Velmanase alfa for treating alpha-mannosidosis [ID800]

For public – AIC and CIC information redacted [redacted]

5th evaluation meeting

HST technology appraisal committee [14 September 2023]

Chair: Peter Jackson

External assessment group: School of Health and Related Research (ScHARR)

Technical team: Owen Swales, Ewa Rupniewska, Richard Diaz

Company: Chiesi

Topic history and overview of considerations at ECM4

NICE National Institute for Health and Care Excellence

RECAP

History of this topic

Negative ECD released following company's resubmission in June 2022

ECD released for consultation

FED suspended for finalisation of commercial arrangement

FED released October 2019

FED withdrawn to allow company to present updated clinical data

ECD released July 2022

Released for 2nd consultation October – November 2022 due to technical issues in 1st consultation

ECM1 ***25th April 2018***	***ECM2*** ***28th June 2018***	***ECM3*** ***29th August 2019***	***ECM4*** ***8th June 2022***	***ECM5*** ***14th September 2023***
Velmanase alfa ***not recommended***	• Committee considered consultation comments and additional analyses from Chiesi • Commercial arrangement not finalised for meeting	***Resubmission*** • Company presented updated PAS and additional analyses • Committee: modelling uncertainties remain, no plausible potential to be cost effective *Velmanase alfa* ***not recommended***	***Resubmission*** *with technical engagement* • Further update to PAS and managed access agreement • Additional clinical effectiveness and natural history data *Velmanase alfa* ***not recommended***	***To consider today:*** • Stakeholder responses to July and October consultations • New population of non-adults starting treatment • Updated modelling assumptions • Clinical evidence updates

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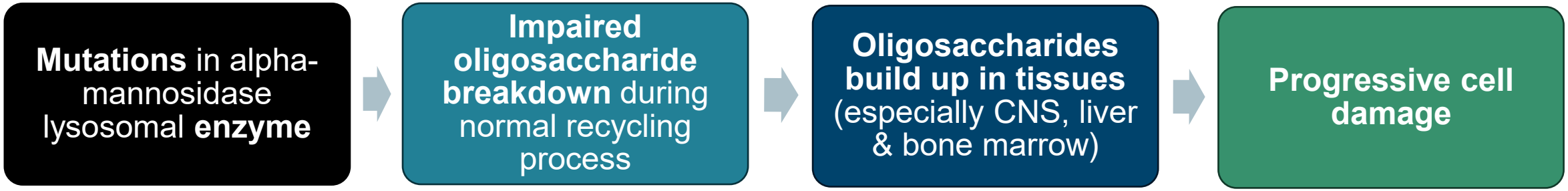
Abbreviations: ECD, evaluation consultation document; ECM, evaluation committee meeting; FED, final evaluation document; PAS, patient access scheme

Background on alpha-mannosidosis (1)

Highly heterogenous disease with poor prognosis and limited treatment options

Inherited lysosomal storage disorder: caused by deficiency of alpha-mannosidase enzyme:



Symptoms: can present at infancy, childhood or early adolescence

- onset and severity of symptoms highly heterogeneous
- progressive disease, characterised by cognitive impairment and skeletal deformities

Epidemiology: Currently 25 cases of alpha-mannosidosis (AM) registered in England

- Incidence: estimated 1 in 500,000 to 1 in 1,000,000, ~1 annual case expected per year*

Quality of life: AM significantly impacts all aspects of life for patients, families and carers

- Social and professional life can be compromised

*Source: company resubmission, March 2022. CNS, central nervous system

Background on alpha-mannosidosis (2)

Prognosis: dependent on severity of disease linked to age at presentation:

Type	Presentation	Progression	Characterised by	Survival
1 - Mild	After 10 years old	Very slow	- Muscle weakness without skeletal deformities	Generally, survive into adulthood
2 - Moderate (most common)	Before 10 years old	Slow	- Skeletal abnormalities leading to ataxia (impaired coordination of voluntary movements) by age 20 to 30	
3 - Severe *(excluded from marketing authorisation)*	Within 1st year of life	Rapid	Easily distinguishable by: - Severe skeletal abnormalities - Recurrent infections - CNS involvement and myopathy	Early death due to CNS involvement or infections

Treatment: No cure or licenced pharmacologic disease-modifying treatment options

Current options aimed at managing symptoms, delaying progression and improving quality of life:

- walking aids, physiotherapy, infection management, ventilation support, supportive measures at home, major surgical interventions, general treatment of comorbidities
- allogeneic HSCT generally used in people with severe disease to treat CNS symptoms

Committee considerations at ECM4, nature of the condition

- Rare, serious and debilitating condition with wide range of clinical manifestations & level of impairment
- Significant unmet need for new treatments
- Severely affects lives of patients, families and carers

Abbreviations: CNS, central nervous system; HSCT, haematopoietic stem cell transplant

Velmanase alfa (Lamzede, Chiesi)

Technology details

Marketing authorisation	• Indicated for the treatment of non-neurological manifestations of patients with mild to moderate alpha-mannosidosis
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	• Intravenous infusion
Dose and duration	• 1 mg/kg of body weight once every week • Lifelong duration
Price	• List price: £886.61 per 10 mg vial • Anticipated mean costs of velmanase alfa per year (list price): £305,279 • Updated simple discount approved by NHS England for ECM4 (unchanged at ECM5)

Summary of clinical data considered at ECM4

Study name	Design	N	Population	Comparator	Duration	In model?
rhLAMAN-05	Phase III randomised controlled	25	Patients with AM aged 5-35	Placebo	12 months	VA discontinuation rate
Updated data cut submitted at ECM4						
rhLAMAN-10	Integrated analysis	33	Patients with AM from rhLAMAN-04, -05 and CU studies	Δ from baseline	48 months	Starting health state of population
New studies submitted at ECM4						
rhLAMAN-08	Phase II open-label study	5	Patients with AM aged <6	Δ from baseline	24 months	No
Etoile Alpha	Real-world retrospective registry study	16	rhLAMAN-07, rhLAMAN-08, nominative ATU	Δ from baseline	54 months	Supports disease progression assumption
AM registry (SPARKLE)* (ongoing)	Noninterventional prospective cohort study	40	European patients with AM	None	15 years	No
Case reports	rhLAMAN-05	2	Adults with AM	Δ from placebo	Various	Supports disease progression assumption
	UK patient	1		None		
	European series	5		None		

*Intervention not specified: includes VA, BSC, HSCT, investigational treatment. All other studies VA = 1 mg/kg. Source: adapted from ERG report ECM4, Table 1

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ATU, temporary utilisation authorisation; BSC, best supportive care; CU, compassionate use; HSCT, haematopoietic stem cell transplant

Committee considerations on clinical data at ECM4

Clinical evidence promising but insufficient to establish extent of benefits

rhLAMAN-05	**1º outcome: Statistically significant improvement** in serum oligosaccharides with VA vs placebo **2º outcomes: No statistically significant differences** between VA and placebo for mobility and functional capacity* and quality of life† **More patients** were 'responders' in VA arm than placebo arm (87% vs 30%)‡
rhLAMAN-10	**Statistically significant differences** compared with baseline in most outcomes at last observation
rhLAMAN-08	**Reduction in serum oligosaccharides and mobility** parameters from baseline to 24 months
Etoile-Alpha	**Improvements or stabilisation** in serum oligosaccharides, mobility and functional capacity measures* • Results suggest **treatment effect larger in children** than adults
Case reports	Describe improvements in multiple parameters including mobility, immune, cognition and social skills

Committee considerations at ECM4 on clinical trial evidence

- Clinical evidence likely generalisable to NHS across population (including <6 year olds)
- Trial evidence potentially promising but insufficient to establish extent of clinical benefits
- VA may have immunological benefits but evidence limited and uncertain
- **Limited follow up so long-term benefit uncertain**
  - Differences in VAs effect in Etoile-Alpha may be partly explained by physiological changes with age
- ERG: case reports are non-comparative, small, non-standardised and at high risk of outcome assessment bias

*3-minute stair climb test, 6-minute walk test, forced vital capacity. †Childhood Health Assessment Questionnaire, EQ-5D-5L. ‡Defined by meeting response criteria in 2 of pharmacodynamic, functional and quality of life domains in multi-domain responder analyses

