5.14 VELMANASE ALFA, Powder for I.V. infusion 10 mg, Lamzede®, CHIESI AUSTRALIA PTY LTD

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for velmanase alfa as an enzyme replacement therapy (ERT) for the treatment of non-neurological manifestations in patients with alpha-mannosidosis (AM).

1.2 Listing was requested on the basis of a cost-utility analysis (CUA) versus best supportive care (BSC).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Treatment of patients with non-neurological manifestations with alpha-mannosidosis
Intervention	Velmanase alfa 1 mg/kg of body weight administered once a week by IV infusion plus BSC
Comparator	BSC based on a needs-based treatment, dealing with symptoms as they arise, for example, walking aids, ventilation support, major and minor surgical interventions.
Outcomes	Primary outcomes: • Change from baseline to month 12 in serum oligosaccharides • Change from baseline to month 12 in 3MSCT • TEAEs Secondary outcomes: • Change from baseline to month 12 in 6MWT • Change from baseline to month 12 in FVC % of predicted normal value • Change from baseline to other visits in QoL using CHAQ and EQ-5D-5L (total score & domain scores)
Clinical claim	Velmanase alfa is superior in terms of efficacy, as assessed by a statistically significant improvement in serum oligosaccharide levels compared with placebo (BSC). Velmanase alfa is associated with some additional AEs compared with placebo and thus has an inferior safety profile. However, with one exception[a], AEs are mild to moderate in severity and no AEs required treatment discontinuation and no TEAE-related deaths were reported.

Source: Table 1.1-2, pp5-6 of the submission.
3MSCT= 3-minute stair climb test; 6MWT = 6-minute walk test; AE = adverse events; BSC = best supportive care; CHAQ = Childhood health assessment questionnaire; EQ-5D-5L = EuroQol-five dimension-five level questionnaire; FVC % = forced vital capacity percentage; IV = intravenous; mg/kg = milligram per kilogram; QoL = quality of life; TEAEs = treatment-emergent adverse events.
[a] One severe serious adverse event of sepsis occurred in the velmanase alfa arm in the pivotal (rhLAMAN-05) trial.

2 Background

2.1 This submission was considered by the PBAC's Drug Utilisation Sub-Committee (DUSC) and Economics Sub-Committee (ESC), hereafter referred to as the Sub-Committees, at a joint meeting.

Registration status

2.2 On 26 March 2025, velmanase alfa was registered on the Australian Register of Therapeutic Goods for the following indication: "enzyme replacement therapy for the treatment of non-central nervous system manifestations in patients with alpha-mannosidosis".

3 Requested listing

3.1 Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VELMANASE ALFA					
velmanase alfa 10 mg injection, 1 vial	Public Hospital: $[redacted] Private Hospital: $[redacted]	~~4~~ *1*	~~4~~ *1*	5	*Lamzede*
velmanase alfa 10 mg injection, 5 vial	Public Hospital: $[redacted] Private Hospital: $[redacted]	~~4~~ *1*	~~20~~ *1*	5	
velmanase alfa 10 mg injection, 10 vial	Public Hospital: $[redacted] Private Hospital: $[redacted]	~~4~~ *1*	~~40~~ *1*	5	

Concept ID	**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒ Medical Practitioners
	Benefit type: ☒ Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Authority type: ☒ *Complex Authority Required (CAR)*
	Prescribing rule level:
	Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)* *Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
	Restriction Summary [new1] / Treatment of Concept: [new1A]
	Episodicity: *[blank]*
	Severity: *[blank]*
	Condition: *Alpha- mannosidosis (AM)*
	Indication: ~~Enzyme replacement therapy for the treatment of non-neurological manifestations in patients with a~~ *Alpha*-mannosidosis (AM)

	~~**Treatment Phase:** Initial and continuing treatment~~
	Clinical criteria:
	Patient must have a confirmed diagnosis of alpha-mannosidosis diagnosed by leukocyte-based assay ~~with or without genetic testing~~
	AND
	Clinical criteria:
	Patient must have non-neurological manifestations of alpha-mannosidosis
	AND
	Clinical criteria:
	The treatment must be given concomitantly with best supportive care for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Treatment criteria:
	~~Must be treated by a specialist medical practitioner experienced in the diagnosis and management of patients with alpha-mannosidase or associated with a metabolic clinic of a recognised hospital in the management of alpha-mannosidase.~~ *Must be treated by a physician with expertise in the diagnosis and management of alpha-mannosidase, OR*
	Must be treated by a physician affiliated with a metabolic clinic or a hospital recognised in the management of alpha-mannosidosis.
	~~**Administrative Advice:**~~ ~~At the time of authority application, medical practitioners must request the appropriate number of vials of appropriate strength(s) to provide sufficient drug, based on the weight of the patient, adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.~~ ~~Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.~~ ***Prescribing Instruction:*** *At the time of authority application, prescribers must request the appropriate number of vials, based on the body weight of the patient, to provide sufficient drug for 4 weeks of treatment, according to the specified dosage in the Therapeutic Goods Administration (TGA) approved Product Information.*
	Prescribing Instruction: *Confirmation of eligibility for treatment with diagnostic reports including leukocyte-based assay, echocardiogram and genetic testing (if applicable) must be documented in the patient's medical records.*
	Prescribing Instruction: *The authority application must be made in writing and must include:* *(1) details of the proposed prescription; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*

3.2 The submission did not propose a Special Pricing Arrangement. The requested ex-manufacturer price per vial was $.

3.3 The requested restriction does not define severity of AM, which may be justified, as both the TGA Delegate's Overview and ACM minutes stated that referencing severity of disease was inappropriate and would limit clinical discretion.

3.4 The requested restriction does not specify an age limit which is consistent with the approved TGA indication. As stated in the TGA Delegates' Overview, AM may present early in life and early treatment may prevent irreversible organ damage. However, the pivotal clinical trial for velmanase alfa (rhLAMAN-05) enrolled patients aged six years and older, and the only study involving younger patients (rhLAMAN-08) included five participants. The Sub-Committees noted patients under 6 years of age are more likely to received haematopoietic stem cell transplants (HSCTs) which are considered curative. The Pre-PBAC Response stated that not all patients will adequately respond to HSCT and, given the high morbidity and mortality risks, stated that HSCT is generally reserved for children aged 6 or younger with severe disease and central nervous system involvement.

3.5 Furthermore, the requested restriction does not define circumstances in which patients may or may not receive HSCT in the population criteria. While the exclusion of HSCT as a comparator was reasonable, as described below in paragraph 5.2, there remains a potential for velmanase alfa to be used in patients as a bridge to HSCT. Evidence supporting the use of velmanase alfa as a bridge therapy to HSCT is limited, with only one case study involving a seven-month-old patient receiving velmanase alfa as supporting therapy whilst awaiting HSCT. The Sub-Committees noted that some young patients may trial treatment with velmanase alfa prior to HSCT. The Pre-PBAC Response acknowledged some young patients may use velmanase alfa in this way but noted there is limited evidence to support use for this purpose.

3.6 Notably, no stopping rule was proposed in the requested restriction. The submission indicated that patients are generally expected to receive velmanase alfa as a lifelong treatment; however, treatment may be discontinued at the discretion of the treating clinician if no clear clinical benefit is observed. The Sub-Committees considered that, due to its administration as an intravenous injection, it was likely that if there was no improvement observed after a period of treatment (2 to 3 years), clinicians would discuss ceasing treatment with the patient.

