submitted evidence from the only randomised controlled trial (rhLAMAN-05[10]). The company's model aggregates the patients simulated experiences into quality-adjusted life years (QALYs) as stipulated in the final scope.[9] The clinical advisors were further surprised that psychiatric problems such as acute psychosis were missing both from the NICE scope[9] and from the trials, as this is also a problem for many patients. The ERG note that the omission of psychiatric outcomes is because velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on these outcomes for patients, even though they are an important symptom of the disease.

3.5 Other relevant factors

The company have applied for a patient access scheme which will take the form of a simple discount on the price per vial resulting in a cost of [redacted] (excluding VAT) per 10mg vial rather than the list price of £886.61 (excluding VAT) per 10mg vial. Societal costs are included in a sensitivity analyses.

4.1.4 Quality assessment

The company confirmed that the quality assessment of the studies was conducted in the same manner as data extraction (response A6),[11] and the ERG is satisfied that the process was of an acceptable standard.

However, the ERG did not initially agree with all the judgements provided by the company, nor the use of an RCT checklist for the assessment of rhLAMAN-10[1] which is a non-controlled study more akin to a cohort study. **Error! Not a valid bookmark self-reference.** and **Error! Reference source not found.** provide the ERG's judgements on the quality of rhLAMAN-05[10] and rhLAMAN-10[1] compared with the company's appraisal. **Error! Reference source not found.** also includes responses to a quality assessment checklist for cohort studies provided by the company in their clarification response A5.[11]

Overall, the ERG initially judged rhLAMAN-05[10] to be of reasonable quality, with some faults. The ERG judged rhLAMAN-05[10] to be at low risk of bias in three domains, compared to six domains judged at low risk by the company. The ERG judged there to be a lack of clarity about randomisation procedure (i.e. how the random sequence was generated), allocation concealment (even after the company's clarification response to A4)[11] and blinding of outcome assessors, whereas the company judged these to be at low risk of bias (see **Error! Reference source not found.**). However, after information provided during the Fact Check by the company, two of these items were scored positively, and whilst the third (allocation concealment) remains somewhat unclear, it is likely allocation concealment was maintained. The ERG concluded that rhLAMAN-05 was at generally low risk of bias.

The ERG and company's judgement of risk of bias in rhLAMAN-10[1] differed in three domains. Overall, the ERG judged rhLAMAN-10[1] to be in some respects a well conducted study, but with some key limitations that make the results subject to high risk of bias. The ERG judged an unclear risk for outcome measurement as some measures were subjective (e.g. Childhood Health Assessment Questionnaire (CHAQ)) and the trial was open label. The ERG judged there to be a lack of clarity around attrition as numbers are inconsistent across Figures 18-21 in the CS.[2] The ERG also judged that the results are possibly confounded and inconsistent with other data (CS, page 137-39);[2] there is a lack of consistency across functional outcomes, for example, 3-minute stair climb test (3MSCT) shows significant improvement but 6-minute walk test (6MWT) does not, and there is no quality of life gain despite statistically significant improvements in function; the findings for 6MWT are not correlated with oligossacharide levels as suggested elsewhere (Beck 2013).[3]

Table 2: Critical appraisal of rhLAMAN-05[10] (randomised and controlled trial) (reproduced in part from CS, Table 22)

Study name	rhLAMAN-05[10]			
	CS critical appraisal[2]		ERG critical appraisal	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Randomisation (in a 3:2 ratio) into active and placebo groups was stratified by age and was used to allocate the patients into blocks. Within the blocks, a standard randomisation into active and placebo was performed.	Yes	CSR: 9.4.6: It is not clear how the randomisation sequence was generated, e.g. by referring to a random number table, using a computer random number generator, etc. Additional information was provided by the company in their Fact Check (issue 16) of the report which stated "SAS program was used for the creation of the randomisation list. The program was generated by a statistician and validated according to internal procedures" The ERG were consequently able to score this item as "yes"
Was the concealment of treatment allocation adequate?	Yes	rhLAMAN-05[10] was double-blind study.	Unclear	Assumption is that vials are identical, but the description provided is not explicit: C.S.R 9.4.2.4[11] (packaging) and 9.4.6 (randomization and blinding): To preserve the blinding no batch number was included, but the batch was identified by the trial reference code (rhLAMAN-05[10]) and the retest date… The subject number, identification and randomization were documented at Larix (a Contract Research Organisation). Three sets of sealed code/label with the randomization number containing information about the treatment for the particular subject were prepared for each subject. One set was kept at the dosing site (during the entire trial period), one set was kept at Larix and one set was kept at the Sponsors Quality Assurance. The randomization code list was kept at Larix and was disclosed to the contract manufacturing organization (CMO) performing the packaging of the trial. The code for a particular subject could be broken in a medical emergency ...

				also clarification response A4[11]: The randomisation code list was kept at the CRO and was disclosed to the contract manufacturing organisation (CMO) performing the packaging of the trial. The code for a particular subject could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject. However, blinding was not broken for any patient in the trial.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Overall, the demographic characteristics were similar between the two groups. In terms of functional capacity (by categorical values arbitrary adopted for 3-MSCT and 6-MWT), PFTs and BOT-2, the two groups were less balanced, with a higher proportion of more compromised patients randomised to the active treatment group.	No	As noted, the patient groups are not balanced for 3MSCT, 6MWT, FVC, BOT-2 or CHAQ Disability Index (CSR, Table 11-1)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Patients and investigators remained blinded to treatment assignment during the study. The blinding for a particular patient could be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the patient.	Yes	Patients and care providers appear to be blinded (see allocation concealment above, CSR[10] sections 9.4.2.4 and 9.4.6), possibly as well as outcome assessors at data review (CSR[10] sections 9.6 and 11.1), but it was only specified during the Fact Check that outcome assessors were also blind. CSR[10] 9.6: After completion of data cleaning, a blinded data review meeting was held to define protocol deviations and patient populations to be analysed. Afterwards, the database was locked, the randomisation codes were opened and the planned statistical analysis was performed.

				CSR[10] 11.1: During the blinded data review, all patients were included in the PK analysis set, but only the 15 patients treated with Lamazym were then analysed. Fact Check issue 17: Patients, investigators and staff (sponsor and clinical CRO) were blinded to treatment allocation (excluding the randomisation statistician who performed the randomisation and the programmer responsible for printing the sealed envelopes at the CRO). The "investigators" were also the "assessors" and were all personnel of the coordinating site (Copenhagen) and not external staff.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	NR	No	No reported drop-outs
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	NR	No	However, the following outcomes were not listed in the protocol, but were reported: BOT-2 motor function; Leiter-R cognitive ability; EQ-5D; CHAQ Disability Index and VAS; and PTA hearing loss tests: https://clinicaltrials.gov/ct2/show/record/NCT01681953[12]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety evaluation was based on a modified ITT analysis and included all patients who received ≥1 dose of trial drug and whose efficacy was evaluated post-baseline.	Yes	CSR[10] 9.7.1: statistical analysis of everyone who had at least 1 dose of study drug (CS, 9.6.2, page 154[2]) and protocol deviations did not suggest any patient was not analysed in the correct group (CSR 10.2.1). Appropriate multiple imputation methods were used to account for missing data.

Abbreviations: CS, company submission; CSR: Clinical Study Report; 3-MSCT, 3-minute stair climb test; 6-MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky test of motor proficiency, 2nd edition; ITT, intention-to-treat; PFT, pulmonary function test; PK: Pharmokenetics; PTA: Pure Tone Audiometry; CHAQ: Childhood Health Assessment Questionnaire; VAS: Visual Analogue Scale; EQ-5D: EuroQol five-dimension questionnaire.

4.1.5 Evidence synthesis

There was no formal synthesis of the data, which the ERG believes was acceptable as there was only a single relevant phase III/IV trial (CS, section 9.8, page 161).[2] The narrative synthesis tabulated results and described these with a good degree of clarity.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The clinical effectiveness review included five studies of velmanase alfa: a Phase I-II trial comprising three individual studies (rhLAMAN-02[13], rhLAMAN-03[15], rhLAMAN-04[14]), and two further Phase III trials, one of which was an RCT (rhLAMAN-05[10]) and the other of which is a long term non-controlled study (rhLAMAN-10).[1] Table 3 details these studies. Of note, patients were eligible to enrol in subsequent trials: patients in rhLAMAN-02[13] could enrol in rhLAMAN-03[15] (and all ten did, exclusively forming the rhLAMAN-03[15] trial); patients in rhLAMAN-03[15] could enrol in rhLAMAN-04[14] (9/10 of whom did, exclusively forming the rhLAMAN-04[14] trial); patients in rhLAMAN-04[14] and -05[10] could enrol in rhLAMAN-07 or -09 (references not provided by the company for either study) or a compassionate use programme (where no efficacy outcomes were assessed). rhLAMAN-07 and -09 were set up to ensure patients could continue treatment in countries that did not want the company to offer a compassionate use programme; -07 was for French patients, and -09 for Norwegian and Polish patients. Both studies include long-term follow-up for safety, with -09 also following-up patients for efficacy (see clarification response Question A18[11]). rhLAMAN-10[1] is an integration of data collected for rhLAMAN -02[13], -03[15], -04[14], -05[10], -07 and -09, and a single efficacy assessment point for patients who enrolled in the compassionate use programme after participating in rhLAMAN-02[13], -03[15] or -04.[14] In this way, all patients had baseline and follow up data. Flow charts of patients through the trials rhLAMAN-02[13], -03[15], -04[14], -07, -09 and -10[1] are provided in Appendix 2.