Committee considerations on clinical evidence at ECM4

Updated population appropriate but there are limitations to clinical evidence

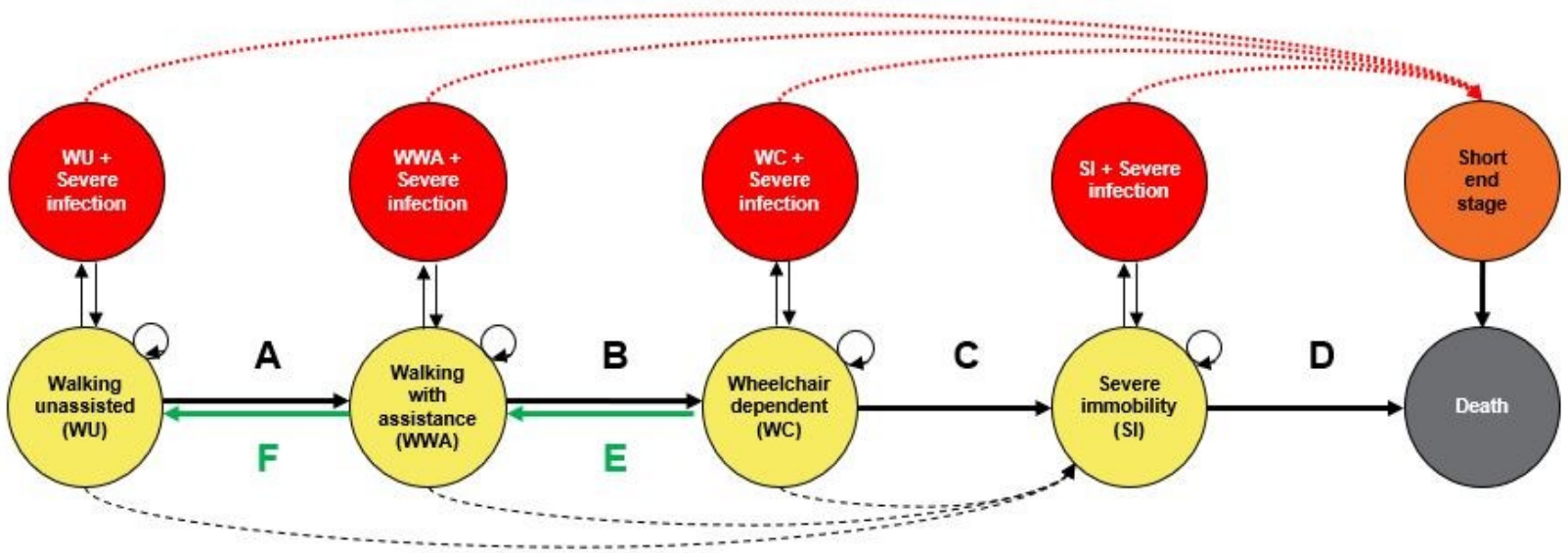
Theme	Company's evidence	Committee consideration ECM4
Positioning	• People with mild-to-moderate AM • Updated population at ECM4 to include people with AM <6 years old	• Population aligned with MA and expected VA use • Small number of people with mild to moderate AM may be diagnosed <6 years old
Comparator	Best supportive care (BSC) • including walking aids, physiotherapy, infection management, ventilation support, general treatment of comorbidities, supportive measures at home and major surgical interventions • Allogeneic HSCT not included	• Some people <5 years may be offered both HSCT and VA (based on mutation type, symptoms and donor availability) • No evidence comparing VA with HSCT or using as bridge to HSCT: cannot make recommendation in this population
Key clinical evidence	• **rhLAMAN-05 (Phase 3)*** • **rhLAMAN-10 (non-controlled)** • rhLAMAN-08 (< 6 years old) • Etoile-Alpha (real-world retrospective registry) • Multi-domain responder analysis (requested by EMA to establish clinically meaningful improvements)	• Surrogate outcome (serum oligosaccharide) provides evidence but highly uncertain benefit • Generalisability of rhLAMAN acceptable • Limitations in Etoile-Alpha study design; influenced by extreme rarity of condition • Limitations to multi-domain responder analysis; relevance of results uncertain

Bold = results directly used in economic model *Patients could enrol in rhLAMAN-10 or compassionate use (CU) programme. HSCT, haematopoietic stem cell transplant

Company's model overview

A Markov model with 4 primary health states based on mobility

- 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
- 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
- Green arrow designates a disease improvement transition due to treatment with velmanase alfa.



- Paediatric (6-11 years), adolescent (12-17 years), adult (≥ 18 years) cohorts
- Lifetime time horizon

Committee consideration ECM4, overall modelling approach

- Mobility based model likely to capture most important aspects of AM for patients, but some potentially important outcomes (e.g. lung function) not captured
- Overall model structure adequate for decision making

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Committee considerations on cost evidence at ECM4 (1)

Limited data to inform modelling and VA delay to progression uncertain

Theme	Company's evidence	Committee consideration ECM4
Model inputs	• Limited observed data used • Expert opinion supported by Etoile-Alpha evidence inform most model parameters	• Lack of observed evidence and use of expert elicited data a significant limitation • Size and direction of any errors or bias unknown
Treatment effect	Compared to BSC, 'responders' to VA assumed to: • Have delayed disease progression: – No progression for 5 years – Extended time in health states after 5 years • Have Improved mobility (unlike BSC) • Have 50% reduction in mortality, complications and recovery time from infections and operations	**Benefit for VA highly uncertain** • Plausible that VA provides additional benefit but modelled magnitude large in context of trials • Model should allow improvements in mobility for people having BSC to align with trial data • Evidence for a 5-year halt in progression uncertain • **Prefer**: 3-year halt in progression + additional time in health states after progression
Stopping rule	Stopping rules based on non-response, treatment withdrawal and additional 10% annual withdrawal	Stopping rules should be clearly defined
Ventilation costs	50% less ventilation assistance for people who had VA and switch to BSC	Size of benefit unlikely in people who stop VA • **Prefer*:*** no ventilation benefit after stopping VA
Infusion	Costs for once weekly home-infusion for VA included	Appropriate

Abbreviations: BSC, best supportive care; VA, velmanase alfa

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Committee considerations on cost evidence at ECM4 (2)

Plausible ICER above cost-effectiveness threshold in all company subgroups

Theme	Company's evidence	Committee consideration ECM4
Utilities	Utility gain for VA compared with BSC:	
	Children: 0.254; adults: 0.1 Captures additional QoL improvement beyond mobility and response time	Mobility improvements are captured by the time spent in health states; but within health-state benefits and benefits missing in EQ-5D may not be captured in the model; 0.254 utility gain for children overestimated **Prefer:** 0.1 for children, 0.05 for adults to align better with trial values
	Utility values for walking unassisted and walking with assistance:	
	MPS survey utilities	**Prefer:** rhLAMAN trial utilities but both approaches highly uncertain
Discounting	3.5%	Appropriate: VA does not return people to full or near-full health
QALY weight	-	Not applicable: Undiscounted incremental QALY gain: < 3 in all analyses
ICERs (including ECM4 PAS)	Paediatric: £88,912 Adolescent: £126,214 Adult: £185,872	**Not cost-effective:** most plausible ICERs above: Paediatric: £159,651 Adolescent: £211,717 Adult: £271,389
Managed access	Proposed	Unlikely to resolve key uncertainties and not aligned to IMF principles

Abbreviations: BSC, best supportive care; VA, velmanase alfa; QoL, quality of life

Response to consultation on ECD

NICE National Institute for Health and Care Excellence

ECD consultation: Responses

	Stakeholder	Comments submitted
Company	Chiesi	Consultation #1 and #2
Patient organisations	The MPS Society	Consultation #1
Online comments	5 commentators	Consultation #2

ECD released July 2022
Released for 2nd consultation October – November 2022 due to technical issues in 1st consultation

Company's new submission and evidence in response to consultation

New submission:

- **Population restricted:** non-adults (patients under 18 years of age)
- **Modelling assumptions:** some are different to committee preferences stated at ECM4 (discussed in detail later)
- **No update** to PAS from ECM4
- **Updated** managed access proposal to align with data collection in Scotland

New evidence:

- rhLAMAN-11 (longer follow up of rhLAMAN-10)
- Interim data from AllStripes registry study
- 2022 European and UK Patient and Caregiver Survey
- 3 new case reports
- Additional information and analyses requested by FDA

EAG suggested evidence to revisit due to new base case:

- Etoile Alpha and rhLAMAN-08 studies
- Case reports

Abbreviations: BSC, best supportive care; PAS, patient access scheme

ECD consultation: Online comments

Committee not fully considered clinical evidence and stakeholder views

Disease "affects all areas of life"
• "Significantly complicates" life for patient and family • Patients may need "constant help" due to poor mental ability and behavioural skills and frequent hospitalisations • Different symptoms present as patient get older • Early detection of mucopolysaccharide (MPS) illnesses beneficial both socially and financially
Consideration of the evidence
• Only a small number of people <6 years in the evidence: confident results generalisable to population? • Long term gains should be considered before short term cost savings • Extended clinical trial would show long-term halt in intellectual and physical decline • Cost-effectiveness analyses should consider cost saving from halting physical decline
VA improved condition and quality of life for patients (4 patient stories, not necessarily from UK)
• Long-term improvement in mobility parameters, endurance, functional capacity and general physical condition • Also reduced joint pain; improved cognitive function, sleep and behavioural/social skills • Seizures and stomach problems stopped for 1 patient • Benefits can be observed early: "My daughter's physical/intellectual decline was halted after first month of VA" • Side effects are mild compared to the illness

Abbreviations: VA, velmanase alfa

ECD consultation: The MPS society (patient org) (1)

Committee not fully considered clinical evidence and stakeholder views

Inconsistencies in consideration of clinical evidence

- Long-term follow-up data and published real-world evidence showing clinical improvements and long-term stabilisation with VA not considered by committee
- Committee question if trial benefits reflect clinical practice but state company rely too much on expert opinion
- Committee concluded no evidence for people with progressed disease using wheelchair but people in trials using wheelchair at baseline
- Unclear which uncertainties are resolved and which remain; cannot fully understand decision-making

Clinical expert and patient viewpoints not fully considered

- Additional stakeholder discussions for ECM4 not included in the Evaluation Consultation Document
- Unclear if patient testimonies for UK patient considered by committee, including clinical opinion that:
  - UK patient outcomes better than trial data
  - Trial data does not reflect positive impact on people's cognitive function, daily life or carer burden