3.7 As the dosing of velmanase alfa is weight -dependent, i.e., 1 mg/kg of body weight administered once every week by intravenous infusion, dose adjustments are often required, particularly in growing children as their weight (and height) changes. Based on the mean (minimum and maximum) weight of patients for three age groups (<12 years [35.7 kg], 12 years to <18 years [68.4 kg], and ≥18 years [70.8 kg]), the number of vials per dose per month (initial script) and the most appropriate combination of vials with pack sizes of one, five and ten of velmanase alfa were determined by the submission. The Secretariat noted that it might be more appropriate to list a single vial, with the ability to request the required number of vials.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 AM is an ultra-rare and progressive lysosomal storage disorder caused by a deficiency in the lysosomal enzyme, alpha-mannosidase, that leads to the accumulation of mannose-rich oligosaccharides in all tissues leading to cell and tissue dysfunction affecting multiple systems. AM is caused by pathogenic variants in the mannosidase alpha class 2B member 1 (*MAN2B1*) gene and is inherited in an autosomal recessive pattern.

4.2 AM is classified into three phenotypic subtypes (Table 2). Only patients with the most severe phenotype are easily recognisable, because of the extensive neurologic involvement and rapidly progressive course associated with this form of the disease.[1] All other patients show a range of symptom severity across a continuum from mild to moderate that cannot be easily classified into specific phenotypes, with most individuals presenting with a moderate form.[1]

Table 2: Three phenotypic subtypes of alpha-mannosidosis and the prominent signs and symptoms

	Type 1	Type 2	Type 3
Severity	Mild	Moderate	Severe
Age at clinical recognition	> 10 years	≤ 10 years	Early infancy
Progression rate	Very slow	Slow, ataxia development at 20-30 years of age	Rapid, early death from primary CNS involvement or myopathy
Skeletal involvement	No	Yes	Yes
Prominent signs and symptoms	Hearing loss, ataxia, psychiatric disorder, skeletal disorder, intellectual disability	Speech delay, hearing loss, developmental delay, motor disturbances/joint laxity, characteristic facial features, infections, mild hepatosplenomegaly, hernia	Skeletal abnormalities, facial dysmorphia, profound hearing loss, hepatosplenomegaly, marked and progressive deterioration in motor and cognitive function

Source: Table 1.1-3, p7 of the submission.
CNS = central nervous system.

4.3 There is limited data relating to the epidemiology of AM internationally, including in Australia. Chin et al. (2011) estimated the incidence and prevalence of AM in Australia at 0.08 per 100,000 live births, with three new post-natal diagnosis based on 2009-2020 data from the National Referral Laboratory for lysosomal storge disorder. Globally, the incidence of AM is higher, at 1 per 1,231,000 live births, with prevalence ranging from 1 per 500,000 to 1 per 1,000,000. The clinicians consulted by the sponsor identified <500 patients with AM in Australia.

4.4 Hennermann et al. (2022), a global retrospective study of 15 patients, reported a median age of death of 45 years (interquartile range [IQR]; 18-56) and a mean age of death (standard deviation [SD]) of 40 ± 13.2 years. In patients with severe AM, death commonly occurred before the end of the first decade. In those with mild to moderate AM, death typically occurs in middle adulthood (approximately 40 years for those with

[1] Santoro et al., (2024), 'Diagnosis of alpha-Mannosidosis: Practical approaches to reducing diagnostic delays in this ultra-rare disease', *Molecular Genetics and Metabolism*, 142(1): 108444.

moderate disease and 50 years for those with mild disease) years. Infection, including pneumonia, and cancer were the most common cause of death.

4.5 Currently, there are no approved pharmacological therapies for AM in Australia. For most patients, the current treatment approach focuses on symptom management, complication prevention, and optimising quality of life (QoL). This includes walking aids, physiotherapy, infection management (e.g., antibiotics to suppress bacterial infections), ventilation support, general treatment of comorbidities, supportive measures at home and major surgical interventions (e.g., ventriculoperitoneal shunts, cervical spine decompression, joint replacement). The Sub-Committees noted non-neurologic manifestations that clinicians hope to see improvement or stabilisation in include muscle wasting, progressive skeletal dysplasia, hepatosplenomegaly, cataracts/ corneal clouding. The Sub-Committees noted the extent to which these manifestations impact individuals is highly variable.

4.6 Velmanase alfa, a recombinant form of human lysosomal alpha-mannosidase, is a first-generation ERT indicated for the treatment of non-neurological manifestations of AM. Upon administration, velmanase alfa supplements or replaces natural alpha-mannosidase, enabling the breakdown of hybrid and complex high-mannose oligosaccharides in the lysosome. This process reduces the accumulation of mannose-rich oligosaccharides, which is the primary pathological driver of the multi-morbid, life-limiting chronic disease.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The Sub-Committees considered that BSC alone, defined as symptomatic and supportive treatment as described in paragraph 4.5, as the main comparator to velmanase alfa plus BSC to be appropriate.

5.2 The submission excluded HSCT as a comparator, as it is typically targeted towards patients aged six years or younger with potentially reversible central nervous system (CNS) involvement. While no universally accepted criteria exist, the submission stated that HSCT is generally not considered for milder AM cases due to the associated risks of the procedure. The Sub-Committees noted that HSCT is essentially a cure for AM as it corrects the underlying enzyme deficiency in all tissues including the CNS. The Sub-Committee further noted that HSCTs for non-malignant diseases generally have excellent engraftment rates and low graft-versus-host-disease. The Pre-PBAC Response stated that HSCT may not always be feasible and outcomes for patients are variable.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The Sponsor requested a hearing for this item. The clinician discussed the clinical need for effective treatments for alpha-mannosidosis and highlighted that the only treatment option currently available to patients in Australia is a HSCT, which comes with a very high morbidity and mortality risk. The clinician also discussed the how the disease manifests in a multi-systemic way, and that patients face many challenges in terms of skeletal development and mobility, infection risk and organ damage, as well as neurological manifestations including developmental delay and psychiatric disturbance. The clinician stated that whilst velmanase alfa is not likely to address neurological manifestations, the hope for stabilisation and improvements in other clinical symptoms will lead to substantial improvements in quality of life and daily function for patients with this ultra-rare condition. In addition, the clinician stated that it was most appropriate for response to treatment and a decision to terminate treatment to be one of clinical judgement, in consultation with patients and their caregivers.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), and consumer organisation The International Society for Mannosidosis and Related Diseases (ISMRD) via the Consumer Comments facility on the PBS website. The Committee acknowledged the input from the parent of a child with alpha-mannosidosis who highlighted the severe impact of disease on everyday life, the mental and physical impacts of the condition, and stated that current symptomatic treatments had not been effective.

6.3 The PBAC welcomed the input from the ISMRD that highlighted the devastating impact of alpha-mannosidosis, which include intellectual disabilities, skeletal abnormalities, ataxia, muscle weakness, mobility issues, seizures and psychiatric symptoms (amongst others) and highlighted the urgent clinical need for velmanase alfa to be made available to Australian patients. The input highlighted the significant positive effects for patients and their families in Europe and the United States and noted studies and anecdotal reports showing improvements in biochemical markers and patient-relevant outcomes like physical function, mobility, ability to engage in daily activities, immune system function, lung function, behaviour and cognitive function. The input also acknowledged that the necessity of weekly infusions represents a significant commitment for both the patient and their family, but that this requirement is vastly outweighed by the potential benefits. Further, the potential for infusion in the home can significantly reduce the disruption to daily life and allow treatment to be provided in a more comfortable and familiar setting.

