EE309

Cost-effectiveness Analysis of Velmanase Alfa in Patients with Alpha Mannosidosis from a UK Health Service Perspective

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Introduction

- Alpha mannosidosis (AM) is a rare genetic disorder that affects the body's ability to break down oligosaccharides, causing symptoms including developmental delays, skeletal abnormalities, hearing loss, and recurrent infections.[1,2]
- AM has an estimated prevalence of 1 in 500,000 to 1 in 1,000,000 individuals worldwide. In general, people with AM have a shortened lifespan, with a median age of death of 45 years.[1-3]
- There is no cure for AM, and the standard of care focuses on relieving symptoms and improving patients' quality of life.[1]
- Velmanase alfa (VA) is the first enzyme replacement therapy approved by regulatory agencies in the US, UK, and EMA-regulated countries for the treatment of AM.[4-6]
- In 2023, the National Institute for Health and Care Excellence (NICE) recommended VA for the treatment of non-neurological symptoms related to mild/moderate AM in patients starting treatment at an age <18 years.[7]

Objective

- To update the NICE cost-utility analysis of AM[7] and the model structure with new long-term data from rhLAMAN studies[8-10] to better reflect disease progression and the treatment benefits of VA.

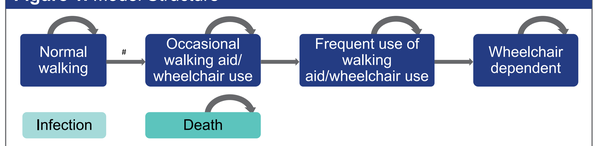
Methods

- The Markov model used in the NICE submission[7] was updated to compare VA with standard of care (symptom control) from a UK National Health System perspective over a lifetime, with annual cycle length and applying 3.5% discount rate on cost and health outcomes.
  - The NICE model[7] comprised four primary health states: walking unassisted, walking with assistance, wheelchair dependent, and severe immobility. Each primary health state was also associated with a "tunnel state" of severe infection, in which patients incurred additional costs, mortality, and disutility associated with a severe infection.
- Patients initiating treatment as adults and those initiating treatment as children (<18 years old) are modeled separately.

Conceptual Framework

- The new VA model was updated to more precisely capture patients' disease progression, such as splitting the "walking with assistance" health state, following suggestions from key opinion leaders and experts in clinical and health economics.[11] The new model structure includes the following health states:
  - The rhLAMAN study data, where patients reported "Yes" or "No" for Childhood Health Assessment Questionnaire (CHAQ) walking aid use (crutches, walking frame, walking stick) or wheelchair use at any timepoints, informed:
    - **Normal walking:** During the past 12 months, patients do not require the use of a walking aid or wheelchair when leaving the house and in their own homes.
    - **Occasional walking aid/wheelchair use:** During the past 12 months, patients require the occasional use of a walking aid or wheelchair.
      - The model allows backward transition as patients improve/transition back from "Occasional walking aid/wheelchair use" to "Normal walking."
    - **Frequent walking aid/wheelchair use:** Patients use a walking aid or wheelchair when they leave the house. Walking aids or a wheelchair may not be needed when patients are in their homes.
    - **Wheelchair dependent:** Patients require the use of a wheelchair when leaving the house and in their own homes.
- The NICE model only accounted for severe infections. In the new VA model, patients can have an infection in any state specified above, defined as:
  - Acute/severe infections are those that require hospitalization (including but not limited to pneumonia and sepsis).
  - Recurrent infections (non-severe) are infections that are managed in primary care (including but not limited to the common cold, gastroenteritis, infections of the urinary tract).
- Within the mobility states, patient descriptors of selected key AM symptoms that impact resource use and/or quality of life were included (**Table 1**), which were derived from structured expert elicitation as well as the long-term data in rhLAMAN-07[9], -09[10] and 10[8] studies.