4.2.1 Description of the design of rhLAMAN-05[10]

rhLAMAN-05[10] was a Phase III multicentre, double blind, placebo-controlled RCT. Patients were randomised to velmanase alfa treatment (1mg/kg by infusion) weekly, or to weekly placebo in a 3:2 ratio stratified by age in a block randomisation. Treatments were administered for 12 months. Inclusion criteria are provided in the footnote to Table 3.

4.2.2 Description of the design of rh-LAMAN-10[1]

rhLAMAN-10[1] was an integrated database(N=33) incorporating data from the Phase I/II trial (rhLAMAN-02[13]/03[13]/04[14]), rhLAMAN-05[10], rhLAMAN-07 and rhLAMAN-09 to form the rhLAMAN-10[1] integrated data set, along with additional patients who entered the compassionate use programme and had a long-term efficacy assessment as part of rhLAMAN-10.[1] The study design is an

Table 3: Summary of key trials of velmanase alfa

Trial Name	Trial design	Inclusion criteria	N	Duration	Intervention	Comparator	Main outcomes
rhLAMAN-02[13] (NCT01268358) Borgwardt et al, 2013[16] (JA)	Phase I, SC, OL Randomised dose escalation	AM[f] pts aged 5-20[a]	10	1-5 weeks[b]	5 dosing groups (n=2 in each) VA, U/kg: 6.25; 12.5; 25; 50; 100	Baseline	**Safety:** AEs, vital signs, haematology, biochemistry, urinalysis, Anti-drug antibody (ADAs)
rhLAMAN-03[15] (NCT01285700) Borgwardt et al, 2013[16] (JA)	Phase IIa, SC, OL Randomised multiple dose	AM[f] pts aged 5-20 (all from rhLAMAN-02[13])[a]	10	6 months efficacy assessment + 6 months extension[c]	2 dosing groups (n=5 in each), weekly, IV VA, U/kg 25 50	Baseline	**Efficacy:** OGS in serum, urine, CSF; CSF neurodegeneration markers; Brain MRS; Functional capacity; cognitive development; pulmonary function; hearing; PK profile **Safety:** as rhLAMAN-02[13]
rhLAMAN-04[14] (NCT01681940) Borgwardt et al, 2014[17] (CA)	Phase IIb, MC,[d] OL	AM[f] pts aged 5-20 (all from rhLAMAN-02[13]/-03[15])[a]	9	6 months	VA 1 mg/kg	Baseline	**Efficacy (primary):** Serum and CSF OGS; 3-MSCT; 6-MWT; pulmonary function; **(secondary):** mannose-rich OGS by MRS and MRI in white matter, grey matter and centrum semiovale; CSF neurodegeneration markers; BOT-2 and hearing loss; Leiter-R; CHAQ
rhLAMAN-05[10] (NCT01681953) Guffon et al, 2017[18] (CA)	Phase III; RCT, MC,[e] DB, PC	AM[f] pts aged 5-35[g]	25	12 months	VA 1 mg/kg (randomised 3:2, VA: placebo)	Placebo	**Efficacy (primary):** Serum OGS; 3-MSCT; **(secondary):** 6-MWT; FVC; PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; EQ-5D
rhLAMAN-10[1] integrated dataset (NCT02478840)	Phase III; NC, SC, OL,	AM[f] Recruited from rhLAMAN-02[13], -03[15], -04[14], and -05.[10] Pts who chose the compassionate	33	Integration of data collected in other rhLAMAN studies, or a one-week assessment for those	VA 1 mg/kg	Baseline	**Efficacy (primary):** Serum OGS; 3-MSCT; **(secondary):** 6-MWT; FVC; PFTs; BOT-2; Leiter-R; CSF OGS; CSF

Guffon et al, 2017[18]; Borgwardt 2017a[19]; Borgwardt 2017b[19] ; Borgwardt 2017c[20] ; Lund 2017[21]; Harmatz 2017[19]; Borgwardt 2017d[22]; Cattaneo 2016[23]; Ardigo 2016 [24]; Borgwardt 2016[25] (all CAs)		use programme after rhLAMAN-04[14] were also eligible. Pts enrolled in rhLAMAN-07 or -09 were included in the dataset.[a g]		who joined the compassionate use programme			neurodegeneration markers; PTA; CHAQ; EQ-5D

3-MSCT, 3 minute stair climb test; 6-MWT, six minute walk test; ADA, anti-drug antibody; AEs, adverse events; AM, alpha-mannosidosis;N, number; BOT-2, Bruininks-Oseretsky test of motor proficiency 2nd edition; CHAQ, childhood health assessment questionnaire; CSF, cerebrospinal fluid; DB, double-blind; MC, multicentre; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NC, non-controlled study; OGS, oligosaccharides; OL, open-label; PC, placebo-controlled; PFT, pulmonary function test; PK, pharmacokinetics; PTA, pure tone audiometry;RCT, randomised controlled trial; SC, single centre; pts, patients; VA, velmanase alfa;

[f] AM confirmed by α-mannosidase activity <10% of normal activity in blood leucocytes

[a] Inclusion criteria: Physical ability to perform 6-MWT, 3-MSCT and PFTs; Ability to mentally cooperate in the cognitive and motor function tests; Ability to hear and follow a request (hearing aids can be worn); signed, informed consent of legal guardian; Exclusion criteria: known chromosomal abnormality and syndromes affecting psychomotor development, other than AM; HSCT; conditions that would preclude participation in the trial including clinically significant cardiovascular, hepatic, pulmonary or renal disease, echocardiogram with abnormalities within half a year, other medical condition or serious intercurrent illness, or extenuating circumstances; pregnancy; psychosis in previous 3 months

[b] Patients in the 6.25U/kg group started in week 1 and continued treatment to week 5. Patients in the 12.5 U/kg started in week 2 and continued treatment to week 5, and so on, with a higher starting dose each subsequent week.

[c] To maintain treatment until enrolment in rhLAMAN-04[14]

[d] Five EU sites in Denmark, UK, France, Spain, and Belgium.

[e] Six countries in the European Union: Denmark, France, Spain, Belgium, Germany and Sweden

[g] Inclusion criteria: ability to physically and mentally co-operate with the tests; echocardiogram without abnormalities that would preclude participation in the trial; ability to comply with protocol; Exclusion criteria: known chromosomal abnormality and syndromes affecting psychomotor development, other than AM; HSCT; conditions/circumstances that would preclude participation in the trial; pregnancy; psychosis (including remission); participation in other interventional trials testing IMP (including VA) within the last three months; Adult patients who would be unable to give consent, and who do not have any legal protection or guardianship; Total IgE >800 IU/ml; Known allergy to the IMP or any excipients (sodium-phosphate, glycine, mannitol)

4.2.4 Critique of the design of rhLAMAN-05[10] and rhLAMAN-10[1]

4.2.4.1 Population

Impact of patient age on detection of effect: The clinical advisors to the ERG felt that the inclusion and exclusion criteria (see footnotes to Table 3) were acceptable but noted that the trial excluded very young patients (<5 years old) and older patients (>35 years old). This probably biased the cohort towards younger patients, and it is possible that it might have been easier to detect an effect in younger patients, as disease progression is more rapid.

Exclusion of severe disease and licence-indicated population: The exclusion of the very young (<5 years) will mean severe disease (which presents at a younger age) patients are excluded. The exclusion of patients who could not complete 3-MSCT or 6-MWT or could not mentally cooperate will also lead to the exclusion of patients with severe disease, and those with mobility problems at the higher end of the spectrum. As such, the spectrum is likely to comprise patients with mild to moderate disease, in accordance with the population proposed for reimbursement.

It should be noted that the [TEXT DELETED] licence does not restrict treatment by age, as the EMA recognises that early treatment could be beneficial. However, the company are not seeking reimbursement for patients under 6 years of age, and currently there is insufficient evidence in this group to judge the clinical effectiveness.

Generalisability concerns: The ERG asked for clarification about the exclusion criterion of "patients with IgE>800 IU/mL". The company clarified that this was to exclude patients who are at high risk of anaphylactic reactions "*or for whom the high background concentrations of immunoglobulin E (IgE) would make it difficult to clearly identify an increase due to a reaction to velmanase alfa.*" (response A15)[11] This reduces the generalisability of safety findings to patients with IgE>800 IU/mL.

Previous treatment: The ERG asked for clarification about why 3 months was chosen as an adequate time for patients who had been on previous IMP treatments (including velmanase alfa). The ERG was satisfied with the company's response, indicating that "*Given that most ERTs are given as weekly or bi-weekly infusions, a total of 12 weeks since the last infusion would ensure that a time significantly longer than 5 times the longest theoretical half-life would have elapsed, ensuring a complete drug wash out*." (response A14).[11]

4.2.4.2 Intervention

The intervention appears to match the [TEXT DELETED] licenced posology and dose.

