Slides for public

Lead team presentation

Velmanase alfa for treating alpha-mannosidosis

1st Evaluation Committee Meeting

Highly Specialised Technology, 25 April 2018

Presentation from Linn Phipps

Company: Chiesi

Chair: Peter Jackson

Evidence review group: School of Health and Related Research (ScHARR)

NICE team: Aminata Thiam, Ian Watson, Sheela Upadhyaya

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."

CONFIDENTIAL

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

- [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)

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"*

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Background and Clinical effectiveness

Lead team: Ayesha Ali, Linn Phipps and Sarah Davis

Company: Chiesi

Chair: Peter Jackson

Evidence review group: School of Health and Related Research (ScHARR)

NICE team: Aminata Thiam, Ian Watson, Sheela Upadhyaya

Disease background

Alpha-mannosidosis (AM)

- Autosomal recessive inherited lysosomal storage disorder caused by deficiency of alpha-mannosidase, which is important for breaking down certain sugar compounds (called mannose-rich oligosaccharides)
- 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
  - Muscle and joint pain

* Extracted from the company submission, scope and expert's statements

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, supportive measures at home (hoists etc.), major surgical interventions (ventriculoperitoneal shunts, cervical spine decompression, joint replacement)
- Allogeneic hematopoietic stem cell transplantation (HSCT)
  - Treatment option for some patients, although associated with significant risks that increase with age
  - Typically reserved for patients with extensive disease in early infancy (≤5 years), no comorbidities, matched sibling or umbilical cord donor
  - However, no universally accepted criteria for suitability of HSCT
  - 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

PAS: patient access scheme

Clinical expert

- 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 complications of alpha-mannosidosis
- Clinically meaningful endpoints difficult to demonstrate in time limited trial duration (although trials demonstrated reversal of some disease manifestations)
- Study showed greater trend for improvement in children and adolescents compared to adults
- VA expected to increase quality of life due to improvement in ambulatory state and infection rate, and better safety profile compared to HSCT
- Patients expected to receive up to 3 infusions in the highly specialist lysosomal storage disorder centre and the subsequent infusions at home
- Early treatment initiation expected to reduce comorbidities and the need for supportive care
- Side effects mostly relate to infusion: infusion-related reactions, need for IV access (may require central line), adjustment of patient activities

Decision problem (1/2)

	NICE final scope	Company submission	ERG comments
Population	People with AM aged ≥ 6 years	As per scope; MA not restricted by age, no evidence available for <5s; clinical and economic case presented for people ≥6 years	• Uncertainty on generalisability of the trial results to children <5 • 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 relevant 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

⊙***Is HSCT a relevant comparator?***

⊙***Is velmanase alfa clinical evidence generalisable to clinical practice in England?***

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	• 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 • Language not measured • Psychiatric problems should have been included in the final scope and company submission although there are not expected to be impacted 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:
  - Accumulation of mannose-rich oligosaccharides due to nature of the condition
  - Reduction in SO demonstrates the effect of VA at cellular level and is a surrogate marker of clinical complications
  - 'Change in SO' is a primary endpoint in the rhLAMAN trials

- 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
  - SO not currently measured in UK practice

Source: section 9.4 (page 86) of company submission

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

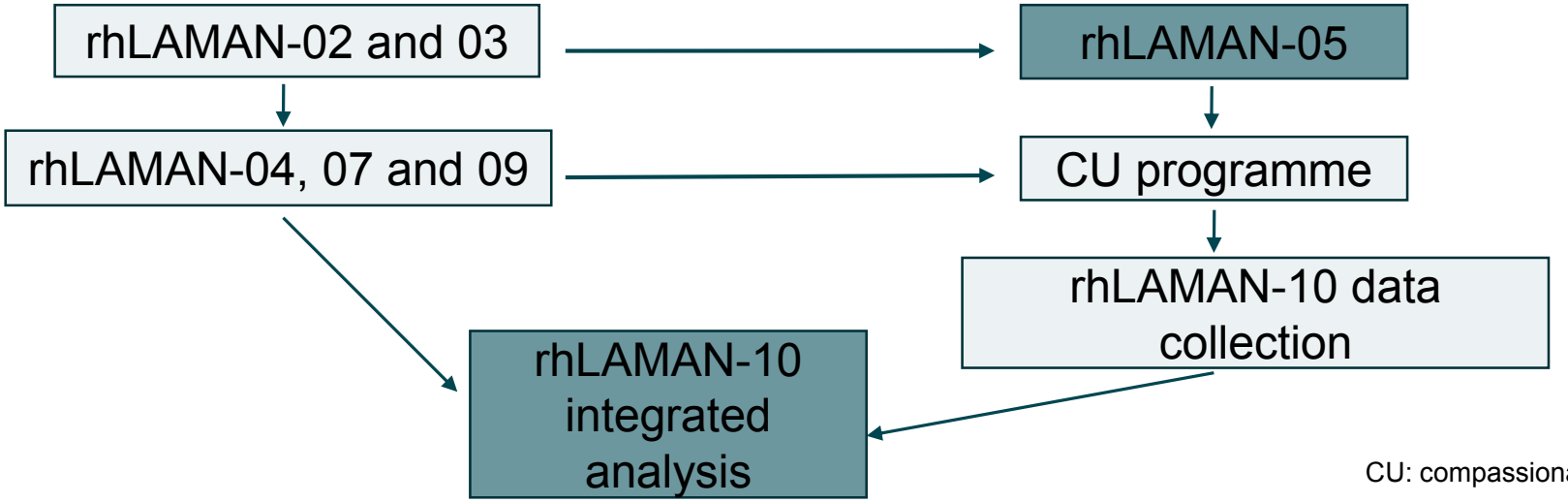
Pivotal evidence relevant to the decision problem