Rationale for not proceeding with managed access agreement contradictory

- Evidence generation expected through Etoile Alpha study and SPARKLE registry
- Unclear if evidence challenges make uncertainties unresolvable or if MAA possible if VA cost effective

Abbreviations: MAA, managed access agreement; VA, velmanase alfa

ECD consultation: The MPS society (patient org) (2)

Noted only 1 UK adult patient on ERT though CU; shared a new case study

Case study of 5.5 years aged male, diagnosed at age 4 years, ERT started at age 4 years 3 months

Disease aspect	Comments
Illnesses and inflammations	• Number of illnesses have significantly reduced, less reliant on fever medication • May occasionally require medicine at night to help fever subside
Hearing difficulties and infections	• Hasn't had a middle ear infection since starting ERT; permanent tubes fitted in ears (due to recurrent infections before ERT) will be removed in early 2024
Speech and language	• Since starting ERT, speech and language have improved; speech therapy helping • Vocabulary significantly expanded, developed passion for learning, talking to peers • Despite speech improvement, reportedly less clear than younger sibling
Toileting	• Now able to go to the toilet on his own and doesn't require support
Sleep	• Doesn't require as much support with sleeping, is less restless at nighttime
Mobility	• No more restrictions to mobility, can now climb play equipment quickly and confidently • Currently attends occupational therapy

Family note that the child is happy and health is steady, attending regular schooling and starting new hobbies
Family members feel happier about child's health but note impact on their social lives due to treatment schedule

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How many patient case studies are from the UK? Are they included in other studies?

CU, compassionate use; ERT, enzyme replacement therapy

ECD consultation: Company

Committee not fully considered or reasonably interpreted clinical evidence

Not taken all relevant evidence into account

- Newly shared evidence and totality of evidence not considered in decision-making or discussed at ECM4

Not made reasonable interpretations of the evidence

- Misunderstanding and/or lack of consideration of the natural history of alpha mannosidosis
- Preferred assumption of 3-year delay in disease progression with VA is not evidence-based
- Preferred assumption of 0.1 additional utility gain may underestimate benefits in ultra-rare heterogenous disease
- Reasons for committee's preferred ICERs were unclear and contradict other conclusions
- Lack of clarity, contradiction and inconsistency in rejecting the draft managed access agreement (MAA)
- Description and interpretations of evidence are inconsistent, contradictory and unclear, and not updated to reflect new evidence or clinical expert and patient testimony at ECM4

Not made sound or suitable recommendations

- Processes not aligned with latest NICE methods guide and real-world evidence framework
- Insufficient flexibility for treatments that are innovative, for rare diseases, and for children
- Proposed starting and stopping rules (not in updated company base case) not included in most plausible ICERs

Other comments

- Processes discriminated against people and children with AM (see later slide); factual inaccuracies within ECD

Abbreviations: ICER, incremental cost-effectiveness ratio

ECD consultation: Equality considerations

Company suggest guidance may be discriminatory

Committee conclusion on equalities considerations at ECM4:

“The committee ... considered that the effect of the disability associated with this condition and the benefits of the technology had been fully captured in the evidence, economic modelling and committee considerations”

Company consultation comments on ECD2:

- Guidance may be discriminatory against people with disability (AM)
- Committee not considered inherent uncertainties with evidence due to the very small patient population
- There are no recommended treatments for AM for which cost comparison approach could be taken as in other ultra-rare diseases such as Pompe disease and Fabry disease
- VA fulfils all 3 categories for additional flexibilities in the NICE methods guide: an innovative treatment (1) for rare disease (2) and for children (3) – but flexibility not given
- Guidance shows committee have not considered additional flexibility for children as there is no mention of the difference in treatment effect between adults and children

Abbreviations: AM, alpha mannosidosis; VA, velmanase alfa

ECD consultation: Company's new evidence

Summary and relevance of new evidence identified by the company

Study name	Overview	Rationale for considering
rhLAMAN-11	Longer follow up of rhLAMAN-10 plus further follow-up data from rhLAMAN-07/-09	Shows latest long-term evidence for key clinical outcomes and supports model assumptions for disease progression
AllStripes registry study	Retrospective natural history cohort study in US, Canada and UK	Supports model assumptions for disease progression and age at diagnosis
2022 European and UK Patient and Caregiver Survey	Survey of patients and caregivers to inform disease progression of patients aged ≥10 years	Supports model assumptions for disease progression and patient and carer quality of life
4 new case reports	2 infants treated with VA as a bridging treatment for HSCT, a 7-year-old in Italy, and a female in Saudi Arabia diagnosed prenatally	Supports model assumptions for disease progression and age at diagnosis Addresses ECD that there is no data for people who may use VA to bridge to HSCT
Information and analyses requested by the FDA	New multicomponent analysis of rhLAMAN-05 using test statistics to identify multicomponent endpoints	Supports in identifying suitable multicomponent endpoints via correlation with serum oligosaccharides

Abbreviations: FDA; food and drug administration; HSCT, haematopoietic stem cell transplant; VA, velmanase alfa

ECD consultation: Company's new base case (1)

Differences between the company's new base case and committee preferences

Key issues: Base case changes for committee discussion

Parameter	Committee preference at ECM4	Approach used by the company	Rationale for considering
Mobility improvements for patients receiving VA and BSC	The improvements should be allowed in both the VA and BSC arms (ECD section 4.15)	The model allows improvements in the VA arm but not in the BSC arm	Previously cited clinical expert opinion now supported by rhLAMAN-11 results and other studies
Delayed progression associated with VA treatment	3 years of delayed disease progression followed by extended time in health states (ECD section 4.16)	6 years of delayed disease progression but no extended time in health states	Based on mean VA treatment duration for children in rhLAMAN-11
Utility gains in children above that associated with mobility health states	0.10 utility gain for children (ECD section 4.17)	0.18 utility gain for children	Improved lung function observed in children in rhLAMAN-11 and reduced respiratory infections in other studies

Abbreviations: BSC, best supportive care; VA, velmanase alfa

ECD consultation: Company's new base case (2)

Changes in the company's base case that do not oppose committee preferences

Key issues: Base case changes for committee discussion

Parameter	Committee preference at ECM4	Approach used by the company
Starting distributions amongst mobility health states	No comment	Model assumes 75% of people start in WU health state, 25% in WWA state *EAG proposes an alternative distribution*
Starting age of patients treated in model	No comment Previously: 6 for paediatric cohort, 12 for adolescent cohort, 18 for adult cohort	The model assumes that non-adult patients are all aged 6 years *EAG explores an alternative age*

Resolved issues: Base case changes for information

Parameter	Committee preference at ECM4	Approach used by the company
Caregiver disutility	No comment	Company changed values for caregiver disutility, but reverted to previously used values in agreement with EAG
Updating of data values	N/A	The most recent values have been used in the model
Correction of model errors	N/A	EAG identified modelling errors which have been amended by the company

Abbreviations: WWA, walking with assistance; WU, walking unaided

New evidence: AllStripes Study (US and UK)

Retrospective natural history study shows disease progression in children

Figure: mobility journey of an untreated US patient from age [redacted]

Interim data from [redacted] patients ([redacted]% male, median age [redacted] years [IQR [redacted]]) show all have mobility difficulties:

- Most (n=[redacted], [redacted]%) able to walk unaided at one time, but gradually [redacted] ([redacted]%) lost ability to walk unaided
- Of [redacted] patients who used mobility aids, all used a wheelchair; [redacted] used other devices including a lift, crutches, a knee scooter and a walker boot
- The age at which patients lost the ability to walk unaided varied widely, ranging from [redacted] years

Abbreviations: AM, alpha mannosidosis; IQR, interquartile range

New evidence: 2022 Patient and Caregiver Survey (1)

European and UK survey to inform disease progression of people aged ≥ 10*

- Final analysis ongoing, results not available by age
- Descriptive results are available from 51 patients
- Mean age: 24.2 years; 51% males; 26 treated with VA
- Mean age started on VA: 18.9 years; mean duration of treatment: 6 years ([redacted])
- *Age at time of survey – respondents were reporting on historical outcomes so for some this covered a time when < 10 years

Table: VAS scores for walking and pain/discomfort over 10 years by treatment

	Walking VAS Score			Pain or discomfort VAS Score		
Scores: 0 = no issues 10 = worst possible	**Mean** (±SD)	**Median**	**Range**	**Mean** (±SD)	**Median**	**Range**
Untreated						
10 yrs ago (n=16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 yrs ago (n=16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Now (n=16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Velmanase alfa (note: people not on VA for entire duration i.e., for 10 years)						
10 yrs ago (n=24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 yrs ago (n=26)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Now (n=26)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG: Does the survey include patients that are included in other studies? Are patients double counted?