4.2.4.4 Outcomes

Omission of outcomes relevant to the disease: As stated in Section 3.4, the clinical advisors to the ERG were surprised that infections were not included as a key outcome, as these are a major contributor to mortality and morbidity. This was also an outcome listed in the NICE scope.[9] The clinicians were further surprised that psychiatric problems such as acute psychosis were missing as this is also a problem for many patients. The NICE scope[9] listed language as an outcome, but this was not measured in any trial. The ERG note that the omission of psychiatric, language and other central nervous system outcomes is because velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on these outcomes for patients, even though they are an important symptom of the disease.

Clinical relevance of serum oligosaccharides: Whilst serum oligosaccharides may have pharmacokinetic relevance, its use as a primary outcome was seen as highly problematic by the clinical advisors to the ERG for a number of reasons:

- The link between oligosaccharide levels and clinical outcomes is poor from a clinical perspective.
- There was no formal assessment of whether oligosaccharide levels were surrogate for clinical outcomes using standard criteria.[29] Correlations between last observation values for serum oligosaccharides and 3-MSCT, 6-MWT and FVC% predicted within rhLAMAN-10[1] were all negligible or marginal (see question A20 in the clarification response[11]). These data were not reported for rhLAMAN-05.[10]
- Serum oligosaccharides are not currently measured in UK practice, and this would have to be implemented as a test on the NHS if it is to be used to monitor response to treatment.
- The cut off of 4µmol/L is arbitrary and has no clinical meaning.

Age matching for outcomes where childhood growth leads to improvement: In cases where outcomes are likely to increase as age increases (e.g. 6-MWT, cognition, motor skills, lung function), age-normalised reference values are usually used. This allows any deterioration due to disease to be observed (in the absence of a control arm) even though such outcomes may improve overall due to growth. The ERG noted that some outcomes were age matched, including lung function, BOT-2 and the Leiter-R test, but that the 3-MSCT and the 6-MWT were not age-matched in the primary analysis.

In their clarification response (response A28),[11] the company explained that there are no reference values for the 3-MSCT and that "*it is of general understanding that the 3-MSCT is less impacted by growth in the scholar age and by the adolescence height burst given that leg length is not a major contributor to staircase climbing performance*" (response A28).[11] They also highlighted baseline data

4.2.5 Description of the analysis of rhLAMAN-05[10] and rhLAMAN-10[1]

4.2.5.1 Analysis of rhLAMAN-05[10]

The statistical plan for rhLAMAN-05[10] is reproduced from Table 12 of the CS,[2] as **Error! Reference source not found.** in this report. Follow-up was for 12 months. The co-primary endpoints were serum oligosaccharides and the 3-MSCT. The prioritised secondary outcomes were 6-MWT and FVC. The other secondary outcomes were: PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; EQ-5D. Primary outcomes were assessed as the relative change from baseline to month 12. Details of the statistical plan are provided in Table 12 of the CS,[2] and in brief comprised an analysis of covariance (ANCOVA) of log-transformed data. The absolute change from baseline to month 12, the log-transformed relative change from baseline to month 6 and the absolute change from baseline to month 6 were also assessed for these endpoints. Demonstration of efficacy was defined as a statistically significant improvement in both primary outcomes at 6 months, or in serum oligosaccharides with a trend for improvement in the 3-MSCT and one prioritised secondary outcome at 12 months. Multiple imputation methods were applied in case of missing data.

Twenty-five patients were recruited but no formal sample size was calculated; the CS[2] states that the number represents a compromise between the total number of patients available who could meet the inclusion criteria and the number required for efficacy assessment.

The company reported a post-hoc analysis of patients aged <18 vs ≥18 years at start of treatment.

4.2.5.2 Analysis of rhLAMAN-10[1]

The statistical plan for rhLAMAN-10[1] is reproduced from Table 13 of the CS,[2] as **Error! Reference source not found.** in this report. Data comprises a database of follow-up data from rhLAMAN-07 and -09 (which comprised solely patients from rhLAMAN-04[14] and -05[10] and included long term treatment and follow-up over an unspecified number of years, but probably until treatment becomes available in that jurisdiction) and new data collected from patients who received treatment after rhLAMAN-04[14] and -05[10] on a compassionate use programme (see **Error! Reference source not found.** for details of the comprehensive evaluation visit (CEV)).

Absolute and relative change from baseline to each time point were estimated and analysed using paired t-tests, but no sample size calculation was conducted and no data were imputed. Missing values were included in the denominator count when calculating percentages, but only non-missing values were included in analyses of continuous data.

The co-primary outcomes were serum oligosaccharides and the 3-MSCT. The secondary outcomes were: 6-MWT; PFTs; BOT-2; Leiter-R; CSF OGS; CSF neurodegeneration markers; PTA; CHAQ; and EQ-5D. Primary outcomes were assessed as the relative change from baseline. The date of the first dose and the date of the assessment were used to calculate how many days of treatment had elapsed, with the assessment assigned to the nearest designated time point, e.g. 6 months is 183 days, thus any assessment between 1-274 days were assigned to the 6-month time point.

The company provided a table outlining how many patients were available for assessment at each time point. The ERG were not sure if this was the same as the number of patients eligible for assessment at each time point (e.g. did some patients miss assessments), and were further unclear why there were 3 patients at 36 months from the Phase I/II trials and 9 at 48 months; this might be because some patients having been on treatment without assessment (in the compassionate use programme) for 48 months, meaning there was no 36-month data for these patients. The table is reproduced here as Table 4.

Table 4: Number of patients with available data per time point – overall, Phase I/II and rhLAMAN-05[10] (reproduction of Table 14 from the CS)

Study contribution, n (% of total rhLAMAN-10[1])	**Total N=33**						
	Baseline	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 36**	**Month 48**
rhLAMAN-10[1]	33 (100.0)	24 (72.7)	31 (93.9)	11 (33.3)	10 (30.3)	7 (21.2)	9 (27.3)
Parental study contribution, n (% of total rhLAMAN-10[1])							
Phase I/II‡	9 (27.3)	9 (27.3)	9 (27.3)	9 (27.3)	0	3 (9.1)	9 (27.3)
rhLAMAN-05[10]							
Active	15 (45.5)	15 (45.5)	15 (45.5)	0	10 (30.3)	4 (12.1)	N/A
Placebo→Active	9 (27.3)†	0	7 (21.2)	2 (6.0)	N/A	N/A	N/A

Key: blue cells indicate data derived from rhLAMAN-07 and 09 (baseline to CEV), or rhLAMAN-10[1] data collection.
Abbreviations: N/A, time point not available; VA, velmanase alfa.
†Although 10 patients were included in the rhLAMAN-05[10] placebo group, patient 502 discontinued VA treatment shortly after starting the compassionate use programme. As this patient had no data collected during the active treatment, the patient was excluded from all analyses.
‡Phase I/II trial comprised rhLAMAN-02[13]/03[13]/04.[14]

Pre-planned subgroup analyses included:

- Age group (<18 years vs ≥18 years); this classification is the age of patients at the time of starting treatment
- Parental study (Phase I/II vs rhLAMAN-05[10])
- Anti-drug antibody (ADA) status (positive or negative) for the following outcomes: CSF oligosaccharides, 6-MWT, 3-MSCT and serum IgG

Adjusted mean difference in absolute change (95%CI)			1.97 (-2.64, 6.59), p=0.384		2.62 (95% CI: -3.81, 9.05), p=0.406	
6-MWT (meters unless stated otherwise)						
Actual value (SD)	459.6 (72.26)	465.7 (140.5)	464.3 (82.68)	466.4 (126.2)	464.0 (82.51)	461.1 (138.7)
Absolute change from baseline (SD)			4.67 (42.80)	0.70 (37.56)	4.40 (46.12)	-4.60 (40.79)
Relative (%) change from baseline (SD)			1.08 (9.65)	1.65 (9.16)	1.17 (9.78)	-0.82 (10.80)
Adjusted mean relative change (95% CI)			0.62 (-4.15, 5.63)	1.29 (-4.56, 7.50)	0.64 (−4.74, 6.32)	−1.20 (−7.63, 5.68)
Adjusted mean difference in relative change (95% CI)			-0.66 (-8.01, 7.28), p=0.860		1.86 (−6.63, 11.12), p=0.664	
Adjusted mean absolute change (95%CI)			3.79 (-17.52, 25.09)	2.02 (-24.09, 28.13)	3.74 (-20.32, 27.80)	-3.61 (-33.10, 25.87)
Adjusted mean difference in absolute change (95%CI)			1.77 (-31.98, 35.52), p=0.914		7.35 (95% CI: -30.76; 45.46), p=0.692	
FVC% predicted normal value						
Actual value (SD)	81.67 (20.66, n=12)	90.44 (10.39, n=9)	90.38 (18.43, n=13)	91.00 (14.12, n=8)	91.36 (21.80, n=14)	92.44 (18.15, n=9)
Absolute change from baseline (SD)			5.82 (9.56, n=11)	-0.63 (5.50, n=8)	8.17 (9.85, n=12)	2.00 (12.61, n=9)
Relative (%) change from baseline (SD)			9.15 (13.93, n=11)	-1.04 (6.41, n=8)	11.37 (13.13, n=12)	1.92 (15.40, n=9)
Adjusted mean relative change (95% CI)			8.05 (0.3, 16.38)	-2.93 (-14.42, 10.12)	10.11 (1.31, 19.67)	1.58 (−9.48, 13.99)
Adjusted mean difference in relative change (95% CI)			11.30 (-4.10, 29.19), p=0.159		8.40 (−6.06, 25.08), p=0.269	
Adjusted mean absolute change (95%CI)			5.97 (0.11, 11.84)	-2.73 (-11.94, 6.49)	8.20 (1.79, 14.63)	2.30 (-6.19, 10.79)
Adjusted mean difference in absolute change (95%CI)			8.70 (-2.39, 19.78), p=0.124		5.91 (95% CI: -4.78; 16.60),p=0.278	
CHAQ disability						
Actual value (SD)	1.37 (0.82)	1.59 (0.64)	1.31 (0.72)	1.75 (0.53)	1.36 (0.76)	1.76 (0.50)
Absolute change from baseline (SD)			-0.06 (0.38)	0.16 (0.41)	-0.01 (0.32)	0.18 (0.36)
CHAQ pain (VAS)						