Clinical trial design

	rhLAMAN-05	rhLAMAN-10
Design	Phase III randomised controlled	Phase III open label non-controlled
Intervention	VA 1 mg/kg	VA 1 mg/kg
Comparator	placebo	baseline
N	25	33
Duration	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 5-35	AM patients from rhLAMAN trials and CU programme
Outcomes	**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; EQ-5D - EuroQol five-dimension questionnaire; FVC - forced vital capacity; PFT - pulmonary function test; PTA - pure tone audiometry; VA – velmanase alfa
*Leiter-R test: non-verbal measure to assess cognitive ability

Patient disposition and baseline characteristics



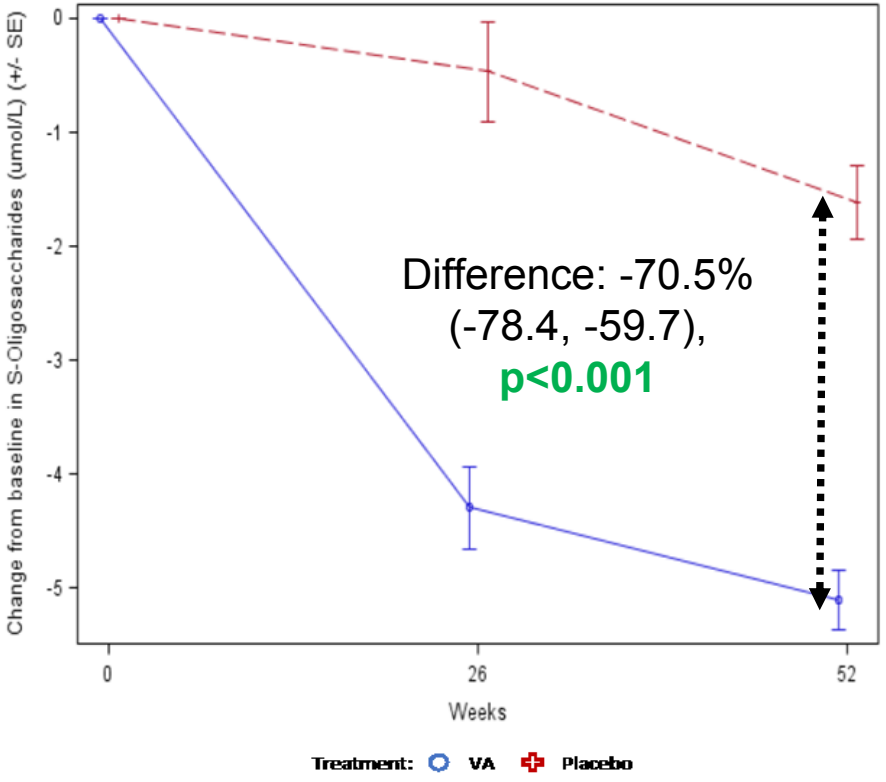
CU: compassionate use

		rhLAMAN-10				rhLAMAN-05	
		Overall (N=33)	<18 years (N=19)	≥18 years (N=14)		VA (N=15)	Placebo (N=10)
Age at baseline (years)	Mean	17.1	11.6	24.6	<12	26.7%	20%
					12–18	20.0%	30%
					≥18	53.3%	50%
Gender	Female, n (%)	13 (39.4)	6 (31.6)	7 (50.0)	Female, n (%)	6 (40.0)	5 (50.0)

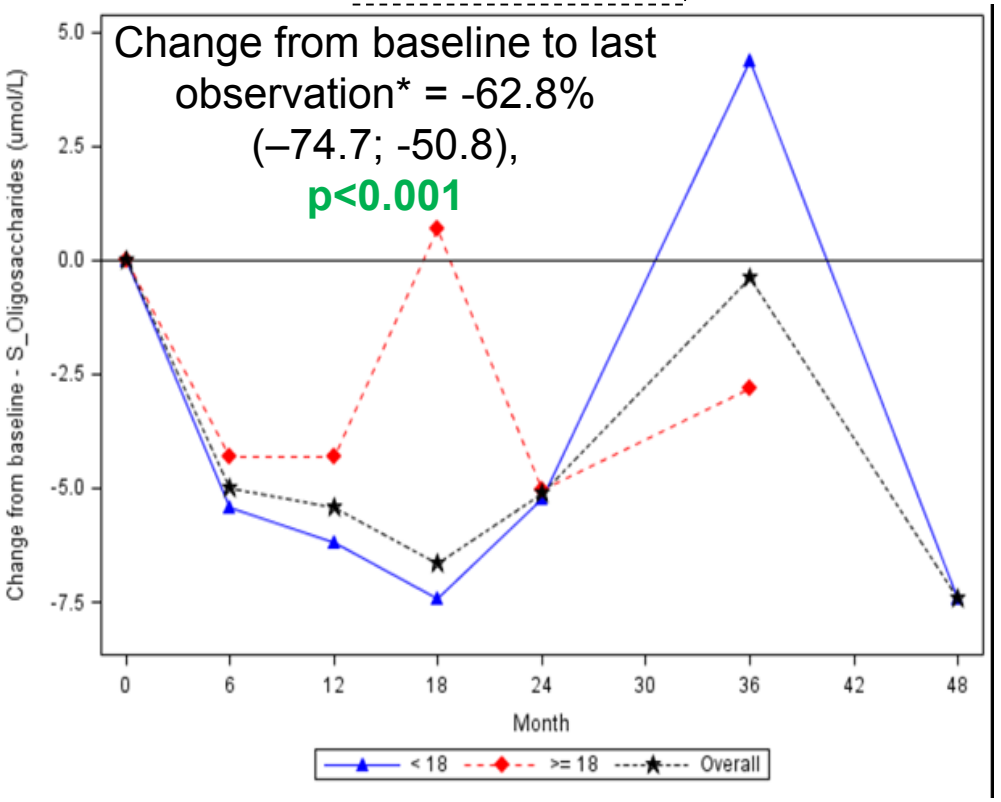
Source: Reproduced from Figures 9 and 10 (page 120) of company submission