Abbreviations: SD, standard deviation; VA, velmanase alfa; VAS, visual-analogue scale

New evidence: 2022 Patient and Caregiver Survey (2)

Interim results provide evidence of the quality of life impact of patients and carers

- Final results for patient and carer QoL not available yet
- Descriptive results calculated by NICE technical team from 21 patients
- Mean age: [redacted] years
- Mean age started on VA: [redacted] years; mean duration of treatment: [redacted] years ([redacted])
- All entries from carer respondents apart from 1 patient treated with VA

Table: VAS scores for patient and carer QoL over 10 years by treatment

	Patient QoL			Carer QoL		
Scores: 0 = no issues 10 = worst possible	**Mean** (±SD)	**Median**	**Range**	**Mean** (±SD)	**Median**	**Range**
Untreated						
10 yrs ago (n=6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 yrs ago (n=6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Now (n=6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Velmanase alfa (note: people not on VA for entire duration i.e., for 10 years)						
10 yrs ago (n=13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 yrs ago (n=13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Now (n=13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QoL, quality of life; SD, standard deviation; VA, velmanase alfa

New evidence: FDA paediatric efficacy analysis

rhLAMAN-05: new FDA multicomponent analysis

FDA requested analysis of rhLAMAN-05 to identify multicomponent endpoints

Results report OLS and GLS statistics which accounts for correlation among endpoints to form a multi-component endpoint - results in greater power which is useful for heterogenous diseases

For paediatric subjects, the most significant combinations for GLS statistic were:

- ([redacted])
- ([redacted])
- ([redacted], equally)

Correlation between serum oligosaccharides and clinical outcomes

Progressive nature of AM means the efficacy profile of VA may differ in adults and paediatric patients

In rhLAMAN-10, a greater proportion of paediatric patients (aged ≥6) than adults had an improvement in **both** serum oligosaccharides and following outcomes at last observation:

- **3MSCT:** 17 of 19 (89.5%) paediatric patients and 6 of 14 (42.9%) adults
- **6MWT:** 13 of 19 (68.4%) paediatric patients and 7 of 14 (50.0%) adults
- **FVC% predicted:** 12 of 17 (70.6%) paediatric patients and 7 of 12 (58.3%) adults

3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; CHAQ-VAS, childhood Health Assessment Questionnaire - visual-analogue scale; FVC, force vital capacity; GLS, generalised least squares OLS, ordinary least squares; SD, standard deviation; VA, velmanase alfa

New evidence: rhLAMAN-11: integrated analysis (1)

Co-primary endpoints show different results for paediatric and adult patients

- rhLAMAN-11 updates rhLAMAN-10 study and integrates further follow-up data from rhLAMAN-07/-09 trials
- 7 years of additional follow up for 15 patients; follow-up in 2 people increased to up to 12 years
- Mean age at the first dose of VA was 17.1 years, median age was 15 years (range: 6 to 35 years)
- Mean (SD) duration of treatment until last observation for 3MSCT was 6.3 (3.8) years for <18 years

Table: rhLAMAN-10/11: co-primary endpoints by age and timepoint

		Serum oligosaccharides (µmol/L)		3MSCT (steps/min)	
Timepoint	**Change from baseline**	**<18 years n=19**	**≥18 years n=14**	**<18 years n=19**	**≥18 years n=14**
Baseline	Actual value (SD)	7.6 (2.5)	5.9 (1.5)	53.0 (11.8)	54.0 (13.3)
rhLAMAN-10 to last observation (up to 4 years)	Mean change (SD)	-5.3 (3.7)	-3.7 (2.2)	+10.7 (10.3)	+0.6 (8.0)
	Relative mean change (SD), %	-66.6% (36.1)	-57.6% (30.5)	+23.1% (27.3)	+1.1% (17.7)
rhLAMAN-11 to last observation (up to 12 years)	Mean change (SD), range	-4.7 (4.0)	-3.5 (2.1)	+7.7 (10.9) p=0.01 [2.4, 12.9]	-0.9 (8.8) p=0.7 [-6.0, 4.2]
	Relative mean change (SD), range	-56.6% (39.7)	-54.0% (28.3)	+18.2% (27.7) p=0.01 [4.8, 31.5]	-1.3% (18.8) p=0.8 [-12.1, 9.5]

NICE

Abbreviations: 3MSCT, 3-minute stair climb test; SD, standard deviation; VA, velmanase alfa

New evidence: rhLAMAN-11: integrated analysis (2)

Secondary endpoints also show different results for paediatric and adult patients

Table: rhLAMAN-11 and rhLAMAN-10: secondary endpoints by age

Endpoint	Patients (n)	Baseline: mean (SD)	rhLAMAN-11 Change from baseline to LO:		rhLAMAN-10 Change from baseline to LO:	
			mean (SD)	% [SD]	mean (SD)	% [SD]
6MWT (metres)	Paediatric (19)	454.2 (86.3)	+40.1[c] (63.7)	+11.3 [20.3]	+39.1[b] (67.6)	+11.9% [26.6]
	Adult (14)	483.3 (95.6)	-33.2[d] (69.9)	-6.6 [16.6]	+0.3[c] (50.5)	+0.7% [11.6]
Age-adjusted 6MWT (% of predicted)	Paediatric (19)	69.3 (12.4)	0.7 (9.4)*	+2.7 [16.0]	+1.9 (10.6)	+5.4 [22.0]
	Adult (14)	68.6 (11.0)	-3.7 (9.7)*	-5.1 [16.1]	+0.2 (7.5)	+1.1 [1.9]
FVC (L)	Paediatric (17)	2.2 (0.9)	+1.3[a] (0.8)	+78.3 [66.8]	+0.9 (0.7)	+45.9 [39.1]
	Adult (12)	3.2 (1.1)	-0.1[d] (0.3)	-3.7 [11.1]	+0.2 (0.4)	+3.5 [16.3]
Age-adjusted FVC (% of predicted)	Paediatric (17)	79.6% (16.4)	+11.9[b] (16.2)	+17.9 [24.9]	+11.6[b] [15.7]	NR
	Adult (12)	92.5% (19.4)	-6.6[d] (11.6)	-8.4 [13.4]	+3.0[d] [12.4]	NR
EQ-5D-5L	Paediatric (10)	0.70 (0.18)	+0.05 (0.16)	+12.38 (30.47)*	+0.08 (0.14)	NR
	Adult (14)	0.57 (0.14)	+0.01 (0.20)	+4.67 (28.19)*	+0.03 (0.13)	NR
Serum IgG (g/L)	Paediatric (19)	8.7 (6.1)	2.6 (2.4)*	+48.2 [32.7]	+3.2 (1.9)	+51.7 [33.3]
	Adult (14)	8.1 (2.3)	3.8 (1.8)*	+48.7 [25.2]	+2.9 (1.3)	+38.6 [21.6]

NICE a: $p < 0.001$; b: $p < 0.01$; c: $p < 0.05$; d: $p \geq 0.05$; * Source: rhLAMAN-11 report

Abbreviations: 6MWT, 6-minute walk test; FVC, force vital capacity; LO, last observation; SD, standard deviation; VA, velmanase alfa

New evidence: rhLAMAN-11: integrated analysis (3)

CHAQ-DI by age group also show different results for paediatric and adult patients

Table: rhLAMAN-11 and rhLAMAN-10: CHAQ-DI by Age Group

	Age	< 18 years			≥ 18 years		
		n	Mean (SD)	Median (Min; Max)	n	Mean (SD)	Median (Min; Max)
Baseline	Actual value	19	1.22 (0.89)	1.25 (0.0; 2.4)	14	1.55 (0.55)	1.56 (0.6; 2.6)
Last observation rhLAMAN-10	Actual value	19	0.97 (0.62)	0.88 (0.1; 2.0)	14	1.57 (0.58)	1.69 (0.6; 2.4)
	Absolute change	19	-0.24 (0.48)	-0.38 (-1.1; 0.5)	14	-0.02 (0.36)	0.13 (-0.8; 0.6)
	% change	17	-6.82 (57.09)	-17.6 (-80.0; 133.3)	14	-2.94 (24.73)	6.70 (-42.9; 45.5)
Last observation rhLAMAN-11	Duration until LO (yrs)	[redacted]					
	Actual value	[redacted]					
	Absolute change	[redacted]					
	% change	[redacted]					

NOTE: mean % change ([redacted]) shows patients have worsened, whereas median % change ([redacted]) indicates patients have improved

NICE

CHAQ-DI, Childhood Health Assessment Questionnaire – Disability Index; LO, last observation; SD, standard deviation

New evidence: Case reports

Paediatric case reports identified by the company, some with HSCT use

Case report	Treatment	Findings
[redacted] (considered eligible for HSCT)	1 mg/kg VA weekly for 8 weeks	• Significant reduction from baseline in urine and serum oligosaccharides ([redacted] and [redacted] mean reduction respectively) • Reductions observed 2 weeks after treatment initiation • Constant increase of serum alpha mannosidase activity
[redacted]	1 mg/kg VA weekly for 59 weeks with HSCT	• Urine oligosaccharides reduced significantly from [redacted] µmol/mmol creatinine to [redacted] • Patient showed notable improvement in walking ability and stability
[redacted]	1 mg/kg VA weekly for 39 weeks	• [redacted](i.e. in utero) due to a symptomatic older sibling diagnosed with AM and continues on treatment
7-year old female in Italy	1 mg/kg VA weekly for 18 months	• Substantial improvements in hyperactivity, 6MWT, comprehension, verbal expression and hearing loss • Net reduction in respiratory infections (reduced antibiotic use) • No apnoea or night desaturation, no more electrical abnormalities on EEG, improved QoL of the family

Abbreviations: 6MWT, 6-minute walking test; EEG, electroencephalogram; HSCT, haematopoietic stem cell transplant; VA, velmanase alfa