Clinical studies

6.4 The submission was based on one head-to-head randomised trial, rhLAMAN-05, that assessed the efficacy and safety of velmanase alfa plus BSC (n=15) compared to placebo (hereafter BSC; n=10).

6.5 Additionally, the submission presented results from single-arm and observational studies to support the longer-term efficacy and safety of velmanase alfa and its impact on the QoL of patients with AM and their caregivers, including: rhLAMAN-08 in paediatric patients aged <6 years, rhLAMAN-10 integrated analysis, rhLAMAN-11, the SPARKLE registry study, the Etoile Alpha study, the AllStripes registry study, the UK Natural History study and the 2022 Patient and Caregiver Survey.

6.6 Details of the studies presented in the submission are provided in Table 3.

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
rhLAMAN-05 (NCT01681953)	A multi-center, double-blind, randomized, Placebo-controlled, parallel group trial, investigating the efficacy and safety of repeated Lamazym treatment of subjects with alpha-mannosidosis	CSR
	Borgwardt L., et al. Efficacy and safety of Velmanase alfa in the treatment of patients with alpha-mannosidosis: results from the core and extension phase analysis of a phase III multicentre, double-blind, randomised, placebo-controlled trial.	Journal of Inherited Metabolic Disease 2018, 41(6):1215-1223
	Hendriksz, C., et al. Velmanase alfa enzyme replacement therapy for alpha-mannosidosis improves patient outcomes over standard of care both in terms of clinically relevant improvement and disease stabilization.	Molecular Genetics and Metabolism, 2020,129(2), S71-S72
	Guffon N., et al. Improvements in endurance, serum immunoglobulin g levels, and quality of life in alpha-mannosidosis patients switching from placebo to velmanase alfa long-term enzyme replacement therapy.	Journal of Inborn Errors of Metabolism and Screening, 2017, 5
rhLAMAN-08 (NCT02998879)	A 24-month Multicenter, Open-label Phase II Trial Investigating the Safety and Efficacy of Repeated velmanase alfa (recombinant human alpha-mannosidase) Treatment in Pediatric Patients below 6 years of age with Alpha-Mannosidosis	CSR
	Guffon N., et al. Long-term safety and efficacy of velmanase alfa treatment in children under 6 years of age with alpha-mannosidosis: A phase 2, open label, multicenter study.	Journal of Inherited Metabolic Disease 2023, 46(4):705-719
rhLAMAN-10 (NCT02478840)	A single center, open label clinical trial investigating the long-term efficacy of rhLAMAN-(recombinant human alpha-mannosidase or Lamazym) treatment in subjects with alpha-mannosidosis who previously participated in Lamazym trials.	CSR
	Lund A.M., et al. Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis.	Journal of Inherited Metabolic Disease 2018, 41(6):1225-1233
	Phillips D., et al. Use of the Bruininks-Oseretsky test of motor proficiency (BOT-2) to assess efficacy of velmanase alfa as enzyme therapy for alpha-mannosidosis.	Molecular Genetics and Metabolism, 2020, 23:100586
	Borgwardt L., et al. Health Related Quality of Life, Disability, and Pain in Alpha Mannosidosis: Long-Term Data of Enzyme Replacement Therapy With Velmanase Alfa (Human Recombinant Alpha Mannosidase).	Journal of Inborn Errors of Metabolism and Screening 2018; 6
	Borgwardt L., et al. Improvement in fine and gross motor proficiency after long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha mannosidase) in alpha-mannosidosis patients.	Molecular Genetics and Metabolism 2017, 1(120), S29-S30

Trial ID	Protocol title/ Publication title	Publication citation
	Borgwardt L., et al. Impact of anti-drug antibodies (ADA) on safety and efficacy of velmanase alfa (human recombinant alpha-mannosidase) long-term enzyme replacement therapy in patients with alpha-mannosidosis.	Journal of Inborn Errors of Metabolism and Screening. 2017, 5
	Harmatz P., et al. Toward establishment of a minimal clinically important difference in the treatment of alpha-mannosidosis: First results from velmanase alfa (human recombinant alpha-mannosidase) development program.	Journal of Inborn Errors of Metabolism and Screening. 2017, 5
	Borgwardt L., et al. Improvement in pulmonary function and serum immunoglobulin G in long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase) in alpha-mannosidosis patients.	Molecular Genetics and Metabolism, 2017: S29.
	Lund, A.M., et al. Long-term enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase) improves mobility in alpha-mannosidosis patients.	Molecular Genetics and Metabolism, 2017, S88-S89.
rhLAMAN-11	A single center, open label clinical trial investigating the long-term efficacy of rhLAMAN (recombinant human alpha-mannosidase Velmanase Alfa) treatment in subjects with alpha-mannosidosis who previously participated in Velmanase Alfa trials.	CSR
	Heron B., et al. Long-term efficacy of velmanase alfa treatment in patients with alpha mannosidosis: updated integrated analysis of data from phase I/II, III, and follow-up clinical trials.	SSEIM; 2023
	Borgwardt L., et al. Enzyme replacement therapy for alpha-mannosidosis: 12 months follow-up of a single centre, randomised, multiple dose study.	Journal of Inherited Metabolic Disease 2013;36(6):1015-1024.
	Harmatz P., et al. Enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase): Novel global treatment response model and outcomes in patients with alpha-mannosidosis.	Molecular Genetics and Metabolism Reports 2018; 124(2):152-160
Observational studies		
Post-authorisation safety study (pass) Interim report	THE ALPHA-MANNOSIDOSIS REGISTRY: A multi-centre, multi-country, non-interventional, prospective cohort, in alpha-mannosidosis patients	CSR
	Hennermann, J.B. et al. The SPARKLE registry: protocol for an international prospective cohort study in patients with alpha-mannosidosis.	Orphanet Journal of Rare Disease 2020, 15, 271.
Etoile Alpha Study	Multi-center, non-comparative, retrospective registry for patients receiving or having received a LAMZEDE therapy in France up to June 2020	CSR
UK Natural History survey	Adam J., et al. Disease progression of alpha-mannosidosis and impact on patients and carers - A UK natural history survey.	Molecular Genetics and Metabolism Reports 2019; 20:100480.
The 2022 Patient and Caregiver Survey	Guffon N et al. Alpha-mannosidosis international caregiver and patient survey: Changes in mobility, pain or discomfort, and patients' self-care over time.	Molecular Genetics and Metabolism Reports; 2024: 107865

Source: Table 2.2-1, pp29-31 of the submission.
ADA = anti-drug antibodies; BOT-2 = Bruininks-Oseretsky test of motor proficiency 2nd edition; CSR = clinical study report; SSEIM = Society for the Study of Inborn Errors of Metabolism; UK = United Kingdom.