Actual value (SD)	0.84 (0.86, n=14)	0.40 (0.56, n=9)	1.00 (0.91)	0.63 (0.76)	0.97 (1.02)	0.50 (0.62)
Absolute change from baseline (SD)			0.20 (0.79, n=14)	0.30 (0.80, n=9)	0.19 (0.69, n=14)	0.15 (0.71, n=9)
EQ-5D-5L index score						
Actual value (SD)	0.61 (0.19)	0.61 (0.18, n=8)	0.66 (0.15, n=14)	0.64 (0.16)	0.64 (0.18, n=14)	0.62 (0.15)
Absolute change from baseline (SD)			0.06 (0.12, n=14)	0.04 (0.09, n=8)	0.04 (0.09, n=14)	0.03 (0.16, n=8)
EQ-5D-5L VAS						
Actual value (SD)	66.07 (20.68, n=14)	64.00 (12.87)	71.67 (16.30)	67.00 (13.98)	68.20 (17.34)	67.70 (16.62)
Absolute change from baseline (SD)			5.71 (16.94, n=14)	3.00 (15.85)	2.00 (17.95, n=14)	3.70 (15.71)
BOT2 – motor function						
Actual value (SD)	94.93 (41.68)	109.2 (51.84)	95.13 (38.02)	108.7 (50.02)	101.3 (38.56)	113.4 (50.75, n=9)
Absolute change from baseline (SD)			0.20 (12.80)	-0.50 (12.26)	6.40 (13.38)	-0.33 (9.59, n=9) (as reported)
Relative (%) change from baseline (SD)			2.30 (20.27)	7.98 (33.52)	12.30 (20.55)	3.53 (14.23, n=9)
Adjusted mean relative change (95% CI)					9.99 (3.89, 16.45)	3.73 (–3.39, 11.37)
Adjusted mean difference in relative change (95% CI)					6.04 (–3.21, 16.17), p=0.208	
Leiter R- cognition TEA-VR (years)						
Actual value (SD)	5.73 (1.74)	6.06 (1.61)	5.72 (1.45)	6.16 (1.49)	5.91 (1.45)	6.22 (1.53)
Absolute change from baseline (SD)			-0.01 (0.67)	0.10 (0.52)	0.17 (0.71)	0.16 (0.65)
Relative (%) change from baseline (SD)			1.73 (12.24) [Text Deleted]	2.10 (8.54)	5.59 (13.66)	3.32 (8.22)
Adjusted mean relative change (95% CI)					4.18 (–0.93, 9.56)	3.89 (–2.33, 10.51)
Adjusted mean difference in relative change (95% CI)					0.28 (–7.43, 8.62), p=0.943	
Leiter R- cognition TEA-AME (years)						
Actual value (SD)	6.30 (2.56)	6.63 (1.80)	6.40 (2.42)	6.91 (2.28)	6.32 (2.12)	6.74 (1.38)
Absolute change from baseline (SD)			0.10 (1.33)	0.27 (0.62)	0.02 (1.41)	0.11 (1.02)

Table 5: Key clinical results from rhLAMAN-10[1]

Analysis	Baseline (n=33)		6 months (n=24)		12 months (n=31)		18 months (n=11)		24 months (n=10)		36 months (n=7)		48 months (n=9)		Last observation (n=33)	
		n		n		n		n		n		n		n		n
Serum Oligosaccharides (µmol/L)																
Actual value (SD)	6.90 (2.30)	33	2.60 (0.97)	24	1.61 (1.12)	31	1.59 (1.56)	11	1.45 (0.57)	10	6.20 (5.46)	3	1.57 (0.90)	9	2.31 (2.19)	33
Absolute change from baseline (SD)			-5.01 (2.33) p<0.001		-5.41 (2.87) **p<0.001**		-6.67 (3.83) **p<0.001**		-5.12 (1.12) **p<0.001**		-0.40 (4.19) p=0.884		-7.43 (2.81), **p<0.001**		-4.59 (3.23) , **p<0.001**	
Relative (%) change from baseline (SD)			-64.1 (14.86) **p<0.001**		-72.7 (23.53) **p<0.001**		-76.0 (31.21) **p<0.001**		-77.7 (9.29) **p<0.001**		-13.6 (59.19) p=0.729		-81.8 (11.65), **p<0.001**		-62.8 (33.61) **, p<0.001**	
3-MSCT																
Actual value (SD)	53.60 (12.53)	33	56.56 (14.48)	24	58.48 (14.85)	31	62.58 (17.03)	11	57.33 (18.22)	10	60.67 (18.95)	6	69.70 (15.14)	9	59.98 (16.29)	33
Absolute change from baseline (SD)			3.736 (7.887), **p=0.030**		4.247 (8.573), p=0.10		11.58 (9.471), **p=0.002**		1.900 (9.300), p=0.534		11.61 (9.296), **p=0.028**		17.07 (9.929), **p<0.001**		6.384 (10.54), **p=0.001**	
Relative (%) change from baseline (SD)			8.315 (18.32), **p=0.036**		9.317 (19.57), **p=0.013**		24.48 (18.76), **p=0.001**		2.487 (16.84), p=0.651		30.88 (32.72), p=0.069		39.11 (31.31), **p=0.006**		13.77 (25.83), **p=0.004**	
6-MWT																
Actual value (SD)	466.6 (90.1)	33	474.6 (84.1)	24	492.4 (83.7)	31	499.9 (95.6)	11	486.6 (90.7)	10	471.2 (83.5)	6	522.6 (77.1)	9	489.0 (85.7)	33
Absolute change			17.6 (62.7), p=0.183		21.9 (65.2), p=0.071		55.5 (66.3), p=0.020		5.0 (58.5), p=0.793		59.3 (85.9), p0.151		69.7 (81.1), **p=0.033**		22.4 (63.2), **p=0.050**	

from baseline (SD)																
Relative (%) change from baseline (SD)			6.1 (21.1), p=0.169		7.3 (23.3), p=0.090		16.4 (25.7), p=0.061		1.2 (12.3), p=0.766		24.4 (46.1), p=0.252		22.5 (35.8), p=0.096		7.1 (22.0), p=0.071	
6-MWT (% predicted for age, height and gender)																
Actual value (SD)	69.04 (11.65)	33	NR		71.8 (10.26)	31	NR		NR		NR		NR		70.20	33
Absolute change from baseline (SD)			NR		2.37 (9.98), p=0.196		NR		NR		NR		NR		1.16 (9.29), p=0.478	
Relative (%) change from baseline (SD)			NR		5.87 (22.14), p=0.150		NR		NR		NR		NR		3.55 (18.30), p=0.273	
FVC % predicted																
Actual value (SD)	84.9(18.6)	29	87.1(18.6)	22	93.2(20.8)	30	84.8(23.6)	8	106.1(18.0)	8	78.8(22.0)	6	98.3(12.4)	7	93.1 (21.7)	31
Absolute change from baseline (SD)			3.5(14.7), p=0.304	20	6.6(12.8, **p=0.011**	28	4.4(13.9), p=0.403		16.1(14.8), **p=0.028**	7	5.6(10.3), p=0.243		13.7(19.6), p=0.114		8.1(14.8), **p=0.007**	29
Relative (%) change from baseline (SD)			6.1(20.3), p=0.194	20	8.5(16.5), **p=0.011**	28	5.0(20.9), p=0.520		20.7(18.5), **p=0.025**	7	7.6(15.2), p=0.277		19.8(28.4), p=0.116		10.5(20.9), p=0.011	29
CHAQ disability index*																
Actual value (SD)	1.36 (0.77)	33	1.12 (0.71)	24	1.20 (0.70)	31	1.07 (0.75)	11	1.44 (0.79)	10	1.16 (0.60)	7	0.88 (0.64)	9	1.23 (0.66)	33
Absolute change			-0.11 (0.37)	24	-0.10 (0.36)	31	-0.14 (0.41)		0.16 (0.35)	10	-0.32 (0.62)		-0.10 (0.42)		-0.13 (0.44)	