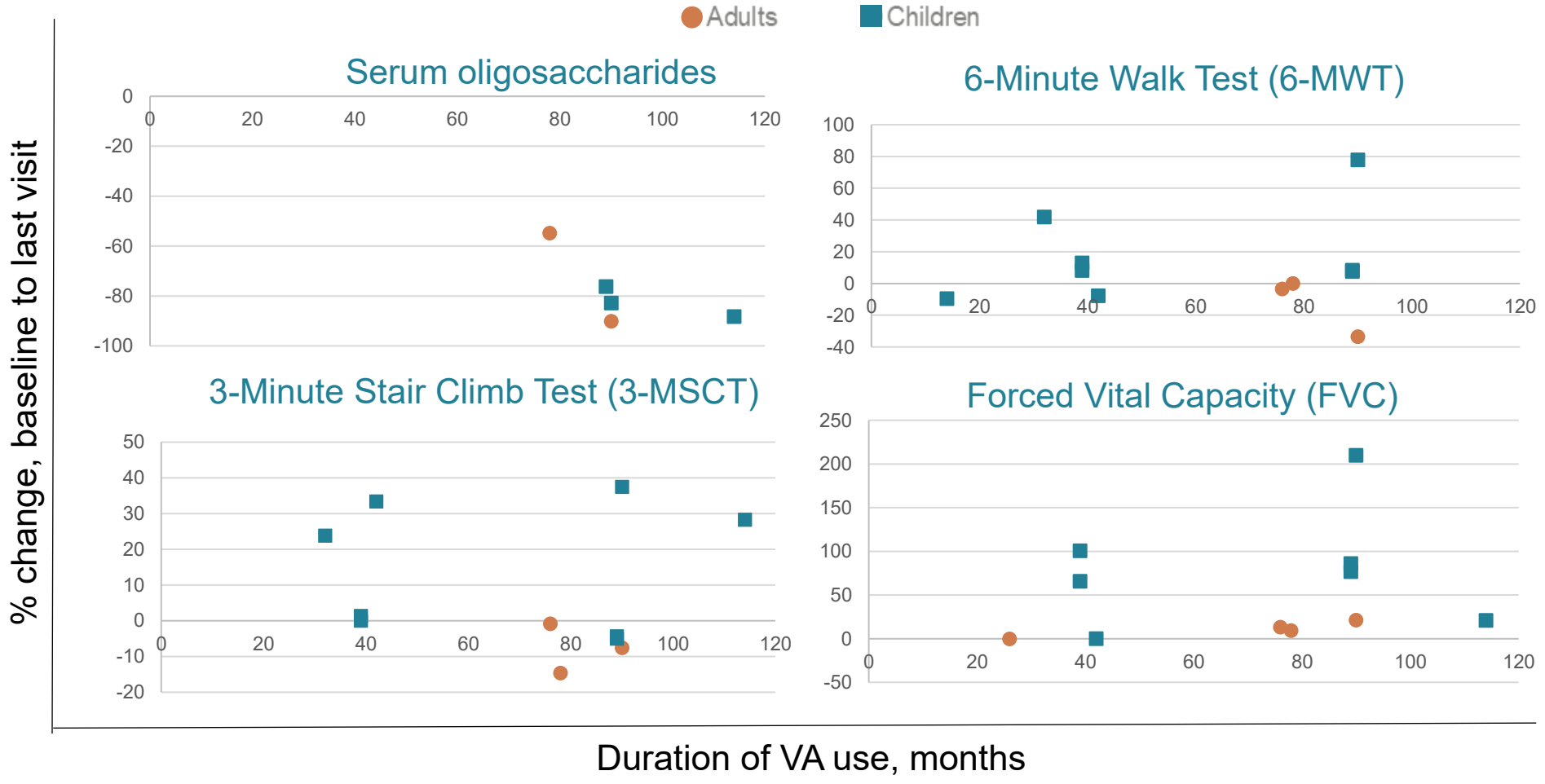
Revisited evidence: Etoile Alpha key results

Data suggests differences in VA's treatment effect in children vs adults

Real-world retrospective registry study (France);
16 patients in 3 cohorts:

- 7 from rhLAMAN-07
- 1 from rhLAMAN-08
- 8 patients in nominative ATU (Autorisation Temporaire d'Utilisation – France's temporary authorisation program)

Note: most patients are already included in rhLAMAN-11 (apart from 4 paediatric patients)



Excludes 2 adults with no results available for any outcomes (20 and 23 months follow up). Change from baseline calculated by technical team

Abbreviations: VA, velmanase alfa

Revisited evidence: rhLAMAN-08 key results

Suggests VA improves mobility and blood parameters in people under 6 years old

Trial details:
Phase 2 paediatric study in 5 patients with AM
< 6 years of age

- **Mobility outcomes after 24 months of VA:**
  - 6-MWT: N=3 had improvements vs. baseline (12%-60%)
  - 3-MSCT: N=2 had improvements vs. baseline (26% and 28%)
- **Results at 40 months (N=1):** improvements of 8% for 6-MWT and 28% for 3-MSCT
- **Treatment emergent adverse events:** most mild or moderate and none resulted in treatment discontinuation
- **Most frequent adverse events:** vomiting (100%), pyrexia (80%), cough (80%), otitis media (80%), nasopharyngitis (60%), rhinitis (60%), diarrhoea (60%)

Laboratory results after 24 months of treatment with VA

Parameter	Change from baseline (N=5) to 24 months		
	N	Actual	%
Mean serum oligosaccharides			
GlcNac(Man)2, µmol/L (SD)	4	-8 (4)	-66
GlcNac(Man)3, µmol/L (SD)	3	-0.6 (0.4)	-33
Mean serum IgG, µmol/L (SD)	4	4 (2)	58

Ig, immunoglobulin; N, number; SD, standard deviation. Source: adapted from company submission, table 8 and page 34.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walking test; SD, standard deviation; VA, velmanase alfa

Revisited evidence: Case reports

Reports of improved physical symptoms, infections and quality of life with VA

Case report	Details	Findings
UK case report (aged 30 at VA treatment, 34 at time of survey)	Treated with VA in rhLAMAN-05, compassionate use continued	• Improve physical symptoms, reduction in joint pain and rate of ear infections, patient-perceived improvement in gait • Health and HRQoL of both the patient and their carers improved • EQ-5D-5L utility value of 0.758 vs 0.378 for other patients in the survey on BSC
Case reports from rhLAMAN-05	2 patients with history of hearing impairment	• Child: experienced 5 episodes of nasopharyngitis and ear discomfort on placebo, no events recorded post-VA treatment • Adult: no infections reported after 12 months of VA treatment • Child achieved (adult approached) decrease in hearing loss of 15 dB
Case reports from Etoile Alpha	16 patients treated with VA in the Etoile Alpha	Many AM clinical manifestations improved or stabilised, such as: • Balance and coordination, muscular weakness, motor skills • Cognitive delay, pain, tiredness, joint abnormalities, infections
Case report series	5 adult patients treated with VA in 3 European centres	• No motor progression, bone pain or difficulty in movement • Improved intellectual ability, communication and socialising • 2 people not required hospitalization in over 7 years, are still able to walk unaided and are not wheelchair-dependent (not expected) • Improved audiometry and ability to “perform usual activities"

Key issue: Mobility improvements

Company challenges committee preference based on new data

Background

- Company's model allows mobility improvements in the VA arm but not in the BSC arm
- Committee concluded that improvements should be allowed in both arms (model has not been changed)

Company

- Both arms now use assumed rate of progression estimated by experts for BSC patients (not VA-specific values), benefit of VA is from:
  - delayed disease progression (next slide)
  - improvement in WC and WWA health states: 20% chance in the initial 2 years, 2.5% afterwards
- Assumed progression rates are validated by rhLAMAN-11 CHAQ-DI improvements, also real-world studies
- Improvement in BSC arm not included in model based on expectations in clinical practice

EAG comments

- No model inputs related to clinical improvement were based on data from clinical studies
- Data values are all estimated from clinical expert opinion which carry considerable uncertainty
- Scenario analysis assuming 10% chance of improvement in BSC arm in first year (based on KoL opinion)

What is the committee's preference for modelling mobility improvements for VA and BSC arms?

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BSC, best supportive care; KoL, key opinion leader; WC, wheelchair dependent; WWA, walking with assistance; VA: velmanase alfa

Key issue: Delayed progression (1)

Company challenges committee preference based on average treatment duration

Background

- Committee preference: 3 years disease progression delay and extended time in health states
- Company's model assumes 6 years disease progression delay and no extended time in health states

Company

- Simplified and conservative 6-year delay in disease progression based on observed effect of VA in children
- Mean treatment duration of children treated with VA in rhLAMAN-11 varies from [redacted] years based on 3MSCT, 6MWT, FVC% predicted, CHAQ-DI and EQ-5D outcomes
- 3 year delay assumption is underestimated as the median treatment duration is 4.5 years
- 6 year delay is conservative as some people have VA for much longer and no effect at 6 years unlikely
- Previously used data on time in health states due to VA not considered due to improvements seen in trial

EAG comments

- Using the mean of the last observation is misleading because the [redacted] people (from 19) have follow-up at or beyond 6 years
- [redacted]
- Median treatment duration is likely a better measure than mean as its less prone to bias from outliers
- Median durations: [redacted] years (3MSCT, 6MWT, CHAQ-DI), [redacted] years (FVC% predicted), [redacted] years (EQ-5D)