6.7 The key features of the velmanase alfa trials are summarised in Table 4. The key features of the observational studies are also presented.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Velmanase alfa versus placebo						
rhLAMAN-05	25 VA: 15 BSC: 10	phase III, MC, DB, R, PBO-controlled, 12 months	Low	Patients aged 5-35 years with AM	Serum oligosaccharides levels, 3MSCT, 6MWT, FVC %, CHAQ, EQ-5D-5L, TEAE	Not used
rhLAMAN-10	33	Pooled data analysis from rhLAMAN-10 data collection study and patients enrolled in rhLAMAN-07 and rhLAMAN-09; up to 48 months of follow-up	High	Patients with AM	Serum oligosaccharides levels, 3MSCT, 6MWT, FVC %, CHAQ, EQ-5D-5L, TEAE	QoL outcomes (CHAQ) to inform transition probabilities
rhLAMAN-11	33	An update of rhLAMAN-10; up to 144 months of follow-up	High	Patients with AM	Serum oligosaccharides levels, 3MSCT, 6MWT, FVC %, CHAQ, EQ-5D-5L	Not used
rhLAMAN-08	5	Phase II, MC, OL 24 months (40 months for 1 patient)	High	Paediatric patients (<6 years) with AM	Serum oligosaccharides levels, 3MSCT, 6MWT, FVC %, PEDI, TEAE	Not used

Source: Table 2.2-3, pp39-40 and Table 2.4-4, p60 of the submission.
3MSCT = 3-minute stair climb test; 6MWT = 6-minute walk test; AM = alpha-mannosidosis; BSC = best supportive care; CHAQ = Childhood Health Assessment Questionnaire; DB = double blind; EQ-5D-5L = EuroQol-five dimension-five level questionnaire; FVC = forced vital capacity; MC = multi-centre; N = total participants in group; OL = open label; OS = overall survival; PBO = placebo; PEDI = Paediatric Evaluation of Disability Inventory; R = randomised; TEAE = treatment-emergent adverse event; VA = velmanase alfa.

6.8 Comparative efficacy was assessed in a placebo-controlled phase III study (rhLAMAN-05; n=25; 12 months). After this, patients continued treatment through after-trial care studies, rhLAMAN-07 (n=13; 144 months follow-up) and rhLAMAN-09 (n=8; 136 months), or via compassionate use (n=20) as per national regulations. The rhLAMAN-10 integrated study (n=33; up to 48 months) combined data from early-phase, phase III, after-trial care, and compassionate use cohorts. rhLAMAN-11 (n=33; up to 144 months) provides an update to rhLAMAN-10, incorporating seven additional years of follow-up from rhLAMAN-07 and rhLAMAN-09. A separate phase II study in paediatric patients under six years (rhLAMAN-08; n=5; 24 months) was also conducted.

6.9 As stated in paragraph 6.4, rhLAMAN-05 is the only comparative study for velmanase alfa compared to BSC. The co-primary efficacy outcomes of the rhLAMAN-05 trial were changes from baseline to Month 12 in serum oligosaccharide levels and 3-minute stair climbing test (3MSCT). The prioritised secondary efficacy outcomes were the changes from baseline to Month 12 in the 6-minute walk test (6MWT) and forced vital capacity percentage (FVC % predicted). Additional secondary efficacy outcomes included in the submission were Childhood Health Assessment Questionnaire (CHAQ) and EuroQol five-dimension five-level questionnaire (EQ-5D-5L).

6.10 The submission highlighted serum oligosaccharide levels as a key biomarker reflecting the cellular level effect of velmanase alfa and as a marker of potential complications of AM. While this was accepted by the National Institute of Care and Excellence (NICE;

HST29, 2023), uncertainty remained regarding the nature and extent of the associated clinical benefits. Based on experience with other lysosomal storage disorders, substrate reduction through ERT may provide clinical benefits; however, outcomes can vary depending on the specific condition and the reversibility of its complications. The correlation between serum oligosaccharide levels and clinical outcomes appeared limited, and the ability to assess surrogacy was constrained by the trial design and small sample size.

6.11 Within the rhLAMAN-05 trial, the demographic and disease characteristics of the patients were generally balanced across the two arms. Notably, the two arms were less balanced in terms of 3MSCT, 6MWT, FVC, CHAQ-Disability Index (DI) score, with a higher proportion of more compromised (lower 3MSCT, 6MWT, FVC, and CHAQ-DI score) patients randomised to the velmanase alfa arm. However, the direction of bias remains unclear, as it is unknown how the higher proportion of severely affected patients in the velmanase alfa arm compared with the BSC arm would affect the efficacy estimates. Compromised patients may have greater potential for improvement, or conversely, may experiences irreversible deterioration due to the disease. The Pre-Sub-Committee Response PSCR agreed that the potential direction of the bias was difficult to quantify but, noting the progressive and irreversible nature of AM, patients with advanced or more severe disease typically accumulate damage that limits their capacity for improvement. As a result, it is unlikely that patients with more severe disease would experience greater benefits from treatment compared to those with milder forms of the condition.

6.12 Minimal clinically important differences (MCID) for the clinical endpoints have not been previously defined for patients with AM. The submission obtained evidence from AM registry (SPARKLE), literature review, and a clinical expert to define de novo MCIDs.

6.13 Outcome measures, such as the 3MSCT, may be too physically demanding for individuals with impaired mobility or balance, limiting their suitability for assessing meaningful clinical change. Although the 6MWT is widely used, its results can be influenced by patient motivation and environmental factors such as space availability. Moreover, in individuals with relatively high baseline function, ceiling effects may prevent detection of small but clinically important improvements.

6.14 The table below summarises the MCID/nominated threshold adopted for each outcome in the submission, along with any limitations identified during the evaluation.

Table 5: Minimal clinically important differences/levels adopted for outcomes in each outcome

Outcome	MCID	Source	Comment
Serum oligosaccharides	≤4 µmol/L	Derived from rhLAMAN-05, in which all patients had pretreatment serum oligosaccharide levels > 4 µmol/L.	While the use of serum oligosaccharides has biological plausibility as a surrogate endpoint, the Sub-Committees noted that the clinical meaningfulness of the nominated threshold of ≤4 µmol/L for patients with AM remains uncertain as it was based on the baseline measure in rhLAMAN-05.
3MSCT	Absolute increase from baseline ≥ 7 steps per min	Based on the MOR-004 study in mucopolysaccharidosis IVA, where a 20% change from a baseline of 27–35 steps/min equated to ~7 steps/min.	An improvement of approximately 7 steps/min may represent a meaningful change in MOR-004 study population; however, its relevance and applicability to patients with higher baseline 3MSCT in rhLAMAN-05 is uncertain.
6MWT	Absolute increase from baseline ≥ 30 m	Derived from late-onset Pompe disease studies, where most showed changes within or above the MCID range of 24–54 m.	While an improvement of more than 30m may represent a meaningful change in Pompe studies, its relevance and applicability to patients with higher baseline 6MWT in rhLAMAN-05 is uncertain.
FVC (% predicted)	Absolute score increase from baseline ≥ 10% of predicted	Based on systemic scleroderma guidelines, which recommend ≥10% change to distinguish true progression from measurement variability.	The chosen MCID may be inappropriate, as baseline values were near normal (85% of predicted), introducing a ceiling effect that limits detection of meaningful improvement.
CHAQ	Absolute score change from baseline ≤ -0.13 in CHAQ-DI and ≤ -0.246 in CHAQ-VAS	Based on the MCID in juvenile arthritis, (Dempster et al., 2001 for CHAQ-DI and Dhanani et al., 2002 for CHAQ-VAS). This was considered applicable given the symptom overlap with AM, including pain, muscle weakness, skeletal abnormalities, and difficulties with activities of daily living.	AM is a more heterogenous disease compared to juvenile arthritis. There is uncertainty regarding the applicability of an MCID given the potential differences in pathophysiology, clinical course, and treatment response.