Clinical results: Serum oligosaccharides

rhLAMAN-05



rhLAMAN-10



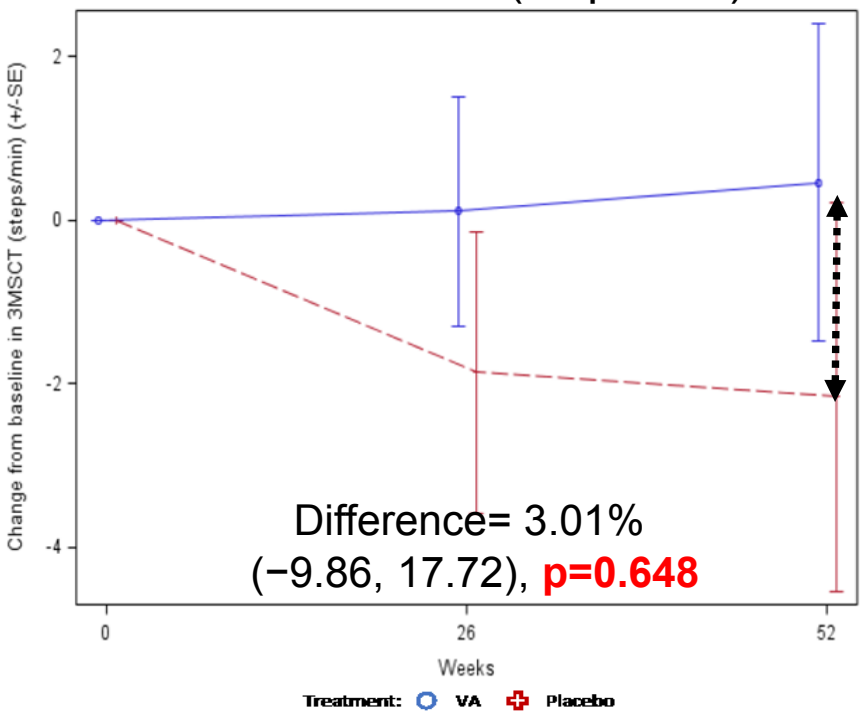
Statistically significant improvement in serum oligosaccharide levels observed at 12 months (vs. placebo) and 48 months (vs. baseline)

*Last observation is a composite value comprising a range of follow-up times (12–48 months of active treatment)

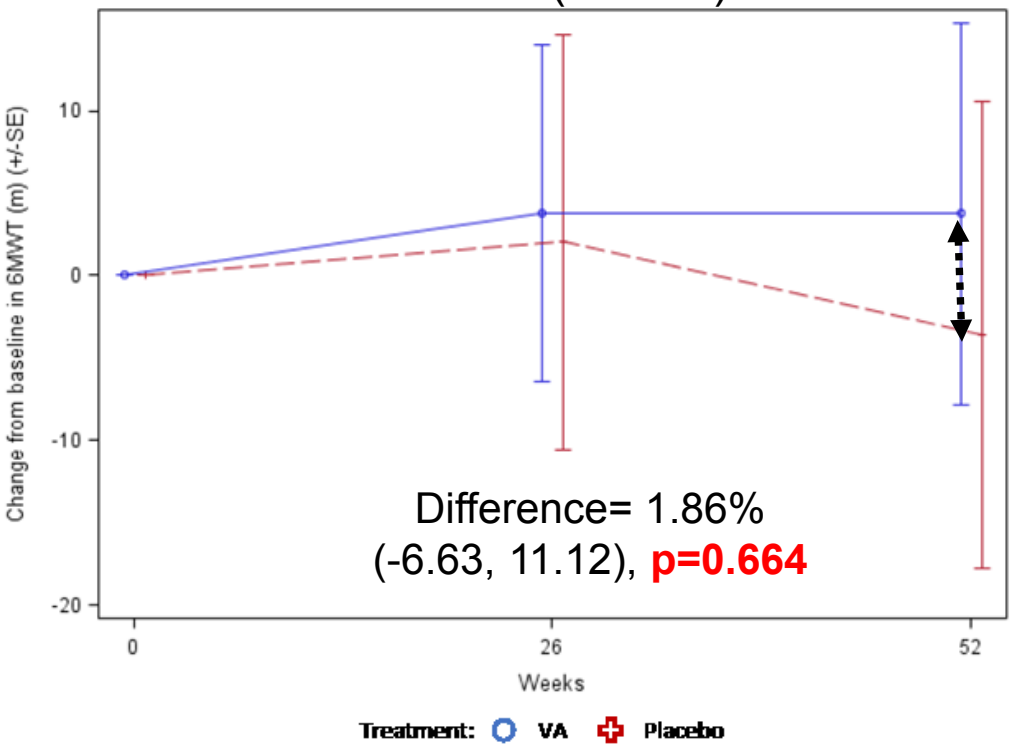
Clinical results: Mobility/functional capacity

rhLAMAN-05

3-MSCT (steps/min)



6-MWT (metres)