Figure 1. Model Structure



(backward transition) Patients reported at least once "Yes" then reported "No" at later timepoints for CHAQ walking aid use (crutches, walking frame, walking stick) or wheelchair use

Model Inputs

- Structured expert elicitation was conducted in January 2024 to obtain clinical expert and patient expert advice on model inputs, involving three inherited metabolic disorder (IMD) consultants and one patient expert. The methods are adapted from the "Investigate" (round 1 survey), "Discuss," "Estimate" (round 2 survey), and "Aggregate" structured expert elicitation method as described in Hemming 2017.[11]
- Structured expert elicitation[12] was used to inform disease progression, mortality associated with acute/severe infections, symptom worsening, annual frequencies of healthcare resource use, and inputs related to productivity loss of patients and caregivers. Disease progression inputs were informed by the rhLAMAN-07[9], -09[10] and 10[8] studies (**Table 2**) where available. The model assumes that (non-severe) recurrent infections are not associated with increased mortality.
- Health state utilities will be informed by the results of an ongoing vignette study. Alternative values accounting symptom worsening will be tested in a scenario analysis. The model will account for disutility associated with acute/severe infections, caregiver disutility, and utility improvement associated with VA treatment.
- Healthcare resource use included different specialist visits such as pediatrician, geneticist, orthopedic specialist, physiotherapist/occupational therapist, neuropsychiatrist, respiratory specialist, metabolic clinic, neurologist, speech therapist, pain specialist, and psychologist. The model also considers surgical procedures including grommets bilateral, foot surgery, knee surgery, and hip surgery.
- The model also includes productivity loss of patients and caregivers as well as costs of professional caregivers.

Model Limitations

- The model structure does not directly capture all benefits of VA (including improvement in lung function or pain) as these symptoms are not explicitly modeled as a model health state.
- The efficacy of treatment on other AM symptoms such as pain, lung functions, and developmental delays will be captured through utility improvement.
- While the updated model includes a refined description of the mobility-related health states, defining these states accurately is challenging due to rare and heterogeneous nature of the disease.
- The updated model uses data reported at baseline of rhLAMAN studies[8-10] to inform transition probabilities of the untreated patients due to limited natural history data in AM. This could overestimate the effect of standard of care.
- The most substantial gap in data was seen for the "Frequent walking aid/ wheelchair use" and "Wheelchair bound" health states because the majority of the population studied in the rhLAMAN studies[8-10] fits the description of the first two model states. This gap was addressed by using structured expert elicitation.

Model Inputs (cont'd)

Table 1. Patient Descriptors

		Normal walking**		Occasional walking aid/ wheelchair use**		Frequent walking aid/ wheelchair use *		Wheelchair dependent*	
		Untreated Patients (Baseline Data) Mean (Min-Max)	Treated Patients (Average of Observations) Mean (Min-Max)	Untreated Patients (Baseline Data) Mean (Min-Max)	Treated Patients (Average of Observations) Mean (Min-Max)	Untreated Patients (% Worsening Compared with "Occasional Walking Aid/Wheelchair Use") Mean (Min-Max)	Treated Patients (% Worsening in Symptoms, Compared with "Occasional Walking Aid/Wheelchair Use") Mean (Min-Max)	Untreated Patients (% Worsening Compared with "Occasional Walking Aid/Wheelchair Use")	Treated Patients (% Worsening in Symptoms, Compared with "Occasional Walking Aid/Wheelchair Use") Mean (Min-Max)
Patients who initiate treatment under the age of 18	FVC (% predicted)	80% (50%-120%)	86% (21%-148%)	82% (64%-99%)	95% (64%-116%)	11.2% (2%-20%)	5.7% (2%-10%)	17.8% (3%-40%)	13.3% (5%-30%)
	CHAQ-VAS pain	0.41 (0-1.53)	0.52 (0-2.94)	0.82 (0.6-1.11)	0.91 (0-2.4)	29.3% (28.6%-30%)	13.3% (6.6%-20%)	61.4% (42.9%-80%)	43.2% (26.4%-60%)
	6MWT (m)	445 (180-586)	495 (300-690)	473 (427-537)	471 (403-581)	26.8% (5%-40%)	18.1% (2%-30%)	100%	67.3% (2%-100%)
Patients who initiate treatment over the age of 18	FVC (% predicted)	93% (51%-114%)	94% (35%-125%)	91% (64%-113%)	96% (70%-127%)	10.5% (5%-20%)	5.7% (2%-10%)	14.7% (5%-30%)	11.2% (2%-20%)
	CHAQ-VAS pain	0.77 (0-2.52)	0.73 (0-2.55)	0.77 (0-2.16)	0.99 (0-2.31)	71.4% (40%-102.7%)	16% (2%-30%)	81.4% (60%-102.7%)	31.4% (12.7%-50%)
	6MWT (m)	516 (430-696)	473 (392-588)	416 (183-627)	468 (0-620)	24.6% (10%-50%)	23.9% (5%-50%)	100%	100%