from baseline (SD)																
Relative (%) change from baseline (SD)			-11.2 (44.08)	22	-7.76 (50.68)	29	-7.00 (68.73)		11.83 (23.88)	8	2.28 (76.66)		13.13 (72.27)		-2.41 (45.03)	
CHAQ – pain VAS (0-3 scale)*																
Actual value (SD)	0.618(0.731)	32	0.895(0.911)	24	0.761(0.931)	31	0.407(0.409)	9	0.339(0.458)	10	0.390(0.326)	7	0.443(0.644)	9	0.431(0.616)	33
Absolute change from baseline (SD)			0.257(0.776)	23	0.148(0.723)	30	0.060(0.487)	9	-0.393(0.697)	9	-0.249(0.476)		0.063(0.771)	9	-0.173(0.647)	32
Relative (%) change from baseline (SD)			45.77(138.8)	16	3.697(107.3)	20	122.3(380.0)	5	-46.0(60.21)	6	32.61(198.2)		51.69(202.7)	5	-17.0(109.8)	21
EQ-5D-5L Index*																
Actual value (SD)	0.6217(0.1698)	24	0.6596(0.1492)	14	0.6678(0.1785)	21	0.6385(0.1181)	2	0.6437(0.2057)	10	0.7158(0.0743)	4	NR		0.6722(0.1674)	24
Absolute change from baseline (SD)			0.0647(0.1199)		0.0346(0.1044)		0.1950(0.1245)		0.0262(0.1303)		0.0993(0.1422)		NR		0.0505(0.1351)	
Relative (%) change from baseline (SD)			17.2811(32.8088)		6.9320(19.0980)		44.1743(28.6949)		7.2199(21.9332)		21.1495(32.1006)		NR		11.2291(24.7218), p=0.036	
EQ-5D-5L VAS*																
Actual value (SD)	67.9(18.2)	23	71.7(16.3)	15	69.0(16.6)	22	80.0(21.2)	2	70.8(14.3)	10	73.8(18.9)	4	NR		71.6(15.0)	24
Absolute change			5.7(16.9)	14	1.6(17.2)	21	6.5(4.9)		9.8(22.7)	9	-2.5(8.7)		NR		3.3(18.1)	

from baseline (SD)															
Relative (%) change from baseline (SD)			15.5(30.9)	14	7.7(32.2)	21	8.3(4.9)		26.6(43.3)	9	0.4(16.7)		NR		11.5(33.8)	
BOT-2 total*																
Actual value (SD)	107.0 (47.6)	33	108.5 (47.7)	24	119.1 (44.9)	31	117.3 (66.0)	11	114.3 (33.5)	10	71.8 (27.9)	4	128.3 (59.4)	9	112.1 (46.0)	33
Absolute change from baseline (SD)			3.9 (12.4)		7.5 (16.5), **p=0.017**		12.2 (21.8)		7.3 (24.9)		16.3 (10.4)		7.7 (35.5)		5.1 (23.9)	
Relative (%) change from baseline (SD)			3.8 (17.8)		10.6 (19.3), **p=0.005**		17.9 (32.3)		16.2 (39.8)		31.5 (16.2), **p=0.03**		13.0 (38.3)		13.0 (33.9), **p=0.035**	
Leiter TEA VR*																
Actual value (SD)	5.879(1.565)	33	5.840(1.380)	24	6.296(1.541)	31	5.788(1.574)	11	6.292(1.317)	10	5.131(1.584)	7	5.898(1.437)	9	6.144(1.612)	33
Absolute change from baseline (SD)			0.122(0.577)		0.320(0.717), **p=0.019**		0.333(0.587)		0.308(0.436)		0.333(0.344), **p=0.043**		0.204(0.632)		0.265(0.637), **p=0.023**	
Relative (%) change from baseline (SD)			3.447(10.28)		6.695(12.17), **p=0.005**		6.251(10.75)		6.724(8.951), **p=0.042**		9.037(10.77)		4.140(11.24)		5.338(10.45), **p=0.006**	
Leiter TEA AME*																
Actual value (SD)	6.514(2.176)	24	6.400(2.424)	15	6.860(1.992)	22	3.792(2.180)	2	6.817(1.529)	10	5.250(0.561)	4	NR		6.670(1.757)	24
Absolute change			0.100(1.331)		0.167(1.254)		-0.750(1.414)		0.108(1.665)		0.833(1.855)		NR		0.156(1.519)	

from baseline (SD)																
Relative (%) change from baseline (SD)			5.219(22.135)		5.849(19.657)		-19.42(34.413)		11.244(33.786)		33.225(47.595)		NR		9.345(32.485)	
Pure tone best ear*																
Actual value (SD)	52.57(12.36)	32	55.44(10.65)	22	53.35(11.41)	31	48.35(16.80)	11	54.76(8.72)	9	56.16(12.86)	7	47.62(13.76)	9	52.16(13.13)	33
Absolute change from baseline (SD)			2.05(4.72)		1.47(6.00)	30	-4.81(9.74)		2.05(6.55)	8	-0.76(8.78)		-3.73(6.21)		-0.49(6.58)	32
Relative (%) change from baseline (SD)			5.76(13.90)		4.26(14.97)	30	-8.89(20.44)		6.85(16.25)	8	-1.71(16.90)		-8.08(12.81)		-0.72(14.54)	32
Serum IgG*																
Actual value (SD)	8.37 (4.20)	24	11.37(4.99)	15	11.76(4.99)	22	10.35(2.47)	2	12.21(6.23)	10	11.75(3.37)	4	NR	NR	11.42(4.52)	24
Absolute change from baseline (SD)			2.37(1.28), **p<0.001**		3.38(1.65), **p<0.001**		2.10(1.13)		3.33(1.47), **p<0.001**		2.95(2.06)		NR		3.05 (2.39, 3.71), **p=<0.001**	
Relative (%) change from baseline (SD)			34.03(23.26) **p<0.001**		47.03(27.26), **p<0.001**		31.46(27.46)		47.07(29.87), **p<0.001**		47.62(33.29)		NR		44.07 (32.58, 55.57), **p=<0.001**	

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

* only statistically significant p values reported.

(p=0.036) for EQ-5D-5L index, though this analysis only included 24/33 patients with the reason for this unclear. **Error! Reference source not found.** provides further detail. The change in CHAQ disability *achieved the MCID of ≥0.13 at -0.13 (SD 0.44)*). No MCID was reported for EQ-5D-5L index.

The CS[2] also highlights data relating to changes to numbers of patients requiring ambulatory assistance taken from the CHAQ. At baseline, ten patients required help, whereas at last observation, 70% of these patients required less help. Conversely, of the 23 who did not require help, 3 (13%) became dependent on some help by the last observation.

In their clarification response A44,[11] the company provided a further analysis where a "walking with assistance" category was created, to more closely mimic the category defined in the model, by combining CHAQ-defined wheelchair users and those requiring walking aids/assistance. The results of this analysis are presented in **Error! Reference source not found.**. The company state "*It is only in the velmanase alfa arm that a net effect (20%) was observed for an improvement in walking ability after 12 months of treatment, i.e. a higher proportion of patients treated with velmanase alfa transitioned to an improved walking ability state (40%) compared to the proportion of patients treated with velmanase alfa that transitioned to a worse walking ability state (20%).*" (clarification response to question A44).[11]

The company also provided the following statement about rhLAMAN-10[1]:
"*It should be noted that longer-term data (up to 48 months of treatment) are available from the rhLAMAN-10[1] trial. Overall, ten patients required help from a person, walking aids (cane, walker, crutches), or a wheelchair at baseline according to the CHAQ 'Helps and Aids' responses. Of the ten patients, seven (70%) became device- or third party-independent at last observation: 4/5 (80%) paediatric patients and 3/5 (60%) adults. In particular, two paediatric patients and one adult forced to adopt the wheelchair for long distance mobility/functional capacity at baseline discontinued use at last observation. Overall, three patients out of the 23 (13%) who did not require help from a person, walking aids, or a wheelchair at baseline, did so at last observation (one adult and two paediatric patients).*"
(A44 clarification response).[11]

Definition of efficacy not met in rhLAMAN-05[10]

The definition of efficacy in rhLAMAN-05[10] was:

- a statistically significant improvement in the two primary endpoints (at significance levels of 0.025 [serum oligosaccharides] and 0.05 [3-MSCT]) at the interim analysis (Month 6)).

Or

- a statistically significant reduction in serum oligosaccharides (at a significance level of 0.025) and a trend for improvement in the 3-MSCT and one of the prioritised secondary endpoints at the 12-month analysis

Whilst a statistically significant improvement in serum oligosaccharides was observed, there is a lack of clarity in the statistical plan as to what should constitute a trend, and consequently it is unclear whether a 2.62 step/minute mean difference in absolute change from baseline (baseline mean: 54 metres) in 3-MSCT and a 7.35 metre mean difference in absolute change from baseline (baseline: 460 metres) in 6-MWT should be considered a trend for improvement. The ERG note that neither outcome met the MCID which was ≥7 steps for 3-MSCT, and ≥30 meters for 6-MWT (see **Error! Reference source not found.**).

Muti-domain responder analysis and minimal clinically important differences

The ERG and the clinical advisors to the ERG believe the multi-domain responder analysis to be problematic for a number of reasons:

- Dichotomising patients according to arbitrary cut-offs results in a loss of power relative to the original continuous data
- Dichotomising patients according to multiple domains assumes that the domains are equally important
- Serum oligosaccharides may not be clinically important
- Setting aside the fundamental problems with dichotomising continuous outcomes, clinical advisors to the ERG were of the opinion that infection rates and central nervous system effects should have been included in the responder analysis. The ERG note that velmanase alfa does not cross the blood-brain barrier and cannot be expected to impact on CNS outcomes for patients, even though they are an important symptom of the disease.
- If serum oligosaccharides are excluded from the analysis, and only two domains are left [redacted], patients could potentially be considered a responder solely on the basis of improvements in any one of the tests included in the domains.