Source: Table 2.4-6, p 64 of the submission.
AM = alpha-mannosidosis; 3MSCT = 3-Minute Stair Climb Test; 6MWT = 6-Minute Walk Test; CHAQ = Childhood Health Assessment Questionnaire; DI = disability index; FVC = forced vital capacity; MCID = Minimal clinically important differences; VAS = visual analogue scale.

Comparative effectiveness

rhLAMAN-05

6.15 The mean (SD) age at treatment initiation with velmanase alfa was 19.0 (8.8) years. Of the patients, 12 (48%) were under 18 years and 13 (52%) were 18 years or older.

6.16 The results of the change in the co-primary and secondary efficacy outcomes from baseline to Month 12 in rhLAMAN-05 are shown in Table 6.

Table 6: Change from baseline to Month 12 in co-primary and secondary efficacy outcomes in rhLAMAN-05 trial

	Velmanase alfa (N=15)	BSC (N=10)	Adjusted mean difference versus BSC (95% CI)
Co-primary outcomes			
Change from baseline to Month 12 in serum oligosaccharide (µmol/L)			
Baseline mean (SD)	6.8 (1.2)	6.6 (1.9)	-
Adjusted mean absolute change (95% CI)[a]	-5.11 (-5.66, -4.56)	-1.61 (-2.28, -0.94)	**-3.50 (-4.37; -2.62)**
Adjusted mean relative change, % (95% CI)[a]	-77.60 (-81.58, -72.76)	-24.14 (-40.31, -3.59)	**-70.47 (-78.35; -59.72)**
Change from baseline to Month 12 in 3MSCT (steps/minute)			
Baseline mean (SD)	52.9 (11.2)	55.5 (16.0)	-
Adjusted mean absolute change (95% CI)[a]	0.46 (-3.58, 4.50)	-2.16 (-7.12, 2.80)	2.62 (-3.81, 9.05)
Adjusted mean relative change, % (95% CI)[a]	-1.07 (-9.05, 7.61)	-3.97 (-13.38, 6.47)	3.01 (-9.86, 17.72)
Secondary outcomes			
Change from baseline to Month 12 in 6MWT (metres)			
Baseline mean (SD)	459.6 (72.26)	465.7 (140.5)	-
Adjusted mean absolute change (95% CI)[a]	3.74 (-20.32, 27.80)	-3.61 (-33.10, 25.87)	7.35 (-30.76, 45.46)
Adjusted mean relative change, % (95% CI)[a]	0.64 (-4.74, 6.32)	-1.20 (-7.63, 5.68)	1.86 (-6.63, 11.12)
Change from baseline to Month 12 in FVC (% of predicted)			
Baseline mean (SD)	81.67 (20.66)	90.44 (10.39)	-
Adjusted mean absolute change (95% CI)[a]	8.20 (1.79, 14.63)	2.30 (-6.19, 10.79)	5.91 (-4.78, 16.60)
Adjusted mean relative change, % (95% CI)[a]	10.11 (1.31, 19.67)	1.58 (-9.48, 13.99)	8.40 (-6.06, 25.08)

Source: Table 2.5-1, p74, Table 2.5-3, p77, Table 2.5-5, p80, and Table 2.5-7, p83 of the submission.
3MSCT = 3-minute stair climb test; 6MWT = 6-minute walk test; BSC = best supportive care; CI = confidence interval; FVC = forced vital capacity; N = total participants in group; SD = standard deviation.
[a] Adjusted for baseline and age
Bold indicates statistical significance.

6.17 In the velmanase alfa arm, mean serum oligosaccharide levels decreased from 6.8 µmol/L at baseline to 1.6 µmol/L at Month 12, thereby reducing to below the nominated threshold of ≤4 µmol/L at Month 12. For patients in the BSC arm, the serum oligosaccharide levels decreased from 6.6 µmol/L at baseline to 5.1 µmol/L at Month 12, thus, not reducing below the nominated threshold.

6.18 After 12 months of treatment, there was a significant decrease (improvement) in the objective outcome, serum oligosaccharide levels in patients treated with velmanase alfa versus BSC. However, this should be interpreted with caution due to the small sample size.

6.19 Responder analysis for change in serum oligosaccharide ≥70% reduction from baseline, showed a higher proportion of responders in the velmanase alfa arm compared to BSC (87% vs 0%; p <0.0001). Furthermore, *post hoc* analyses showed a greater reduction in serum oligosaccharide levels with velmanase alfa compared to BSC in the paediatric subgroup (-5.2 vs -0.8 µmol/L) than in the adult subgroup (-5.1 vs -2.4 µmol/L).

6.20 Although a numerical improvement was observed in velmanase alfa arm, there was no statistically significant difference between velmanase alfa and BSC in 3MSCT, 6MWT, or FVC (% predicted) outcomes. The submission stated that the ability to detect a statistically significant treatment was limited by the small patient numbers,

which reduced the statistical power of study, and heterogeneity in AM disease phenotype, severity, and progression. No outcomes exceeded their respective MCID thresholds either in velmanase alfa or BSC arm.

6.21 The proportion of responders, defined as ≥10% increase from baseline, was higher in velmanase alfa arm compared to BSC arm for 3MSCT (27% vs 10%), 6MWT (13% vs. 10%), and FVC (% predicted; 50% vs. 22%). Similarly, the results of the *post hoc* analyses showed that velmanase alfa compared to BSC may be more beneficial in paediatric subgroup than in the adult subgroup.

6.22 Table 7 summarises the change from baseline to Month 12 in the patient reported outcomes of CHAQ and EQ-5D-5L scores in the rhLAMAN-05 trial. Notably, CHAQ was administered to both paediatric and adult patients. Although CHAQ is a validated instrument for assessing functional ability in paediatric populations, its use in adults is not established. As such, interpretation of CHAQ results in adult patients should be approached with caution.

Table 7: Change from baseline to Month 12 in CHAQ and EQ-5D-5L scores in rhLAMAN-05 trial

		Velmanase alfa (N=15)	BSC (N=10)
Change from baseline to Month 12 in CHAQ-DI score			
Mean (SD) (score)	Baseline	1.37 (0.82)	1.59 (0.64)
	Month 12	1.36 (0.76)	1.76 (0.50)
Absolute change (score)	Mean (SD)	-0.01 (0.32)	0.18 (0.36)
Change from baseline to Month 12 in CHAQ - VAS Pain score			
Mean (SD) (score)	Baseline	0.84 (0.86)	0.40 (0.56)
	Month 12	0.97 (1.02)	0.50 (0.62)
Absolute change (score)	Mean (SD)	0.19 (0.69; n=14)	0.15 (0.71; n=9)
Change from baseline to Month 12 in CHAQ - General (VAS) score			
Mean (SD) (score)	Baseline	1.00 (0.83)	1.02 (0.80)
	Month 12	1.46 (0.62)	1.46 (0.61)
Absolute change (score)	Mean (SD)	0.51 (0.93; n=14)	0.44 (0.62)
Change from baseline to Month 12 in EQ-5D-5L index score			
Mean (SD) (score)	Baseline	0.61 (0.19)	0.61 (0.18)
	Month 12	0.64 (0.18)	0.62 (0.15)
Absolute change (score)	Mean (SD)	0.04 (0.09, n=14)	0.03 (0.16, n=8)
Change from baseline to Month 12 in EQ-5D-5L VAS score			
Mean (SD) (score)	Baseline	66.07 (20.68)	64.00 (12.87)
	Month 12	68.20 (17.34)	67.70 (16.62)
Absolute change (score)	Mean (SD)	2.00 (17.95; n=14)	3.70 (15.71)

Source: Table 2.5-9, pp87-88 of the submission. Table 14.2.1.41, p226 of the CSE for rhLAMAN-05 (Attachment 7 to the submission).
CHAQ = Childhood Health Assessment Questionnaire; CI = confidence interval; DI = disability index; EQ-5D-5L = EuroQol-five dimension-five level questionnaire; N = total participants in group; n = number of participants reporting data; SD = standard deviation; VAS = visual analogue scale.