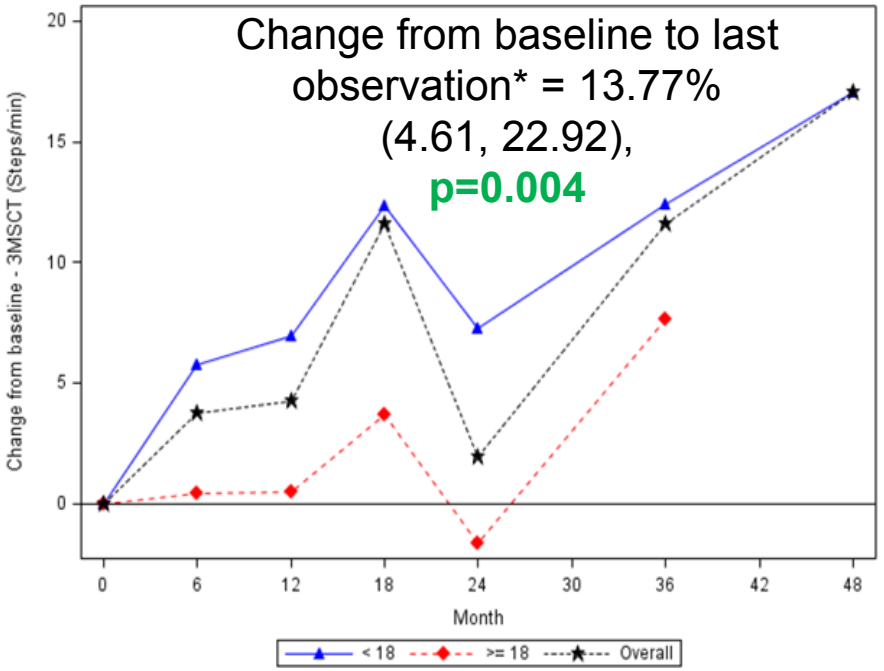


- **No statistically significant difference** between VA and placebo in 3-MSCT and 6-MWT at 12 months

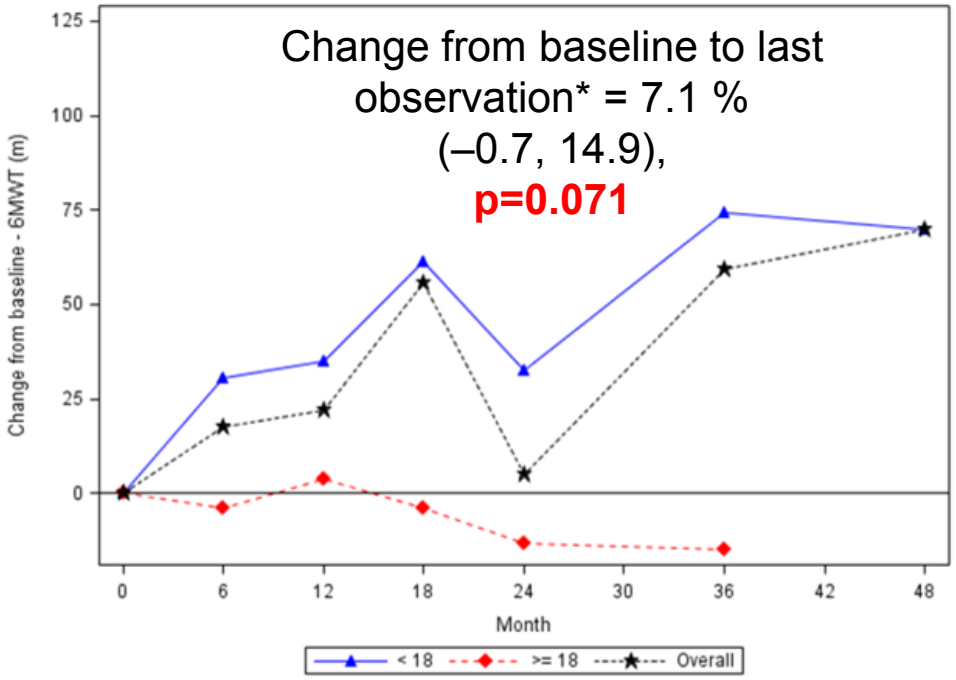
Clinical results: Mobility/functional capacity

rhLAMAN-10

3-MSCT (steps/min)



6-MWT (metres)



3-MSCT: **statistically significant difference** at last observation in favour of VA

6-MWT: **no statistically significant difference** at last observation (with baseline)

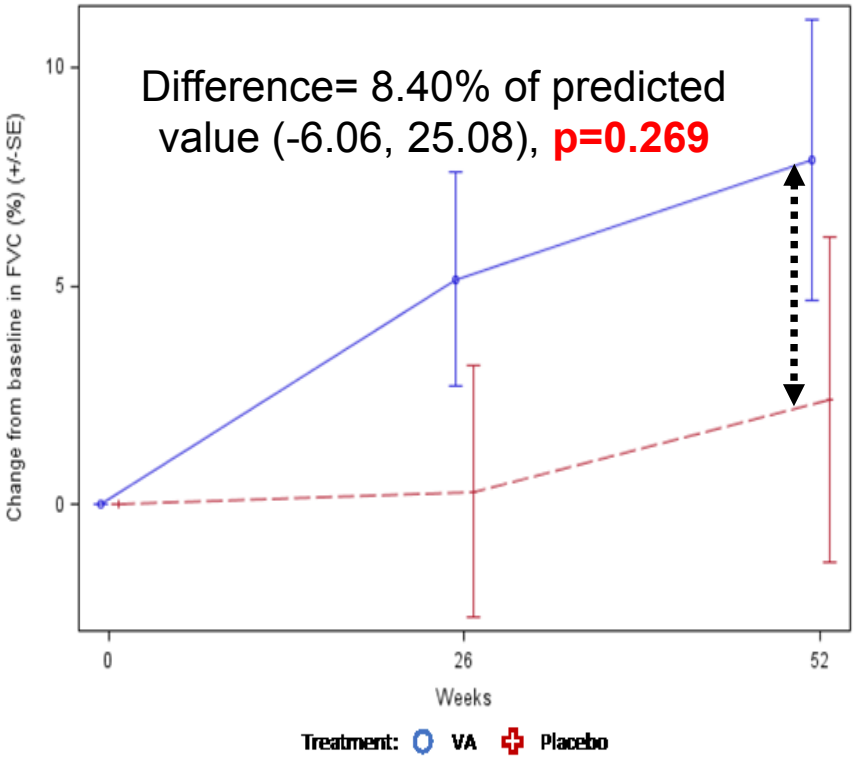
*Last observation is a composite value comprising a range of follow-up times (12–48 months of active treatment)