- Some of the MCIDs were defined after the trials results were un-blinded, and there is the potential for bias in their definition. This was, however, conducted in response to a request from the EMA, quoted in the clarification response to question A19[11] as:

""*The clinical relevance of the various changes compared to baseline or compared to placebo cannot be assessed for all endpoints due to the lack of predefined clinically important changes. Clinically relevant changes based on experience with comparable conditions for the various endpoints should be identified based on relevant literature. For example, 3MSCT and 6MWT might be related to the experience in patients with JIA. Responder analyses based on these clinically relevant differences should be submitted. Also the 3MSTC and 6MWT results should be presented as scatter plots of change (style shown in fig 11-6 in study report rhLAMAN-05[10]) in order to further appreciate the individual responses."*

- The ERG notes that, based on this quote, the EMA did not request a multi-domain responder analysis, only a responder analysis. In addition, the specifics of how the analysis was conducted were specified post-hoc and were not defined by the EMA. There is therefore a high risk of bias in these analyses in addition to concerns regarding the appropriateness of responder analyses.
- The methods used to define MCIDs comprised a literature review of values in conditions with similar clinical characteristics to AM. It appears only one clinical expert was asked to verify the domains selected: "*An expert was consulted and they concurred with the heterogeneity of AM and relevance of the domain response approach given the heterogeneity of disease manifestation and severity, and small patient numbers*." (CS Appendix 2, section 17.7.3.1.)[2]

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

There are no MCIDs reported for motor function (BOT-2); hearing; Leiter-R; rates of infections; or EQ-5D.

Attrition in the trials

There is a lack of clarity around attrition in the later months of rhLAMAN-10.[1] Whilst some of this attrition could be down to length of time enrolled, there are some clear examples of missing data in the secondary outcomes (see **Error! Reference source not found.**). It is unclear what impact this may have, given no imputation was performed in rhLAMAN-10.[1]

Lack of adjustment for age and height

The ERG is satisfied that a lack of reference values for the 3-MSCT and assertion that it is not affected by age mean that the values can be interpreted as they stand. However, the change in rhLAMAN-05[10] was quite small (an absolute difference in change from baseline at 12 months of around 3 steps from a baseline of 53-56 steps), and the changes from baseline observed in rhLAMAN-10[1] were highly variable, possibly due to missing values and patients who had not been on treatment.

experienced 11 events categorised as Infusion Related Reactions (IRRs) (chills, nausea, hyperhidrosis and vomiting),[2] but these were all considered to be mild or moderate in intensity (CS, page 155[2] and CSR[10], p121). As a result of five of these events, the drug was interrupted (n=4) or the infusion rate was reduced (n=1) (CSR[10], p121).

According to the CSR[10] (pages 58-59)[11] a Serious Adverse Event (SAE) was defined as any AE that resulted in one of the following outcomes: death; life-threatening experience; required or prolonged in-patient hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect; or any important medical events that jeopardised the patient or subject and might require medical or surgical intervention to prevent one of the outcomes listed above. Five patients (33.3%) reported experiencing a treatment-emergent SAE: knee deformity (genua valga both sites), joint swelling (swollen ankle), Sjogren's syndrome, sepsis and acute renal failure. Only one patient was considered to have a treatment-related SAE (acute renal failure, CS, p155[2]), although there was no reported SAE in the placebo arm. According to the CS[2] and CSR[10], no patients discontinued treatment due to any AE during the rhLAMAN-05[10] trial, and there was also no death in any arm during the trial. These data were confirmed by the company following a clarification request (clarification response to question A35).[11]

Table 6: Numbers of overall adverse events, severe and treatment-related adverse events, and events leading to treatment discontinuation (rhLAMAN-05[10]) (reproduced from CS, Table 32)

AE	VA (n=15)		Placebo (n=10)	
	n (%)	Events	n (%)	Events
Summary of AEs				
Any AE	15 (100.0)	157	9 (90.0)	113
Treatment-related AE	7 (46.7)	30	5 (50.0)	9
SAE	5 (33.3)	5	0	0
Treatment-related SAE	1 (6.7)	1	0	0
Severe AE*	1 (6.7)	1	0	0
Discontinuations due to AE	0	0	0	0

Abbreviations: AE, adverse event; VA, velmanase alfa. *No definition provided in CS or CSR.

The most frequent AEs experienced by two or more patients receiving velmanase alfa in the 12-month rhLAMAN-05[10] trial were: infections (86.7%), principally nasopharyngitis (66.7%); gastrointestinal disorders (60%), especially vomiting (20.0%); pyrexia (40.0%); headache (33.3%) and arthralgia (20.0%) (Table 7). The reported rates of many adverse events were similar between study arms, but some adverse events were reported more frequently in the velmanase alfa arm than the placebo arm: toothache, syncope, hypersensitivity and the infections of acute tonsillitis, influenza and gastroenteritis were reported in two patients (13.3%) in the velmanase alfa group compared with no patients (0%) in the placebo group. A number of AEs were also reported more frequently in the placebo arm than the velmanase alfa arm: vomiting (40.0% in the placebo group vs

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

Table 7: Numbers of patients experiencing adverse events, >2 patients in any arm (rhLAMAN-05[10]) (reproduced in part from CS, Table 32 and CSR Table 12-2)

AE	VA (n=15)		Placebo (n=10)	
	n (%)	Events	n (%)	Events
Infections and infestations	13 (86.7)	48	7 (70.0)	23
Nasopharyngitis	10 (66.7)	30	7 (70.0)	16
Ear infection	2 (13.3)	2	1 (10.0)	1
Acute tonsillitis	2 (13.3)	2	0	0
Influenza	2 (13.3)	2	0	0
Gastroenteritis	2 (13.3)	2	0	0
Gastrointestinal disorders	9 (60.0)	18	8 (80.0)	24
Vomiting	3 (20.0)	5	4 (40.0)	6
Diarrhoea	2 (13.3)	2	3 (30.0)	3
Toothache	2 (13.3)	3	0	0
General disorders and administration site conditions	6 (40.0)	20	7 (70.0)	18
Pyrexia	6 (40.0)	11	5 (50.0)	11
Musculoskeletal and connective tissue disorders	7 (46.7)	11	5 (50.0)	16
Arthralgia	3 (20.0)	4	1 (10.0)	6
Back pain	2 (13.3)	2	1 (10.0)	1
Nervous system disorders	6 (40.0)	11	5 (50.0)	12
Headache	5 (33.3)	7	3 (30.0)	9
Dizziness	1 (6.7)	1	2 (20.0)	2
Syncope	2 (13.3)	2	0	0
Respiratory, thoracic and mediastinal disorders	4 (26.7)	7	2 (20.0)	4
Immune system disorders	2 (13.3)	5	2 (20.0)	2
Hypersensitivity	2 (13.3)	5	0	0
Ear and labyrinth disorders	0	0	3 (30.0)	3
Ear discomfort	0	0	2 (20.0)	2

Abbreviations: AE, adverse event; VA, velmanase alfa.

rhLAMAN-10[1]

The mean (SD) number of infusions reported in the CSR[1], p.150, for the rhLAMAN-10[1] study was 84.8 (63.1) overall (compared with 62.8 in the rhLAMAN-05 trial[10]), with a higher number reported in patients who participated in the rhLAMAN-02[13] study, and therefore in patients aged <18 years. In this study, the actual exposure of patients to velmanase alfa ranged from 357 to 1625 days, with greater exposure in patients who participated in the earliest phase I/II study, rhLAMAN-02[13] (mean exposure 1585.2 days), than in the more recent rhLAMAN-05[10] phase III study (mean exposure 630.0 days).

Almost all patients in the treatment-arm of the rhLAMAN-10[1] study reported at least one AE (**Error! Reference source not found.**). The proportions of patients in rhLAMAN-10[1] (n=33) being treated with velmanase alfa and experiencing AEs were similar to the proportions in the treatment arm of the rhLAMAN-05[10] trial (n=15): 17 patients (51.5%) reported 'treatment-related AEs'(weight increase,

pyrexia and diarrhoea all affected three or more patients: CSR[1], page 156); 12 patients (36.4%) experienced a SAE; two

4.3 Conclusions of the clinical effectiveness section

The ERG believes the CS[2] is complete with respect to evidence relating to velmanase alfa. The evidence base comprised one double-blind, placebo controlled RCT (rhLAMAN-05,[10] n=25) and one long-term, single arm, open label study (rhLAMAN-10,[1] n=33).

The patient spectrum of the evidence base is likely to be younger than the population in England due to the inclusion criteria (5 to 35 years old), and it may be easier to detect an effect in younger patients if disease progression is more rapid. It is unclear whether some of the patients included in the studies may have been eligible for HSCT in some clinical practices in England. The company provided draft start/stop criteria which, if applied in clinical practice, would be likely to exclude some patients who continued treatment in the trials. In clinical practice, therefore, fewer patients may be eligible for long term treatment, but for those who are, the studies are likely to have underestimated population-level efficacy.