6.23 Overall, there was an increase (worsening) in CHAQ-DI score in BSC arm whereas the score remained stable in the velmanase alfa arm. CHAQ-pain scores and CHAQ-general, assessed via visual analogue scale (VAS), increased (worsened) over 12 months in both treatment arms. The change in CHAQ-DI and CHAQ-pain (VAS) score from baseline to Month 12 for patients in velmanase alfa treated arm (and the BSC

arm) did not exceed the adopted MCID for patients with AM, which was a reduction in CHAQ-DI score of ≥0.13 and CHAQ-pain (VAS) score of ≥0.246.

6.24 A minimal change was observed in the EQ-5D-5L Index scores; however, EQ-5D-5L VAS scores increased (improved) in both treatment arms over 12 months.

rhLAMAN-10 integrated analysis and rhLAMAN-11

6.25 Patients in the rhLAMAN-10 study were previously enrolled in rhLAMAN-02 (9 patients; 27.3%) and rhLAMAN-05 (24 patients, 72.7%). The mean (SD) age at treatment initiation with velmanase alfa was 17.1 (7.8) years. Of the patients, 19 (58%) were under 18 years and 14 (42%) were 18 years or older. The rhLAMAN-11 trial (N=33) was an update of the rhLAMAN-10 study.

6.26 The results of the change in efficacy outcomes from baseline to last observation in rhLAMAN-10 integrated analysis and rhLAMAN-11 trials are shown in Table 8.

Table 8: Change in outcomes from baseline to last observation in rhLAMAN-10 trial integrated analysis

	Baseline value	rhLAMAN-10 (Last observation [up to 48 months])			rhLAMAN-11 (Last observation [up to a maximum of 144 months])		
		Actual value	Absolute change from baseline	% change from baseline	Actual value	Absolute change from baseline	% change from baseline
Change in serum oligosaccharides (µmol/L) from baseline to last observation							
N	33	33	33	33	33	33	33
Mean (SD)	6.90 (2.30)	2.31 (2.19)	**-4.59 (3.23)**	**-62.76 (33.61)**	2.74 (2.22)	**-4.16 (3.33)**	**-55.5 (34.87)**
Median (min, max)	7.00 (2.3; 15.0)	1.70 (0.5, 12.5)	-5.00 (-13.3, 4.40)	-75.00 (-91.8, 54.3)	2.10 (0.9, 12.5)	-4.60 (-13.3, 4.4)	-69.0 (-91.8, 54.3)
Change in 3MSCT (steps/min) from baseline to last observation							
N	33	33	33	33	33	33	33
Mean (SD)	53.60 (12.53)	59.98 (16.29)	**6.38 (10.54)**	**13.77 (25.83)**	57.64 (14.80)	**4.05 (10.82)**	**9.9 (25.85)**
Median (min, max)	55.00 (16.67, 83.33)	60.67 (31.33, 99.67)	5.67 (-14.00, 36.67)	12.14 (-30.88, 100.0)	57.00 (31.33, 84.38)	3.667 (-14.0, 36.67)	8.0 (-30.9, 92.00)
Change in 6MWT (metres) from baseline to last observation							
N	33	33	33	33	33	33	33
Mean (SD)	466.6 (90.1)	489.0 (85.7)	22.4 (63.2)	7.1 (22.0)	475.6 (98.2)	9.0 (74.9)	3.7 (20.6)
Median (min, max)	454.0 (180, 690)	468.0 (335, 659)	24.0 (-87, 198)	5.9 (-21, 110)	468.0 (228, 652)	5.0 (-194, 177)	0.8 (-46, 73)
Change in FVC (% predicted) from baseline to last observation							
N	29	31	29	29	32	29	29
Mean (SD)	84.9 (18.6)	93.1 (21.7)	**8.1 (14.8)**	**10.5 (20.9)**	89.1 (20.1)	4.2 (16.9)	7.0 (24.5)
Median (min, max)	91.0 (50, 119)	95.0 (35, 130)	7.0 (-17, 43)	7.2 (-31, 62)	90.5 (35, 125)	5.0 (-24, 43)	4.8 (-31, 64)

Source: Table 2.5-10, pp89-90, Table 2.5-11, p90, Table 2.5-15, p93 and Table 2.5-16, p93 of the submission.
3MSCT = 3-Minute Stair Climb Test; 6MWT = 6-Minute Walk Test; CI = confidence interval; FAS = full analysis set; FVC = forced vital capacity; min = minimum; max = maximum; n = number of participants reporting data; SD = standard deviation.
Bold indicates a statistically significant change from baseline at the last observation.

6.27 In rhLAMAN-10, there was a statistically significant improvement in the absolute and percentage change from baseline to the last observation (up to 48 months) of -4.59 (SD 3.23) µmol/L and -62.76% (SD 33.61%), respectively. The improvement was

sustained in all patients through the last observation (up to a maximum of 144 months) in rhLAMAN-11.

6.28 In both rhLAMAN-10 and rhLAMAN-11, a statistically significant improvement in 3MSCT was observed from baseline to the last observation. In contrast, no statistically significant change was observed in 6MWT over the same period. A modest improvement in FVC (% predicted) was observed from baseline to the last observation in both rhLAMAN-10 and rhLAMAN-11. While the change was statistically significant in rhLAMAN-10, it did not reach statistical significance in rhLAMAN-11.

6.29 Table 9 summarises the change from baseline to last observation in CHAQ and EQ-5D-5L scores in the rhLAMAN-10 and rhLAMAN-11 trial.

Table 9: Change in QoL outcomes from baseline to last observation in rhLAMAN-10 integrated analysis