Source: structured expert elicitation
**Source: the rhLAMAN-07, -09 and -10 studies; total sample N of 21 pediatric patients 18/21 classified as Normal walking and 3/21 as Occasional walking aid/ wheelchair use; total sample N of 14 adult patients – 7/14 classified as Normal walking and 7/14 as Occasional walking aid/ wheelchair use.
Abbreviations: 6MWT = 6-minute walk test; CHAQ = Childhood Health Assessment Questionnaire; FVC = forced vital capacity; VAS = visual analogue scale

Table 2. Model Inputs: Transition Probability

	Pediatric Population		Adult Population		
	SoC	VA	SoC	VA	
Forward Transition Probability (annual) [mean]*					
Normal walking	12.1%	11.8%	9.0%	8.6%	Calculated transition probability (annual) is based on time (years) spent in health states reported from structured expert elicitation
Occasional walking aid / wheelchair use	15.1%	11.8%	14.0%	10.7%	
Frequent walking aid / wheelchair use	14.8%	11.8%	9.1%	9.4%	
Wheelchair dependent	-	-	-	-	
Rate of acute/ severe infection (per patient per year) [mean (min-max)]*					
Normal walking	0.83 (0-2)	0.53 (0-2)	0.70 (0-2)	0.37 (0-1)	Structured expert elicitation
Occasional walking aid / wheelchair use	0.83 (0-2)	0.53 (0-2)	0.70 (0-2)	0.37 (0-1)	
Frequent walking aid / wheelchair use	1.00 (0-2)	0.67 (0-2)	0.90 (0-2)	0.40 (0-1)	
Wheelchair dependent	1.33 (1-2)	1.00 (0-2)	1.67 (0-3)	1.00 (0-2)	
Risk of death due to infection (annual): SoC or VA [mean (min-max)]*					
Normal walking	3.9% (0%-5%)	3.9% (0%-5%)	4.0% (0%-5%)	4.0% (0%-5%)	Structured expert elicitation
Occasional walking aid / wheelchair use	3.9% (0%-5%)	3.9% (0%-5%)	4.0% (0%-5%)	4.0% (0%-5%)	
Frequent walking aid / wheelchair use	5.1% (0%-10%)	5.1% (0%-10%)	4.0% (0%-5%)	4.0% (0%-5%)	
Wheelchair dependent	8.6% (0%-20%)	8.6% (0%-20%)	8.3% (1%-20%)	8.3% (1%-20%)	

*N=4 expert responses, mean (min, max)
Abbreviations: SoC = standard of care; VA = Velmanase alfa

Conclusions

- The updated VA cost-effectiveness model better reflects disease progression in patients with AM compared with the previous NICE model[7] due to encompassing more detailed differentiation of mobility health states.
- This updated analysis incorporates long-term data from rhLAMAN studies[8-10] and additional disease descriptors, strengthening the evidence of the cost-effectiveness of VA for all patients with AM.
- Results of the ongoing utility vignette study are expected to accurately estimate health state utilities for the refined health states incorporating mobility and other AM symptoms.
- In addition to the drug treatment costs, the updated VA model is sensitive to health state utilities, caregiver costs, treatment discontinuation, and mortality.

References

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Acknowledgements and Disclosures

ALS, FD, KA, and PD are employees of Chiesi. SC-D, PK, and AB are employees of Evidera, a business unit of PPD, part of Thermo Fisher Scientific. The study and the associated research disseminations are funded by Chiesi.

The poster outline was prepared by Ruth Sharf-Williams. Editorial support and graphic design were provided by Mike Grossi and Shani Berger of Evidera, a business unit of PPD, part of Thermo Fisher Scientific.

Poster Presented at: ISPOR—The Professional Society for Health Economics and Outcomes Research; Atlanta, GA; May 5–8, 2024