The ERG were concerned about serum oligosaccharides being the co-primary outcome as this is a surrogate biomarker with pharmacokinetic relevance, but low clinical relevance and which has not been assessed as a surrogate using standard criteria. 3-MSCT, 6-MWT and FVC were the co-primary and prioritised (rhLAMAN-05)[10] secondary outcomes. Quality of life was measured using CHAQ and EQ-5D-5L. These are other secondary outcomes appeared relevant, but infections, which have a big impact on patients and which were listed in the NICE scope, were not measured.

rhLAMAN-05[10] appears to be at generally low risk of bias. The small numbers (n=25) are to be expected given the rarity of the condition. There was a statistically significant decrease in serum oligosaccharides, but no statistically significant decreases in the clinical co-primary and prioritised secondary outcomes or on the other secondary outcomes of motor function, cognition and hearing. It is unclear if the study met its definition for demonstrating efficacy. No comparative analyses of quality of life outcomes were provided. The observed differences for most outcomes did not meet MCIDs where these were provided. The lack of statistically significant results for the clinical outcomes means it is unclear whether the effect of velmanase alfa on the biomarker translates to an impact on clinical outcomes.

rhLAMAN-10[1] is a non-controlled, experimental study akin to a cohort study. The design has some risk of bias and due to the lack of a control arm the results are difficult to interpret. The length of follow-up varied a great deal for patients (12 months to 48 months), with variable and smaller numbers, sometimes comprising different patients altogether, at the time points beyond 12 months. The last observation analysis generally included all patients and for the four main outcomes (serum oligosaccharides, 3-MSCT, 6-MWT, FVC % predicted) there was very little difference between the

5.2.3.1 Details of the elicitation exercise.

The company described the elicitation process in Section 12.2.5 of the CS.[2] Additionally the company provided a 174-page document extensively detailing the elicitation process. In brief, five clinical experts (out of ten contacted) participated, representing four LSD centres in the UK. The Sheffield Elicitation Framework (SHELF) methodology was followed which is appropriate. All experts received honoraria (funded by Chiesi) to cover the time required to prepare for the elicitation exercise (pre-reading of the evidence dossier) and attendance at a one-day elicitation panel.

5.2.3.2 Details of the interviews with KOLs.

The company described the KOL interview process in Section 12.2.5 of the CS.[2] In brief, the interview process had three stages. The company stated that the first (18 questions) supported the early scoping / design stages of developing the model, the second (29 questions) generated and validated key assumptions in the model, and the third (36 questions) generated and validated key model parameters for which published data in AM patients did not exist. Ten KOLs were contacted of which five participated in at least one stage of the interview process. All five KOLS had experience of treating AM with BSC, although only one had experience of treating AM with an ERT. However, all five had experience of using an ERT in LSD. Pre-reading was supplied to KOLs before each interview. In each interview, questions and data were displayed to KOLs via teleconference and a WebEX link. Each KOL had to confirm in writing that the minutes and summary were an accurate reflection of the discussions and their responses provided during the interview.

Each KOL received honoraria (funded by Chiesi) to cover the time required to prepare for the interviews (pre-reading of the interview brief and questions) and time to attend at each interview.

5.2.3.3 The population being modelled

The company designated three cohorts: (i) a paediatric cohort; (ii) an adolescent cohort and (iii) an adult cohort.

The starting age of patients within each cohort and the assumed distribution between primary health states assumed by the company are reproduced in **Error! Reference source not found.**. The company assumed that all patients were at the lowest age within each age band, and the distribution of patients' functional status across primary health states was taken from rhLAMAN-10.[1]

patient was receiving BSC. It should be noted that the values reported in the CS do not match those used in the model although the numbers were similar[2]

Table 8 reports the values used in the model.

Table 8: Assumed annual costs by health state

	Year 1		Year 2 and beyond	
Health State	**Paediatric**	**Adult**	**Paediatric**	**Adult**
WU	£4395	£4361	£4108	£4042
WWA	£4089	£4069	£3802	£3750
WC	£3739	£3720	£3453	£3400
SI	£2156	£2145	£1888	£1875
WU + S Inf	£13,040	£16,038	£12,753	£15,718
WWA + S Inf	£12,957	£15,968	£12,670	£15,649
WC + S Inf	£13,029	£16,040	£12,742	£15,721
SI + S Inf	£13,244	£16,264	£12,977	£15,994
SES*	£46.782	£36.603	£46.782	£36.603

SI – Severe Immobility; S Inf – Severe Infection; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance

* four weeks' cost only.

5.2.3.9 The additional costs associated with velmanase alfa treatment

The largest cost component of velmanase alfa treatment is that associated with purchasing the intervention, which has a list price of £886.61 (excluding VAT) per 10mg vial. The company have applied for a PAS, [redacted], which will take the form of a simple discount on the price per vial resulting in a cost of [redacted] (excluding VAT) per 10mg vial. Dosing is weight-based with one vial required for patients weighing up to 10kg, two vials required for patients weighing between 10kg and 20kg and so on. For information, this would result in patients weighing between 60 and 70kg having an annual drug acquisition cost of [redacted] (excluding VAT).

The company assumed that the drug would be initiated in a LSD centre for the first three infusions, before the patient moves on to having an infusion in the home setting (98%) or at a local hospital (2%). These proportions were stated by the company to '*capture the minority of patients that may revert to hospital briefly for the management of Infusion-Related Reactions (IRRs), before returning to homecare once the IRRs are resolved.*' Costs associated with infusions at either an LSD centre or a local hospital were assumed to be £213 based on the Outpatient procedure tariff for vascular access except for renal replacement therapy without complication and comorbidity based on NHS National prices and national tariff 2015-16.[32] Home infusions were assumed to be associated with no additional costs. The number of infusions before leaving the care of the LSD centre, and the proportion of patients receiving home infusions were estimated through interviews with UK KOLs.

The weights for each age group were assumed to be fixed by the company as 'clinical data were not available to derive a population distribution from which to estimate an expected number of vials.' The use of fixed weights is likely to produce inaccurate answers, but it is not clear whether this would favour or disadvantage velmanase alfa.

Table 9: Assumed costs of ventilation by health state for patients on best supportive care

Health State	Overnight ventilation	24-hour care ventilation at home	24-hour care ventilation at institution	Total ventilation cost per year
Annual Cost *	£95,448	£285,176	£358,930	-
WU	0%	0%	0%	£0
WWA	0%	0%	0%	£0
WC	20%	0%	0%	£19,090
SI	50%	25%	25%	£208,751

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
* Taken from Noyes *et al.*[35] and inflated to 2016 prices

5.2.3.14 The requirement for caregiver time and associated costs

The company assumed that data included in Hendriksz et al.[36] relating to the hours of caregiver time required per day in patients with Morquio A syndrome were appropriate for patients with AM. An assumption (without further explanation), was used to estimate the proportion of care delivered by professionals in each primary health state. The estimated carer cost per year was calculated by multiplying the proportion of professional carer time by the anticipated hours of care provided by year. These calculations are reproduced in Table 10.

Table 10: Assumed annual costs of professional care by health state

Health State	Hours of Care required per day (95% Credible Interval) [36]	Proportion of care provided by professionals (95% Credible Interval) †	Cost per Year *
WU	1.3 (0.98 – 1.63)	10% (7.5% - 12.5%)	£1139
WWA	3.9 (2.93 – 4.88)	20% (15% - 25%)	£6833
WC	13.8 (10.35 – 17.25)	50% (37.5%- 62.5%)	£60,444
SI	13.8(10.35 – 17.25)	80% (60% - 100%)	£96,710

SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
† Assumption (no further details provided).
* Assuming a cost per hour of £24.00 for professional care[37]

During the clarification period, the company commissioned a survey that assessed the caregiver requirements for patients with AM.[38] This report was marked as AIC in its entirety. [redacted]

[redacted]

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

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

[redacted]

Base case: Patient utility as reported by the carer (by proxy) regardless of prior treatment

Scenario 1: Comparison of patient utility reported by the carer (by proxy) and by the patient (by self-report). This analysis is only applicable for the three patients with both carer-reported and patient-reported patient utilities.

Scenario 2: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC, i.e. patients who had received stem cell transplant or velmanase alfa were excluded from the pooled analyses. A resulting missing data point for the 'walking with assistance' health state was imputed using the EQ-5D-5L utility for this health state as in the CS[2] by use of KOL input.

Scenario 3: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC. A resulting missing data point for the 'walking with assistance' health state was imputed using the mean of the utility values calculated for the 'walking unassisted' and 'wheelchair dependent' states.