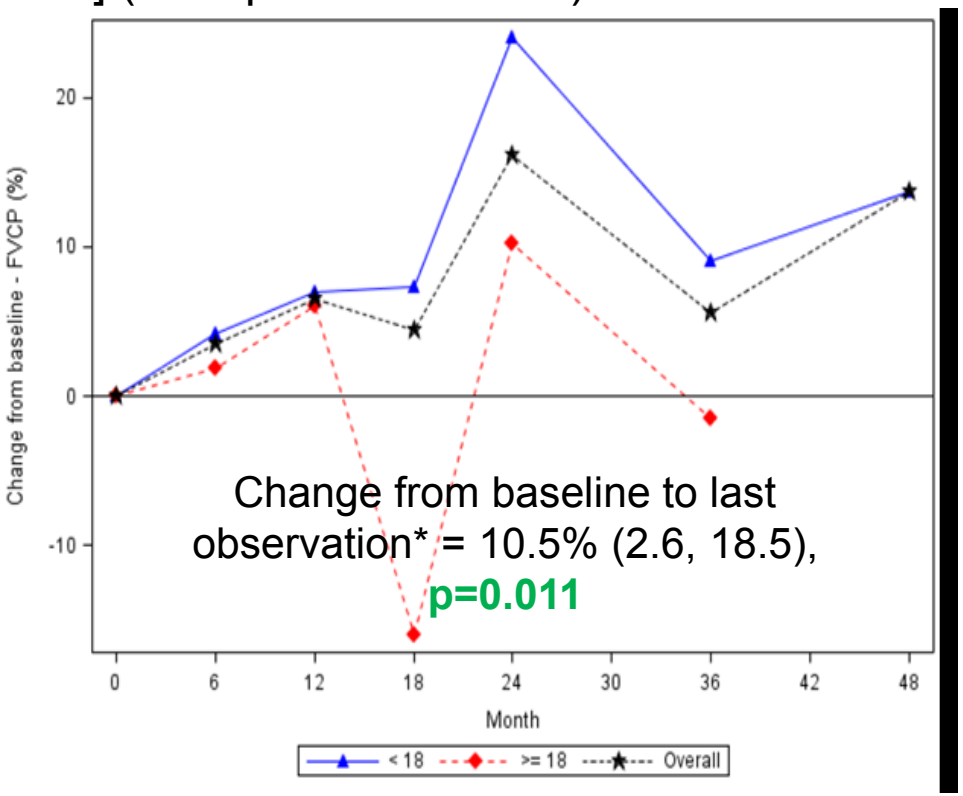
Clinical results: Lung function

rhLAMAN-05

rhLAMAN-10

Forced Vital Capacity [FVC] (% of predicted value)





rhLAMAN-05: **no statistically significant difference** between placebo and VA at 12 months

rhLAMAN-10: **statistically significant difference** at last observation in favour of VA

*Last observation is a composite value comprising a range of follow-up times (12–48 months of active treatment)

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
- 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

⊙***What is the committee's view on the significance of the findings from rhLAMAN-05 and rhLAMAN-10?***

IgG: immunoglobulin G

Clinical results: quality of life

rhLAMAN-05

Analysis at 12 months	VA (n=15)	Placebo (n=10)
CHAQ disability		
Average score (SD)	1.4 (0.8)	1.8 (0.5)
Absolute change from baseline (SD)	-0.01 (0.3)	0.2 (0.4)
CHAQ pain (VAS)		
Average score (SD)	1.0 (1.0)	0.5 (0.6)
Absolute change from baseline (SD)	0.2 (0.7)	0.2 (0.7)
EQ-5D-5L index score		
Average score (SD)	0.6 (0.2)	0.6 (0.2)
Absolute change from baseline (SD)	0.04 (0.1)	0.03 (0.2)
EQ-5D-5L VAS		
Average score (SD)	68.2 (17.3)	67.7 (16.6)
Absolute change from baseline (SD)	2.0 (18.0)	3.7 (15.7)

- No comparative or adjusted analyses were provided
- Company interpreted data as demonstrating a trend towards improvement
- ERG considers the data inconclusive