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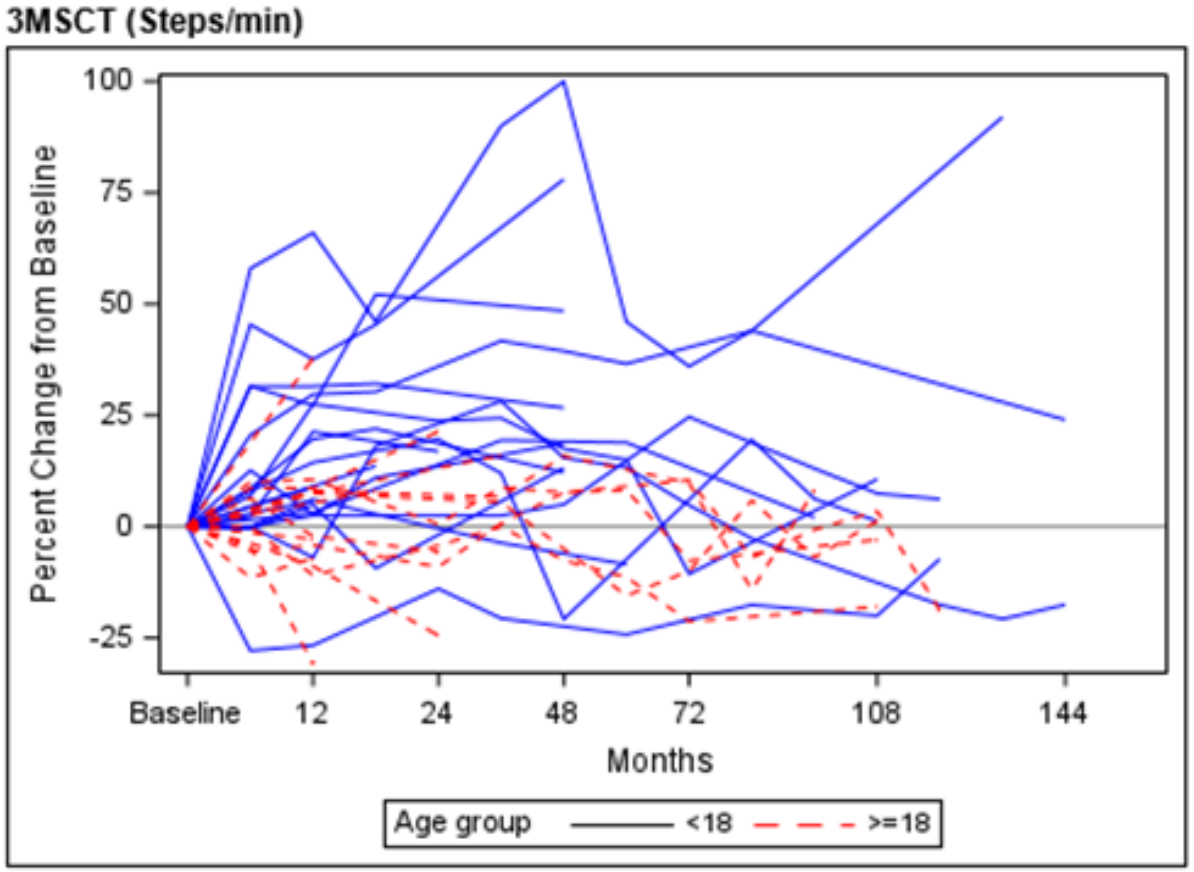
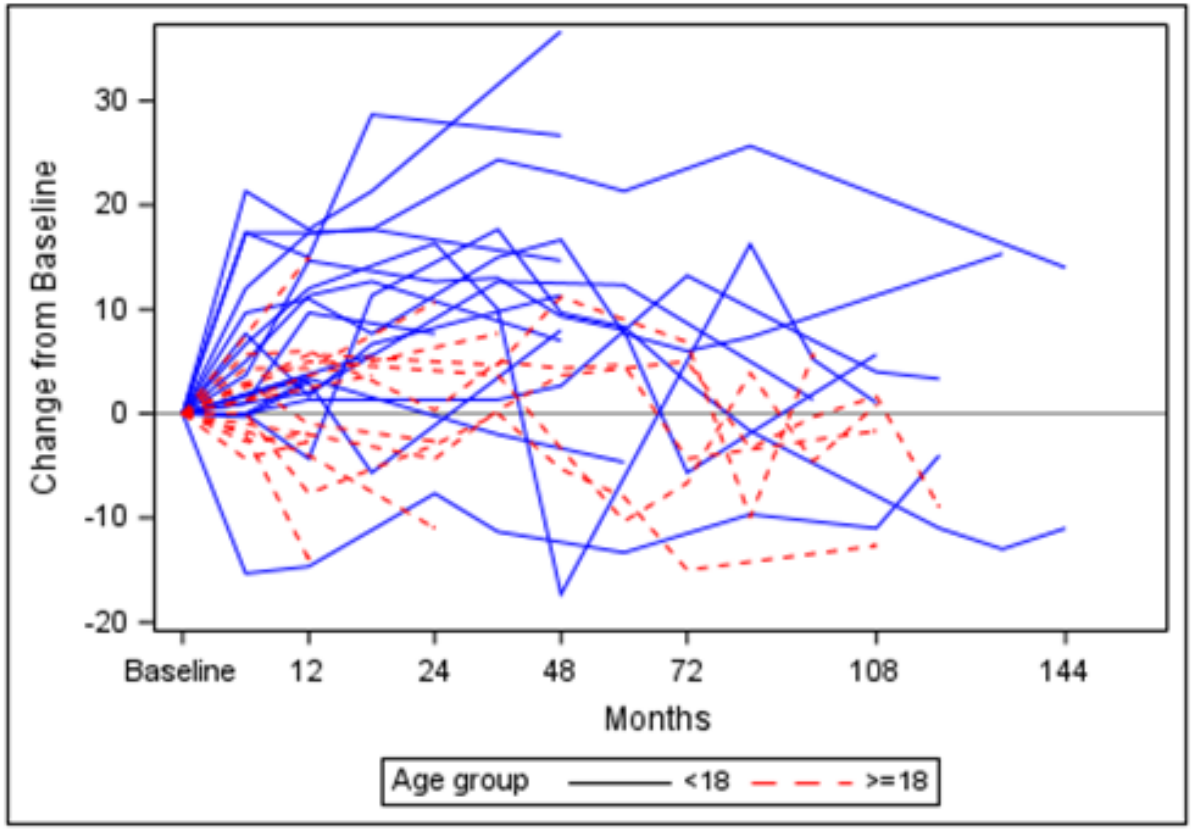
rhLAMAN-11 individual plots of 3MSCT, 6MWT and CHAQ-DI shown on next slides

Key issue: Delayed progression (2)