N=33	Baseline value	rhLAMAN-10 (Last observation [up to 48 months])			rhLAMAN-11 (Last observation [up to a maximum of 144 months])		
		Actual value	Absolute change from baseline	% change from baseline	Actual value	Absolute change from baseline	% change from baseline
Change in CHAQ-DI score from baseline to last observation							
N	33	33	33	31	33	33	31
Mean (SD)	1.36 (0.77)	1.23 (0.66)	-0.13 (0.44)	-2.41 (45.03)	1.34 (0.69)	-0.02 (0.61)	15.68 (80.88)
Median (min, max)	1.50 (0.0, 2.6)	1.25 (0.1, 2.4)	0.00 (-1.1, 0.6)	-2.41 (-80.0, 133.3)	1.33 (0.1, 2.6)	0.00 (-1.0, 1.4)	-5.56 (-80.0, 266.7)
Change in CHAQ-Pain score (VAS) from baseline to last observation							
N	32	33	32	21	33	32	21
Mean (SD)	0.62 (0.73)	0.43 (0.62)	-0.17 (0.647)	-17.0 (109.8)	0.67 (0.764)	0.07 (0.80)	72.32 (212.9)
Median (min, max)	0.47 (0.00, 2.52)	0.18 (0.00, 2.55)	0.02 (-1.83, 1.59)	-44.2 (-100, 400.0)	0.33 (0.00, 2.55)	0.045 (-1.83, 1.62)	9.52 (-100, 766.7)
Change in CHAQ general score (VAS) from baseline to last observation							
N	32	33	32	27	NR	NR	NR
Mean (SD)	1.05 (0.77)	0.95 (0.72)	-0.07 (0.62)	10.36 (73.63)	NR	NR	NR
Median (min, max)	1.05 (0.00, 2.55)	0.84 (0.00, 2.58)	0.00 (-1.20, 1.20)	-12.7 (-100, 237.5)	NR	NR	NR
Change in EQ-5D-5L Health Index score from baseline to last observation							
N	24	24	24	24	24	24	24
Mean (SD)	0.62 (0.17)	0.67 (0.17)	**0.05 (0.14)**	**11.23 (24.72)**	0.65 (0.18)	0.03 (0.18)	7.88 (28.77)
Median (min, max)	0.61 (0.27, 1.00)	0.65 (0.28,1.00)	0.02 (-0.26, 0.30)	5.24 (-31.4, 67.87)	0.65 (0.24, 1.00)	0.01 (-0.59, 0.30)	2.80 (-71.1, 67.87)

Source: Table 2.5-12, p91, Table 2.5-13, p92, Table 2.5-17, p94 of the submission.
CHAQ = Childhood Health Assessment Questionnaire; CI =confidence interval; DI = disability index; EQ-5D-5L = EuroQol-5 Dimension-5 Level; FAS = full analysis set; min = minimum; max = maximum; N = total participants in group; n = number of participants reporting data; NR = not reported; SD = standard deviation; VAS = visual analogue scale.
Bold indicates a statistically significant change from baseline at the last observation.

6.30 In rhLAMAN-10, only minimal improvements were observed in CHAQ-DI, CHAQ-pain VAS, and CHAQ-general VAS scores from baseline to last observation, while the change in EQ-5D-5L score was statistically significant.

6.31 Notably, ten patients (33%; five paediatric patients and five adult patients) required walking assistance at baseline. At last observation, seven patients (four paediatric patients and three adult patients) became assistance independent, including three

who had initially used wheelchairs but no longer required mobility aids following treatment. However, two paediatric patients and one adult patient who did not require assistance at baseline required walking assistance at last observation.

6.32 In rhLAMAN-11, no change was seen in CHAQ-DI, CHAQ-pain, or EQ-5D-5L scores from baseline, though CHAQ-DI scores showed considerable variability. Additionally, percentage change in pain score could not be calculated for 11 patients who reported zero pain at baseline.

6.33 Furthermore, *post hoc* subgroup analyses by age in both rhLAMAN-10 and rhLAMAN-11 suggested that velmanase alfa treatment provided greater benefit in paediatric patients compared to adults.

Post-hoc multi-domain responder analysis

6.34 The submission developed a Global Treatment Response (GTR) model to assess treatment efficacy in a heterogeneous AM population. Key outcomes from rhLAMAN-05 and rhLAMAN-10 were grouped into three domains reflecting disease pathophysiology: pharmacodynamic (serum oligosaccharides), functional (3-MSCT, 6-MWT, FVC [% predicted]), and QoL (CHAQ-disability, CHAQ-pain [VAS]).

6.35 In the GTR model, a patient was defined as a responder if they achieved the MCID, as detailed in Table 5, in the key biomarker (i.e., serum oligosaccharides) and in at least one clinically relevant outcome within at least one clinical domain. The results of the multi-domain responder analysis are presented in the table below.

Table 10: Results of multi-domain responder analysis for rhLAMAN-05 and rhLAMAN-10 studies

Domain	Criterion	rhLAMAN-05 trial (N=25) Month 12		rhLAMAN-10 study (N=33) Last observation
		BSC (N=10); n (%)	Velmanase alfa (N=15); n (%)	Velmanase Alfa (N=33); n (%)
Pharmacodynamic	Oligosaccharides	2 (20.0%)	15 (100.0%)	30 (91.0%)
Pharmacodynamic domain response	Oligosaccharides	2 (20.0%)	15 (100.0%)	30 (91.0%)
Functional	3MSCT	1 (10.0%)	3 (20.0%)	16 (48.5%)
	6MWT	1 (10.0%)	3 (20.0%)	16 (48.5%)
	FVC (% predicted)	2 (20.0%)	5 (33.3%)	13 (39.4%)
Functional domain response	Combined	3 (30.0%)	9 (60.0%)	24 (72.7%)
Quality of Life	CHAQ-DI	2 (20.0%)	3 (20.0%)	14 (42.2%)
	CHAQ-VAS	4 (40.0%)	5 (33.3%)	15 (45.5%)
QoL domain	Combined	4 (40.0%)	6 (40.0%)	22 (66.7%)
Overall response	Responder (≥ 2 domains)	30.0%	86.6%	87.9%
	Three domains	0.0%	13.3%	45.5%
	Two domains	30.0%	73.3%	42.4%
	One domain	30.0%	13.3%	9.1%
	No domains	40.0%	0.0%	3.0%

Source: Table 2.6-19, p130 of the submission.

3MSCT = 3-Minute Stair Climb Test; 6MWT = 6-Minute Walk Test; BSC = best supportive care; CHAQ = Childhood Health Assessment Questionnaire; DI = disability index; FVC = forced vital capacity; n = number of participants reporting data; N = total participants in group; QoL = quality of life; VAS = visual analogue scale.

6.36 In rhLAMAN-05, a GTR (defined by response to ≥ two domains) was achieved by 87% of patients in the velmanase alfa arm compared to 30% in the BSC arm after 12 months of treatment. Following long-term treatment (up to 48 months) with velmanase alfa in the rhLAMAN-10 integrated analysis, 88% of patients achieved GTR. Based on the subgroup analyses, 100% of paediatric patients and 71% of adult patients achieved GTR at last observation in rhLAMAN-10 study. The submission stated that the higher proportion of three-domain responders at the last observation in rhLAMAN-10 compared to rhLAMAN-05 may reflect the benefits of long-term treatment with velmanase alfa.

6.37 The GTR model was developed as a multiple variable responder analysis by the sponsor. However, the GTR model has several notable limitations, including its *post hoc* application to the clinical study, the lack of age normalisation for certain outcomes (serum oligosaccharides, 3MSCT, and 6MWT), the absence of validated MCIDs for the outcomes in AM patients, and the small population size.

Patients switching from placebo to velmanase alfa

6.38 A *post hoc* analysis was conducted to assess the treatment response in patients who transitioned from BSC (received during rhLAMAN-05) to velmanase alfa upon entering the after-trial studies (rhLAMAN-07 or rhLAMAN-09) or the compassionate use program. Patients who switched to velmanase alfa showed improvements compared to baseline, with changes observed in 3MSCT (-4% to 9%) and 6MWT (-1% to 2%). Additionally, a reduction (improvement) was seen in mean CHAQ-DI scores (1.56 to 1.43) and CHAQ-pain (VAS) scores (0.42 to 0.36). Notably, the analysis was based on only nine patients at last observation (12 to 18 months of active treatment), limiting robustness of the findings.

rhLAMAN-08

6.39 rhLAMAN-08 was a phase II, multi-centre, open-label, single arm study of 24-month duration (40 months for one patient) that evaluated the pharmacokinetics, safety, and efficacy of velmanase alfa in paediatric patients aged under six years. The study enrolled five patients with a mean age of 4.5 years (range: 3.7 to 5.9 years).