Clinical results: quality of life

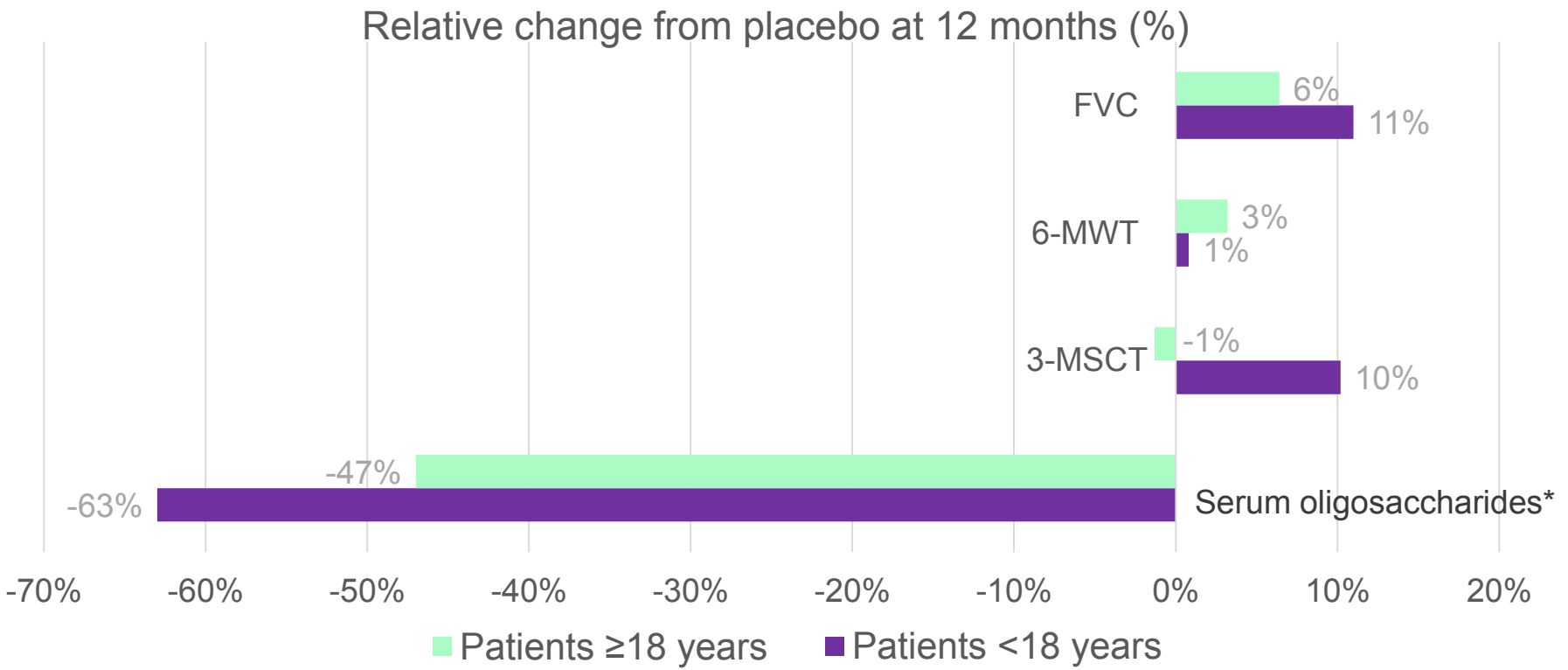
rhLAMAN-10

Analysis at last observation	Overall (N=33)
CHAQ disability	
Average score (SD)	1.2 (0.7)
Absolute mean from baseline (95% CI)	–0.1 (–0.3, 0.02), p=0.095
CHAQ pain (VAS)	
Average score (SD)	0.4 (0.6)
Absolute change from baseline (95% CI)	–0.2 (–0.4, 0.1), p=0.139, n=32
EQ-5D-5L index score	
Average score (SD)	0.7 (0.17)
Absolute change from baseline (95% CI)	0.1 (0.01, 0.1), p=0.080, n=24
EQ-5D-5L VAS	
Average score (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' is statistically significant (p=0.036) although this analysis only included 24/33 patients with the reason for this unclear

Clinical results by age group

rhLAMAN-05 post-hoc analyses: patients <18 years benefit the most from VA for most outcomes



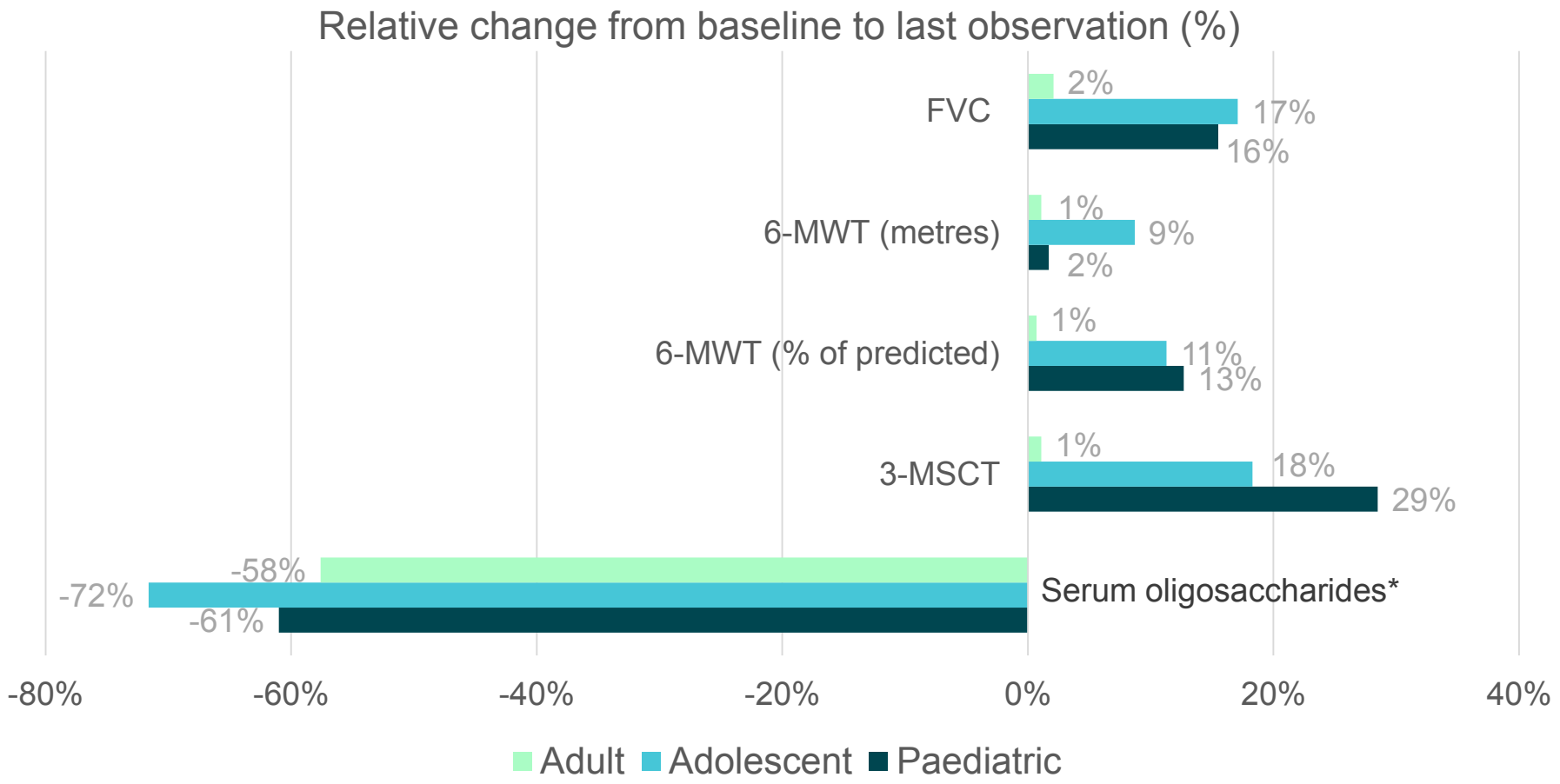
- Except for 6-MWT: difference between VA and placebo was greater in adult patients, however this was largely due to a decrease in scores in adult placebo group, while scores increased in the paediatric placebo group