rhLAMAN-11: Individual plots of 3MSCT over time

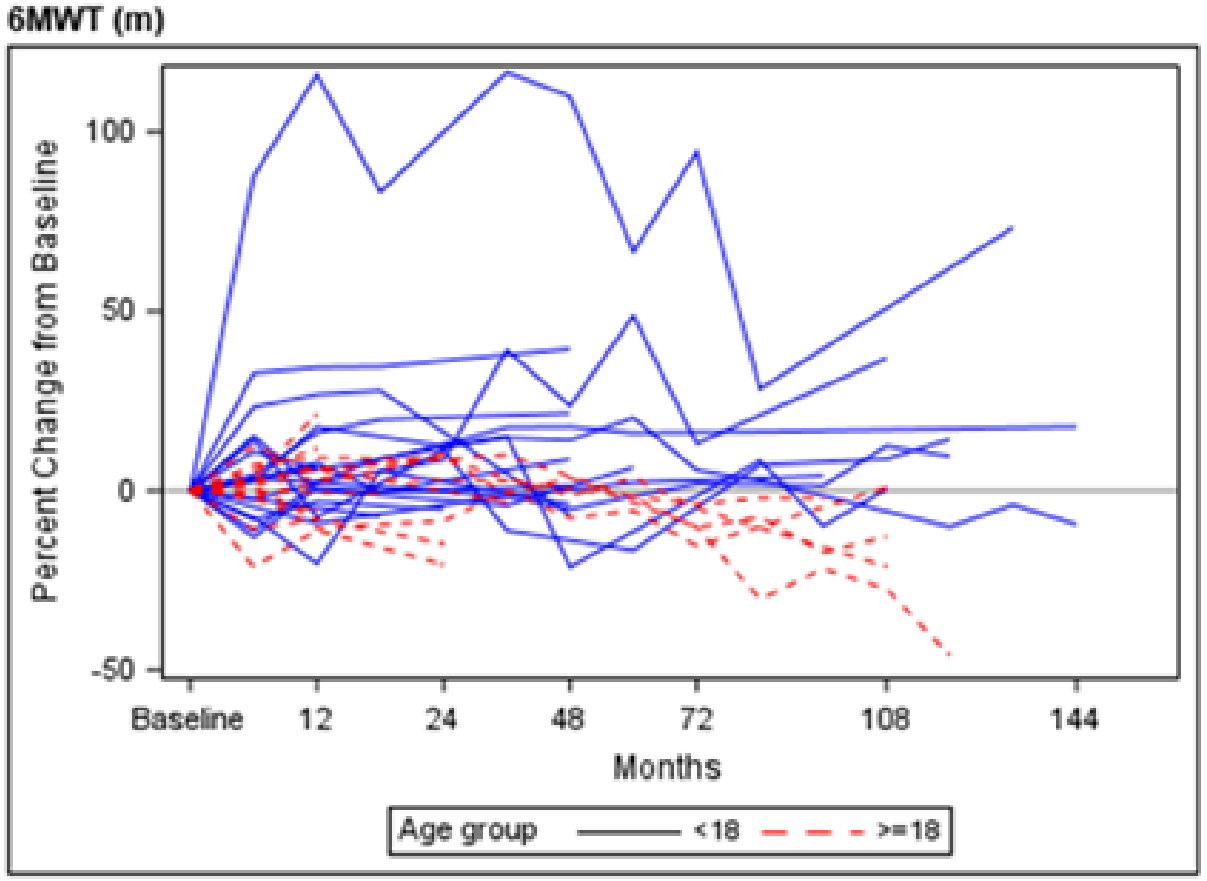


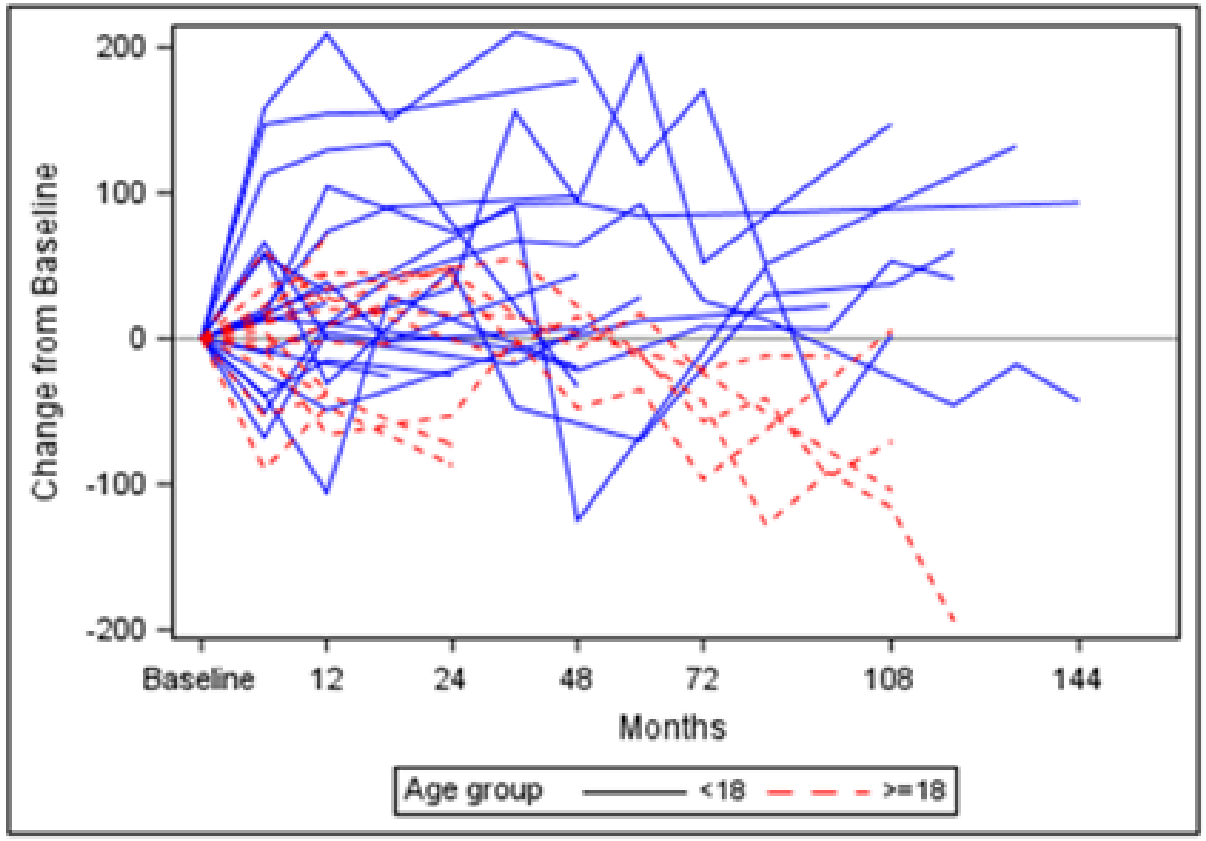


3MSCT, 3-minute stair climb test

Key issue: Delayed progression (3)

rhLAMAN-11: Individual plots of 6MWT over time





6MWT, 6-minute walking test

Key issue: Delayed progression (4)

rhLAMAN-11: Individual plots of CHAQ-DI over time

What is the committee's preference for modelling delayed disease progression for VA?

CHAQ-DI, Childhood Health Assessment Questionnaire – Disability Index

RECAP

Key issue: Utility gains in children (1)

Recap of committee considerations at ECM4

Company resubmission for ECM4:

- Applied additional utility benefit to VA arm to account for aspects of AM not captured in the model such as:
  - improving lung function
  - reducing rates of minor infections and minor surgery
  - reducing rates of psychiatric problems, and improving cognition and mental health
  - improving hearing, upper extremity and fine motor deficits
  - reducing pain and fatigue
  - reducing ventilation dependency
  - providing improvements in the ambulatory health states (walking unassisted, walking with assistance)
  - the possibility that some further benefits of velmanase alfa would appear after several years of treatment.
- Used additional **0.254 utility gain** for children, mapped from functional capacity tests in Etoile Alpha (0.2 utility gain per 1 L of additional FVC; 0.02 utility gain per additional 10 m walked in 6MWT; per HST19)

Committee considerations at ECM4:

- Agreed there may be additional benefits from VA, but exact value uncertain
- Noted large differences from EQ-5D trial data for children; EAG: missing EQ-5D data may not be missing at random and subject to bias
- Company's approach lacked face validity because:
  - physiological measures would improve in people under age 10 due to growth
  - benefit was considerably larger than utility gain from moving between mobility-based health states
  - people whose disease responded to VA in WWA state had similar utility to the general population
- Preferred **0.1 utility gain** for children based on:
  - 0.08 directly observed from rhLAMAN-10
  - within health-state benefits (such as reduced fatigue and pain, improved cognition)
  - benefits not captured in EQ-5D measurements

Abbreviations: 6MWT, 6-minute walking test; FVC, forced vital capacity; VA, velmanase alfa

Key issue: Utility gains in children (2)

Company maintains higher utility benefit based on uncaptured benefits

Committee preference at ECM4

- Committee preference of 0.10 utility benefit for VA in children (company uses 0.18 in latest base case)

Company

- Model keeps increased utility benefit (0.18) based on long-term improvements in age-adjusted lung function observed in children in rhLAMAN-11 and no respiratory infections seen in studies
- Model has no extended time in health states so utility benefit of VA as patients progress is underestimated, also current model does not capture improvements in lung function or minor infections seen in studies
- 0.18 utility benefit based on +0.9L FVC in rhLAMAN-10 at 4 years (HST 19 accepted 0.2 utility gain per 1L)
- Long-term respiratory benefit in rhLAMAN-11 (+1.2L) reduces the ICER further, shown in scenario analyses

EAG comments

- This issue and associated evidence has already been considered by committee at ECM4 (previous slide)
- Absolute gain in lung volume may be confounded by the growth of children with AM
- rhLAMAN-11 data suggests EQ-5D-5L improvement has fallen to [redacted] from 0.083 in rhLAMAN-10 but notes that caution is needed in interpreting these results

What is the committee's preference for utility gains with VA in children?

Abbreviations: FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; VA, velmanase alfa

Key issue: Starting distributions amongst health states

Company and EAG have different approaches to model starting distributions

Background

- Company's model now assumes that 75% of people start in WU health state, 25% in WWA state
- EAG queries these numbers and proposes an alternative distribution

Company

- Acknowledge the starting distribution for people entering the model is uncertain
- Adopt the EAG's scenario analyses

MPS Society: All children known to them were mobile and required no assistance walking at diagnosis

EAG comments

- Distribution of patients in rhLAMAN-10 at baseline: 12 WU, 2 WWA and 2 WC
- Company assumed that patients in WC state could be grouped with patients in WWA health state
- EAG believe that alternative plausible scenario is patients in WC state would not be treated
- When WC state is excluded, distribution would be 86% (12/14) in WU state and 14% (2/14) in WWA state (EAG base case), but also provide scenario analysis with distribution in 3 health states as above
- Scenario analysis assuming people in WC at baseline start in WC health state

What is the likely walking ability of children with AM in NHS practice when starting VA? If VA was available, would those already in wheelchair be eligible?

Abbreviations: WC, wheelchair dependent; WU, walking unaided; WWA, walking with assistance

Key issue: Age of people treated

Uncertainty about starting age of VA is explored in scenario analyses

Background

- Company's model assumes all patients start treatment at age 6 years; EAG proposes alternative starting age

Company

- Updated label of VA covers paediatric patients from birth - as an autosomal recessive disease, there is a 25% chance of siblings being affected, so these patients are likely to be diagnosed at birth
- Zielonka et al. reported median age of diagnosis of 7 years (but patients from 1967-2014 and multiple countries)
- In the UK, age of diagnosis is plausibly lower as diagnostic testing is improving rapidly with the advent of next-generation sequencing and newer gene panels, plus the possibility of newborn screening in the future
- **MPS Society:** All children known to them were diagnosed at mean age of 4 years (range 2 – 5 years)

EAG comments

- Notes age when starting VA is uncertain but agrees it's plausible it is lower than observed in clinical trial
- EAG base case maintains 6 years of age but provides scenario analysis with 8 years of age (average age of patients under 18 years in rhLAMAN-10, as per company's economic model)
- **NICE tech team:** SPARKLE registry (n=59; incl. adults)[a]: mean age at enrolment: 21.9 ± 12.2 (median 20.0 [3.0–51.0]) years; mean age at diagnosis: 8.4 ± 10.5 (median 4.0 [0–50]) years; rhLAMAN-10 mean age at baseline among paediatric patients (n=19): 11.6 ± 3.7 (median 12.0 [6.0-17.0]) years

NICE

What is the mean age at diagnosis/potential start of VA among children with AM in NHS practice?