Scenario 4: Patient utility as reported by the carer (by proxy) for patients without any prior treatment other than BSC. A resulting missing data point for the 'walking with assistance' health state was imputed using a ratio of utility for 'walking with assistance' relative to 'walking unassisted' determined through KOL input.[redacted]

[redacted]

[redacted]**Error! Reference source not found.**[redacted]

[redacted] [TEXT DELETED]

Table 11: Utility estimates (standard deviation) by primary health state produced by the company

Health State	n	WU	WWA	WC	SI
Base case	9	0.794 (0.200)	0.758 (N/A)	0.100 (N/A)	-0.011 (0.053)
Scenario 1 – carer-reported	3	0.906 (0.000)	0.758 (N/A)	N/A	N/A
Scenario 1 – patient reported	3	0.918 (0.000)	0.642 (N/A)	N/A	N/A
Scenario 2†	5†	0.906 (0.000)	[redacted])	0.100 (N/A)	-0.011 (0.053)
Scenario 3	5†	0.906 (0.000)	0.503 (N/A)	0.100 (N/A)	-0.011 (0.053)
Scenario 4	5†	0.906 (0.000)	0.345 (N/A)	0.100 (N/A)	-0.011 (0.053)
rhLAMAN-10[1] baseline	24	0.652 (0.149)	0.577 (0.200)	N/A	N/A
rhLAMAN-10[1] Last observation	31	0.702 (0.171)	0.635 (0.085)	N/A	N/A

N/A – Not Available; SES – Short End State; SI – Severe Immobility; WC – Wheelchair Dependent; WU – Walking Unassisted; WWA – Walking With Assistance
† Plus one value in the WWA state estimated from UK KOL estimates
† Used in the model

5.2.3.17 The assumed utility benefit associated with velmanase alfa treatment

Of note, the company has assumed that any patient treated with velmanase alfa would receive a utility gain of 0.1. This value was stated to have been validated with UK KOLs, with the company further stating in the clarification response[11] (question B15) that there were many aspects of AM that were not completely accounted for in the model including: 'reducing rates of minor infections; reducing rates of psychiatric problems with investigators noticing that in '[redacted]'; reduced ventilator dependency; providing intra-ambulatory health state improvements', for example, moving from multiple aids/assistance for walking to only requiring one minimal aid for walking (e.g. footwear for stability); and the provision of a structured homecare visit programme with regular (weekly) nurse visits [redacted]. Four UK KOLs confirmed that '*applying an 'on-treatment utility increment' was appropriate, to account for these additional benefits that treatment with velmanase alfa may incur, which are not formally accounted for in the model by other existing parameters.*' The company report that a value of 0.1 was chosen with reference to the improvements of 0.05 and 0.058 in the Walking Unassisted and Walking With Assistance states that had been seen in the EQ-5D analyses using data from the rhLAMAN-10[1] trial and the possibility that some benefits of velmanase alfa '*will only be apparent after a number of years of treatment*.'

5.2.3.18 The assumed disutility associated with severe infection

The disutility associated with severe infection for patients receiving BSC was assumed to be approximated by that reported for patients with sepsis by Drabinski et al.[43] which was a value of 0.18

for a period of six months. This resulted in an undiscounted quality-adjusted life year (QALY) loss of 0.09 per severe infection. The company assumed that this disutility would be halved for patients

Table 12: The data sources for key parameters within the company model

Parameter	Source for company base case analysis
Age of population	Assumption
Starting health state of population	Taken from data observed in rhLAMAN-10[1]
Time to disease progression when treated with BSC	UK Expert Elicitation Panel
Additional time to disease progression when treated with velmanase alfa	UK Expert Elicitation Panel
Improvement in health state associated with velmanase alfa treatment	Interviews with UK KOLs
Treatment discontinuation due to lack of efficacy	Data from the multi-domain responder analysis conducted in rhLAMAN-05[10]
Treatment discontinuation due to other reasons	Interviews with UK KOLs
Probability of major surgery conditional on health state	UK Expert Elicitation Panel
Probability of mortality and complications associated with major surgery	Interviews with UK KOLs
Reduction in the risks of mortality and complications associated with surgery due to velmanase alfa treatment	Interviews with UK KOLs
Probability of severe infection conditional on health state	UK Expert Elicitation Panel
Probability of mortality associated with severe infection	UK Expert Elicitation Panel
Reduction in the risks of mortality and complications associated with severe infections due to velmanase alfa treatment	Interviews with UK KOLs
Requirement for ventilation conditional on health state	Interviews with UK KOLs
Reduction in the requirement for ventilation due to the use of velmanase alfa	Interviews with UK KOLs
Utility in each health state	Survey conducted by the UK MPS Society.
Utility gain associated with being on velmanase alfa	Assumption
BSC – Best Supportive Care; KOLs – Key Opinion Leaders; MPS - mucopolysaccharidosis	

5.2.4 Model evaluation methods

The CS presents the results of the economic analysis in terms of the incremental cost per QALY gained for velmanase alfa versus BSC.[2] The base case results are presented deterministically using the base case estimate for each parameters. The CS[2] also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSA) and scenario analyses. The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The results of the DSA are presented in tabular form with an additional tornado diagram which is limited to the ten most influential model parameters. The distributions applied in the company's PSA are summarised in Table 63. These values have been provided in the relevant sub-section of Section 5.2.3.

5.2.5 Company's model results

Error! Reference source not found. presents the estimates of cost-effectiveness derived from the company's revised model following the clarification process. Based on the probabilistic versions of the model, in the paediatric cohort velmanase alfa is expected to generate an additional 2.50 QALYs at an additional cost of [redacted] per patient: the ICER is £[redacted] per QALY gained. In the adolescent cohort these values were an additional 2.64 QALYs at an additional cost of [redacted] per patient:

the ICER is £[redacted] five-year period, increasing from £[redacted] million in year 1 to [redacted] million in year 5. The ERG has no reason to believe these values are likely to be significantly inaccurate.

5.3 Critique of the company's model and exploratory and sensitivity analyses undertaken by the ERG

The ERG has endeavoured to produce an ERG base case ICER subject to the constraints of the model submitted by the company, detailed at the end of this section. Within the ERG base case changes are only made to the company's base case where the ERG has a strong preference for a different assumption to the one made by the company. Where the ERG believes that the means of the parameters values are open to debate, but the ERG does not have a preferred value scenario analyses have been undertaken.

The ERG reiterates that many parameters are not populated with observed data but are instead populated by using distributions elicited from experts or estimated from interviews. The values from the interviews and arbitrary distributions used by the company do not benefit from using a formal elicitation process. The ERG is therefore concerned that the parameter estimates may not reflect genuine beliefs which leads to questions regarding the appropriateness of both the company's and the ERG's base case analysis.

Five changes were made to the company's base case ICER:

1) Using the utility values for the Walking Unaided and Walking With Assistance states that were reported at baseline in the rhLAMAN-10[1] study.

   [redacted] patients recruited to rhLAMAN-10[1] provided baseline utility values for the Walking Unaided and the Walking With Assistance health states. This is greater than the number ([redacted]) that responded to the MPS Survey used in the company base case. The baseline value has been chosen rather than the last observation value as [redacted]

2) Using a discount rate value of 3.5% per annum rather than 1.5% per annum

In their clarification response[11] (Question B30) the company stated that '*NICE recommends that a discount rate of 1.5% can be used for costs and QALYs in treatments where patients would otherwise not survive, patients suffer from severely impaired life conditions or when the condition is sustained for over 30 years.*' The ERG notes that in the latest methods guide to

highly specialised technology appraisals[45] it is stated that '*In line with the Guide to the Methods of Technology Appraisal, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered.*' The ERG does not think that velmanase alfa meets these criteria as the intervention does not restore a patient to full or near full health.

3) Using a utility increase associated with velmanase alfa treatment of 0.00 rather than 0.10

The company's rationale for using a utility increase of 0.10 associated with velmanase alfa treatment is reported in Section 5.2.3.15. The ERG comments that the gain shown between the baseline and the last observation n rhLAMAN-10[1] is non-comparative (as no patient received BSC) and that the values could be confounded by different patient numbers, with different disease severities. The ERG comments that utility gains would be double-counted if a patient improved health state as there would be an increase related to the health state and also a utility increase associated with being on velmanase alfa treatment. Further double-counting would exist when patients have been maintained in the same health state rather than progressing due to velmanase alfa treatment. Finally, the ERG believes that the additional years in each state elicited from the clinical experts (**Error! Reference source not found.**) are not sufficiently high to support evidence of clear ongoing utility gain for patients receiving velmanase alfa.

4) Amending an assumption in the model relating to transition probabilities

After the clarification period, the ERG identified an assumption in that patients who had received velmanase alfa treatment but had discontinued and were receiving BSC, did not have the same transition probabilities as those patients who were on BSC. This discrepancy was amended by the ERG setting these probabilities equal to the values for patients in the comparator arm.

5) Amending an assumption in the model relating to costs post discontinuation of velmanase alfa

After the clarification period, the ERG identified an assumption in that patients who had received velmanase alfa treatment but had discontinued and were receiving BSC, did not have the same ventilation costs as patients on BSC. The model has been amended so that patients who have discontinued treatment have the ventilation costs associated with BSC.

The following scenario analyses were run adapting the ERG's base case. These have been run to provide additional potentially informative data to the committee. These are ordered in terms of the headings in Section 5.2.3 and not in order of perceived importance.

Table 13: Comparing the ERG's base case analyses and the company's base case analyses

			CPQ given individual change		
Parameter	**Company's value(s)**	**ERG's preferred value(s)**	**Paediatric (CS base case £[redacted])**	**Adolescent (CS base case £[redacted])**	**Adult (CS base case £[redacted])**
Utility in the WU and WWA state using baseline values from rhLAMAN-10[1]	0.906; [redacted]	0.652; 0.577	[redacted]	[redacted]	[redacted]
The discount rate for costs and benefits	1.5%	3.5%	[redacted]	[redacted]	[redacted]
Assumed increase in utility associated with velmanase alfa treatment	0.10	0.00	[redacted]	[redacted]	[redacted]
Amending transition probabilities for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
Amending ventilation costs for patients who discontinue velmanase alfa	-	-	[redacted]	[redacted]	[redacted]
All changes simultaneously			[redacted]	[redacted]	[redacted]

CPQ – cost per quality-adjusted life year gained; CS – company submission; WU – Walking Unassisted; WWA – Walking With Assistance