*For serum oligosaccharides, negative values indicate a treatment effect in favour of velmanase alfa

3-MSCT, 3-minute stair climb test (in steps/min); 6-MWT, 6-minute walk test (in metres) ; FVC, forced vital capacity (in % of predicted)

Clinical results by age group

rhLAMAN-10 post-hoc analyses: paediatrics and adolescents benefit the most from VA



*For serum oligosaccharides, negative values indicate a treatment effect in favour of velmanase alfa

3-MSCT, 3-minute stair climb test (in steps/min); 6-MWT, 6-minute walk test; FVC, forced vital capacity (in % of predicted)

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%

More responders in group <18 years than in group ≥18 years

Responder rate: 87% with VA; vs. 30% with placebo

⊙ ***What is the committee's view on the multi-domain responder analysis? How does it inform decision-making?***

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 (86.7% and 72.7% of VA-treated patients in rhLAMAN-05 and rhLAMAN-10 trials)
- No patient discontinued treatment due to AEs
- No deaths were reported
- ERG notes that safety over lifetime treatment is unknown and there is a possible correlation between treatment exposure and higher rates of AEs

⊙ ***How does the committee view the safety profile of velmanase alfa?***

*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

ERG critique of clinical evidence (1/3)

Issue	Critique
Quality of trials	• Well conducted studies, reasonable quality
Generalisability	• Trial population (age 5–35) likely to be younger than clinical practice in England as disease progress more rapidly in younger patients • Exclusion of patients with IgE >800 IU/mL reduces the generalisability of safety findings
rhLAMAN-10 has high risk of bias and results difficult to interpret	• No comparator arm 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 due to disease heterogeneity; subjective measures impacted by open-label design • Variation of follow-up duration; last observation analysis generally included all patients • No imputation was used (for missing data): 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	• More-compromised patients in VA arm than placebo that could affect 3-MSCT, 6-MWT, FVC, BOT-2 or CHAQ disability but unclear how • may have more scope for improvement, or may have irreversible deterioration • 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 did not meet the minimal clinically important differences
3-MSCT and 6-MWT not normalised for age	6-MWT is likely to increase with age but company did not conduct age-normalised assessment for rhLAMAN-05

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 extremely low and no statistical analysis provided • Inclusion of only patients with low IgG: unclear what happened to the remaining patients • patients with low IgG was the only group where a correlation between serum IgG and 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 and bring into question the relevance of the results reported • IgG analysis & carer report do not match trial infection rate
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?

Slides for public

Lead team presentation

Velmanase alfa for treating alpha-mannosidosis

1st Evaluation Committee Meeting

Highly Specialised Technology, 25 April 2018

Economic evidence

Lead team: Sarah Davis

Company: Chiesi

Chair: Peter Jackson

Evidence review group: School of Health and Related Research (ScHARR)

NICE team: Aminata Thiam, Ian Watson, Sheela Upadhyaya

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

VA, BSC

- Assumed patients were at lowest age within each age band to reflect KOLs' points:
  - *"the earlier the intervention with an ERT, 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"*
- Starting health state of population was taken from rhLAMAN-10

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)
- ERG explored a scenario analysis where the average age per band was used

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)

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 disease progression for VA treatment compared with BSC (from rhLAMAN-05) when considering transitions from WU to WAA

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

BSC: 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) when considering transitions from WWA to WU
- ERG explored a scenario analysis when 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]

VA: it was assumed that the annual risks of surgery were reduced by 50% for patients receiving VA

- 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

- Company: stopping rules likely to result in **more favourable outcomes in the long term** than those observed in 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 or ‘Short end Stage’ state would have treatment withdrawn

⊙ ***What is the committee’s view of the structure and assumptions in the economic model? Is the model fit for decision-making?***