Abbreviations: VA, velmanase alfa. [a] Source: Muschol et al 2023.

Cost effectiveness results

NICE National Institute for Health and Care Excellence

Cost-effectiveness results

Table: Company base case deterministic ICERs with changes made to derive EAG base case ICERs

Treatment/ EAG scenario	Discounted		Incremental		ICER (£)	
	Costs (£)	QALYs	Costs (£)	QALYs		
VA	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**104,103**	**Company base case**
EAG 1: Delay in progression for VA = 3 years with extended time in health states			[redacted]	[redacted]	127,434	
EAG 2: Utility gain from VA = 0.10			[redacted]	[redacted]	125,240	
EAG 3: Distribution across HSs set to 0.86 for the WU HS and 0.14 for WWA HS			[redacted]	[redacted]	114,974	
EAG 1, EAG 2 and EAG 3			[redacted]	[redacted]	**174,369**	**EAG base case**

EAG: probabilistic ICERs not shared due to model functionality but model was relatively linear and thus the deterministic ICER should be a good indicator of the probabilistic one

Abbreviations: BSC, best supportive care; HS, health state; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VA, velmanase alfa; WU, walking unaided; WWA, walking with assistance

Cost-effectiveness results – company scenario analysis

Scenario	ICER
Company base case	**£104,103**
Time horizon: 50 years	£101,003
No treatment discontinuation for responders until entering 'WC' health state	£220,629
Permanent delay in disease progression in VA responders until treatment discontinuation	£62,977
Treatment is discontinued upon entering the 'WC dependent' health state	£97,898
UK MPS Society health state utilities	£82,398
Include long-term on-treatment respiratory utility benefit from rhLAMAN-11 (+0.256)	£89,719
Exclude carer disutility	£105,202
Include 2.2 caregivers	£103,599
Starting age of 7 based on Zielonka 2019	£112,189
Starting distribution: 75% WU, 12.5% WWA, 12.5% WC (as observed in trial)	£112,432
4-year disease progression delay + extended time in health states	£129,287

Abbreviations: WC, wheelchair dependent; WU, walking unaided; WWA, walking with assistance

Cost-effectiveness results – EAG scenario analysis

Scenario	ICER
EAG base case	**£174,369**
SA1: Improvement allowed for BSC patients for 10% of patients in year 1	£181,853
SA2: Baseline age of patients = 8 years	£198,320
SA3: Assumed delay in disease progression for 4 years with no extended time in HSs	£169,044
SA4: Assumed delay in disease progression for 5 years with no extended time in HSs	£152,553
SA5: Assumed in disease progression for 6 years with no extended time in HSs	£139,862
SA6: Starting distribution: 75% WU, 12.5% WWA, 12.5% WC (as observed in trial)	£167,771
SA7: SA1 and SA2	£206,418
SA8: SA5 and SA7	£167,228

Abbreviations: HS, health state; WC, wheelchair dependent; WU, walking unaided; WWA, walking with assistance

Managed access (1)

Company's managed access proposal

Key uncertainties:

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

Proposed data sources:

- **SPARKLE registry (main source):**
  - Real-world registry with 3 additional years of follow-up (5 years total) will be available by end of 2025
  - 4 sites recruited in England (1 pending in Wales), any new VA patients in England can be recruited
  - **Recruitment update Feb 2023:** total 76 patients (100 expected), 47 were <18 years at time of treatment initiation, 14 paediatric patients treated with VA with a median duration of 248 days (range 1 – 1138 days), 8 were treated less than 1 year
- **All Stripes study:** real-world retrospective study reporting at least 25 untreated patients, including in England (final analysis ongoing)
- **rhLAMAN-11:** up to 12 years of follow-up data available from 33 patients treated long-term with VA (already shared in resubmission)
- **Etoile Alpha:** Real-world retrospective registry study in France with 16 patients (final results shared, relevant for analyses in next slides)

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Abbreviations: HRQoL, health related quality of life; VA, velmanase alpha

NOTE: only 4 paediatric patients not in rhLAMAN-11

Managed access (2)

Company's managed access proposal

Proposed analysis after a period of managed access:

- Data to be collected in SPARKLE: natural functional deterioration, infection rates and length of infections, EQ-5D-5L, CHAQ-DI, CHAQ-VAS for treated and untreated people (interim reports available every Feb)
- An ITC could be done using long-term functional and QoL data from treated patients (rhLAMAN-07/-09, Etoile Alpha and SPARKLE) compared with available data from untreated patients (SPARKLE)
- This ITC could provide evidence for the long-term functional and QoL improvements and delay in disease progression seen in VA patients compared with BSC patients
- Data would also be analysed to inform transition probabilities for untreated patients, infection rates, major surgery and baseline utility values for treated and untreated patients

Comments from Managed Access Team and the EAG:

- **Managed Access Team:** data collection is feasible and could reduce uncertainty, but committee judgement required, the company should explain about data completeness as follow-up assessments not compulsory
- **EAG:** not clear how many patients will provide data on non-adults who are untreated with VA, unclear whether data uncertainties associated with the natural history of the disease and outcomes under BSC will be resolved by the data collection plan, echo above concerns with missing data points

Abbreviations: BSC, best supportive care; CHAQ, childhood health assessment questionnaire; DI, disability index; ITC, indirect treatment comparison; QoL, quality of life; VAS, visual-analogue scale

Managed access (3)

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

Key questions for committee consideration:

- Would an additional 3 years of follow-up data from the SPARKLE registry be sufficient to resolve uncertainty on long-term effectiveness?
- Would committee prefer the proposed ITC of rhLAMAN-07/-09, Etoile Alpha and SPARKLE vs data from untreated patients in SPARKLE (instead of current inputs based on clinical opinion only)?
- Would committee prefer a new model structure following a period of managed access?

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Abbreviations: ITC, indirect treatment comparison

Additional considerations

Considerations for committee in determining cost-effectiveness estimates

Has all newly shared evidence and the totality of evidence been taken into account?

- New evidence, previously considered evidence, clinical and patient expert submissions and case reports

Has the committee considered accepting a higher degree of uncertainty?

- Additional flexibilities may apply for treatments that are innovative, for rare diseases, and for children.
- How does the nature of the condition or technology affect the ability to generate high-quality evidence?
- Has the highest standard of evidence generation that should be expected in the circumstances been achieved?
- Are there strong reasons to suggest that the health benefits of the technology have been inadequately captured and may therefore misrepresent the health utility gained?

Has the committee fully considered the real-world evidence data provided?

- Does the real-world data help to reduce uncertainties and improve guidance?
- Has a clear justification of the need for non-randomised evidence been provided?

Equality considerations

Considerations for committee in its approach to equality issues

Key comments from company on equality considerations:

- Company have self-optimised to paediatric population, with treatment proposed to start only for people <18-year-olds
- Company comments:
    - Guidance may be discriminatory against people with disability (AM) and children
    - Committee may be discriminatory by not considering inherent uncertainties with evidence due to the very small patient population
    - Committee did not consider difficulties in demonstrating cost-effectiveness where there are no recommended treatment options

Committee considerations on equalities issues at ECM4

- Committee noted the following considerations that are standard in the HST methods and processes were reflected in the evidence, economic modelling and in its understanding of the nature of the condition, and taken into account in its decision making:
  - AM affects children
  - AM is serious and debilitating condition that often falls within the provision of the 2010 Equality Act
  - AM population is very small, which poses challenges and disadvantages with collecting appropriate evidence
  - Committee applied greater weight to non-clinical trial evidence
  - Collecting quality of life data in people with disability, cognitive impairment and children is challenging, but is accommodated by the proxy EQ-5D
- Committee fully considered all available evidence including case studies, clinical expert opinion and patient testimony which helped committee consider utility gains that may not be captured by EQ-5D
- Committee considered full range of factors affecting decision-making in the HST programme (nature of the condition, clinical evidence, value for money, impact of the technology beyond direct health benefits)

Have the committee fully considered equality issues and made reasonable adjustments where needed?

Committee preferred assumptions and recommendation

Committee's preferred assumptions/ICERs:	Committee's recommendation
For modelling mobility improvements for VA and BSC arms?	Is the technology recommended for routine commissioning? Is this impacted by any additional flexibilities or uncaptured benefits?
For modelling delayed disease progression for VA?	If not recommended, could key uncertainties be sufficiently resolved during a period of managed access?
For utility gains with VA in children?	• Has company made a feasible managed access proposal? • Are any updates or amendments required to the managed access proposal? • Has committee answered the questions in NICE's feasibility assessment? • What is committee's preferred threshold for managed access? • Which ICERs/assumptions represent committee's lower/upper end of uncertainty?
For starting distributions amongst mobility health states?	
For starting age of patients treated in the model?	
Preferred ICER threshold?	
Preferred ICER or ICER range?	What, if any, are the key remaining uncertainties?

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Thank you.