Resource use (1/2): Drug acquisition

Velmanase alfa acquisition cost

- List price: £886.61 per 10-mg vial
  - *Confidential simple discount PAS approved*
- Estimated annual cost per patient (list price): **£138,000 – £323,000**
  - *Based on 1 mg/kg per week, for a patient of average weight at model start in the paediatric (age 6 years, 22 kg) and adult (age 18 years, 68 kg for males)*

Resource use (2/2): Other resources

Resource use items		Value	Source
Administration of VA	Administration cost in hospital, per infusion	£213	NHS National prices and national tariff
	Number of infusions at LSD centre	3 once weekly	UK KOL Interviews
	% home infusion	98% (no additional cost)	
	% local hospital infusion	2%	
AE	Infusion-related reactions (only AE included in model)	0	Assumption
Ventilation	% requiring ventilation (VA)	50% reduction vs. BSC	UK KOL Interviews; Assumption
	Ventilation annual cost	£80,279 – £301,888	Noyes 2006
Carer	Hours of care per day by health state	1.3 (WU), 3.9 (WWA), 13.8 (WC and SI)	Assumption (based on MPS IVa)
	% care provided by health professional	10% (WU), 20% (WWA), 50% (WC), 80% (SI)	Assumption

- ERG noted the company did not use the outcome of the MPS Society survey on carer's time spent by day ([redacted]
- 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

- *[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 trial	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

* [redacted]

⊙ ***What is the most appropriate source of utility for each health state? from the MPS Society survey (company) or from the rhLAMAN-10 integrated trial (ERG)?***

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 analyses on: utility gain for VA patients (0 in ERG base case, 0.05 in scenario), 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

⊙ ***Is a utility gain associated with velmanase alfa (0.1) realistic?***

Cost effectiveness result

PAS price (deterministic analysis)

	Total costs (£)	Total QALYs (disc.)	Total QALYs (undisc.)	Inc. costs (£)	Inc. QALYs (disc.)	ICER (£/QALY)
Paediatrics						
VA	[redacted]	10.32	12.17	[redacted]	2.53	[redacted]
BSC	[redacted]	7.79	9.08	-	-	-
Adolescents						
VA	[redacted]	10.04	11.84	[redacted]	2.66	[redacted]
BSC	[redacted]	7.39	8.60	-	-	-
Adults						
VA	[redacted]	9.17	10.78	[redacted]	2.67	[redacted]
BSC	[redacted]	6.51	7.54	-	-	-

Whole cohort: ICER = £[redacted] per QALY

Weighted average: assuming 40% paediatric, 20% adolescent and 40% adult patients

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

Note: As the economic model is linear, the deterministic ICER is almost identical to the probabilistic ICER. Only the deterministic analyses are presented on this slide.

Sensitivity and scenario analyses

PAS price

- Deterministic sensitivity analysis – ICERs are most sensitive to:
  - acquisition cost
  - discount rate applied on outcomes
  - probability of disease improvement at years 1 and 2 with VA
  - time to disease progression with BSC
- 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)	Upper estimate of EEP	[redacted]	[redacted]	[redacted]	↓
	Reduced by 50% with VA	[redacted]	[redacted]	[redacted]	↓↓
	No progression	[redacted]	[redacted]	[redacted]	↓↓
Improvement (WWA→WU) (2.5%)	5% from year 3 onwards	[redacted]	[redacted]	[redacted]	↓
	No improvement from yr3	[redacted]	[redacted]	[redacted]	↑
Utility wheelchair dependent (0.100)	Equal to SI (-0.010)	[redacted]	[redacted]	[redacted]	↑

↓↓ *shows larger decrease than* ↓

ERG critique (1/3)

Limitations	ERG justification	Corrected in ERG's base case
General concerns on appropriateness of model	• Most estimates 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 formal elicitation process • Estimates may not reflect genuine beliefs	**No possible change** – ERG's base ICERs constraints to same limitations
Utilities for WU and WWA in company base case reported from MPS Society survey	[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: [redacted]
Discount rate of 1.5% per annum	VA does not meet NICE method criteria as it does not restore a patient to full or near full health	**Yes** – 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 company based their choice on (EQ-5D in rhLAMAN-10) may be confounded • Possible double-counting when patient improves or maintains health state • Additional time to progression (from elicitation) is not sufficiently high to support utility gain	**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 discontinued VA have BSC costs
Implementation error transition probabilities	-	**Yes**
Model does not allow improvement for BSC	Likely to change ICER, although unknown direction, it could be large	**No***
Increase in life expectancy elicited from clinicians	Increase in life expectancy 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***
Discontinuation of treatment assumed to be at midpoint of 1st year rather than at 12 months	Implementation issue which will be unfavourable to VA as 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

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 ventilation costs assumption when patients discontinue VA	50% reduction vs. BSC	Same as BSC	[redacted]	[redacted]	[redacted]
Amending error in 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)

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]

⊙ ***What are the most plausible ICERs? What rates of discounting should apply?***

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 most 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

- ***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***

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 *(rate)*	
Company base case	Paediatric	3.09	2.53	*(1.5%)*
	Adolescent	3.25	2.66	
	Adults	3.23	2.67	
ERG base case	Paediatric	1.89	1.08	*(3.5%)*
	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	*(3.5%)*
	Adolescent	2.35	1.43	
	Adults	2.35	1.45	

⊙ ***Application of QALY weighting?***

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
  - [redacted] patients will be treated with VA in Year 5

	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
- Training: Some training of staff on this specific drug will be needed

Equality

- No equality issues were 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

⊙ ***What factors affecting the guidance need to be taken into account?***

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?
- Application of QALY weighting?