6.40 The mean absolute (percentage) change in serum oligosaccharides was -61% at 6 months, -72% at 12 months, -79% at 18 months and -66% at 24 months. After 24 months of treatment with velmanase alfa, 6MWT improved for three patients, decreased for one patient and could not be obtained from one patient. At the same timepoint, the 3MSCT improved for two patients, decreased for two patients and could not be obtained from one patient. QoL questionnaires administered to parents tended to show improvements in all domains, which included self-care, mobility and social function.

Long-term benefits of velmanase alfa

6.41 The results of single arm trial (rhLAMAN-10 and rhLAMAN-11) and observational studies (the Etoile Alpha study, The Alpha Mannosidosis Registry, the UK Natural History study and the 2022 Patient and Caregiver Survey) supported the long-term effectiveness of velmanase alfa in managing non-neurological symptoms of AM. However, as the studies were limited by their small sample sizes, absence of control groups, inconsistent assessment timepoints and missing data, the results should be interpreted with caution.

Comparative harms

6.42 Summary of safety profile of velmanase alfa in rhLAMAN-5 and rhLAMAN-10 are presented in Table 11. Only the rhLAMAN-05 trial provided the comparative safety profile of velmanase alfa versus BSC.

Table 11: Overall summary of adverse events in rhLAMAN-05 and rhLAMAN-10 trials

	rhLAMAN-05				rhLAMAN-10	
	Velmanase alfa (N=15)		BSC (N=10)		Overall (N=33)	
	n (%)	Events	n (%)	Events	n (%)	Events
TEAEs	15 (100.0%)	157	9 (90.0%)	113	29 (87.9%)	546
Treatment-related TEAEs	7 (46.7%)	30	5 (50%)	9	17 (51.5%)	84
Serious TEAEs	5 (33.3%)	5	0 (0%)	0	12 (36.4%)	14
Serious treatment-related TEAEs	1 (6.7%)	1	0 (0%)	0	2 (6.1%)	2
Severe TEAEs	1 (6.7%)	1	0 (0%)	0	3 (9.1%)	4
TEAEs Leading to Dose Reduction	0 (0%)	0	0 (0%)	NR	NR	NR
TEAEs Leading to Study Drug Interruption	1 (6.7%)	NR	0 (0%)	NR	NR	NR
TEAEs Leading to Study Drug Discontinuation	0 (0%)	0	0 (0%)	0	0 (0%)	0
TEAEs Leading to Death	0 (0%)	0	0 (0%)	0	0 (0%)	0

Source: Table 2.5-18, p97 and Table 2.5-24, p100 of the submission.
AE = adverse event; BSC = best supportive care; n = number of participants reporting data; N = total participants in group; NR = not reported; TEAE = treatment-emergent adverse event.

6.43 In rhLAMAN-05, any treatment-emergent adverse event (TEAE) was reported by 100% of patients in the velmanase alfa group and 90% in the BSC group. These were considered treatment-related in 47% and 50% of patients respectively. In the velmanase alfa arm 33% of patients reported a serious TEAE, as compared to 0% in the BSC arm; only one (sepsis) was classified as a severe TEAE. One patient in the velmanase alfa arm experienced a treatment-related serious TEAE (acute renal failure of moderate severity), leading to temporary discontinuation of study drug. No patients discontinued study treatment or died due to TEAEs.

6.44 The most frequently reported any grade TEAEs occurring in two or more patients in the velmanase alfa group versus the BSC group were: nasopharyngitis (66% vs. 70%), pyrexia (40% vs. 50%), headache (33% vs. 30%), arthralgia (20% vs. 10%), vomiting (20% vs. 40%), acute tonsillitis (13% vs. 0%), diarrhoea (13% vs. 30%), syncope (13% vs. 0%), back pain (13% vs. 10%), ear infection (13% vs. 10%), influenza (13% vs. 10%),

gastroenteritis (13% vs. 10%), dizziness (6.7% vs. 20%), and ear discomfort (0% vs. 20%).

6.45 In the rhLAMAN-10 integrated analysis, 88% of patients reported a total of 546 TEAEs, 52% of which were considered treatment-related. A total of 36% of patients reported experiencing serious TEAEs, 6% reported treatment-related serious TEAEs, while 9% reported experiencing severe TEAEs. No patients discontinued study treatment or died due to TEAEs. The most frequently reported AEs in the rhLAMAN-10 integrated analysis were nasopharyngitis (70%), headache (39%), pyrexia (33%), vomiting (30%) and diarrhoea (27%), and cough (27%). The safety profile observed in rhLAMAN-10 integrated analysis was consistent with that reported in rhLAMAN-05 trial, with similar frequency, type, and severity of AEs. Notably, TEAEs were not reported for rhLAMAN-11.

6.46 In rhLAMAN-08, all patients (100%) experienced TEAEs, none of which led to death or study drug discontinuation. The most frequent TEAEs (≥ 40% of children) were vomiting (100%), pyrexia (80%), cough (80%), otitis media (80%), nasopharyngitis (60%), rhinitis (60%), and diarrhoea (60%). The submission stated that velmanase alfa was well tolerated in paediatric patients (aged ≤6 years), with the majority of TEAEs being mild or moderate in intensity. Additionally, of the 16 adverse drug reactions (ADRs) reported in four children, most were infusion-related reactions (IRRs). One child experienced a serious IRR (chills and hyperthermia) requiring overnight hospitalisation; symptoms resolved the same day.

6.47 Safety data is also available from the real-word evidence in the Alpha-Mannosidosis Registry (SPARKLE study). As of 5 March 2024, the fourth interim report (approximately 2.5 years) reported 142 study-emergent AEs in 31 patients (35%). A total of 108 events in 19 patients were classified as TEAE, mostly mild to moderate severity and assessed as unrelated to velmanase alfa. Seventeen serious TEAEs were experienced in five patients, all unrelated to velmanase alfa and requiring hospitalisation, except one seizure considered unlikely related but did not require hospitalisation.

Benefits/harms

6.48 On the basis of direct evidence presented by the submission from rhLAMAN-05, as presented in Table 6, the comparison of velmanase alfa and BSC at Month 12 resulted in an:

- Average incremental reduction of 3.50 µmol/L from baseline in serum oligosaccharide levels.

Clinical claim

6.49 The submission described velmanase alfa as superior in terms of effectiveness compared with BSC and inferior in terms of safety compared to BSC.

6.50 The Sub-Committees considered that the claim of superior effectiveness to BSC was reasonably supported by the evidence presented in the submission; however, noted that the following issues should be considered:

- The comparative evidence was limited to only one head-to-head RCT trial (rhLAMAN-05, n=25). While there was a statistically significant improvement in serum oligosaccharides levels, functional outcomes (3MSCT, 6MWT, and FVC [% predicted]) improved only numerically, and HRQoL outcomes (CHAQ and EQ-5D-5L) showed minimal change.
- MCID thresholds have not previously been defined for AM. *Post hoc* thresholds based on other diseases were applied to outcomes, limiting applicability as described in Table 5. Further, the Subcommittees noted that the nominated threshold for serum oligosaccharides was based on a baseline measure in the rh-LAMAN-05 trial. The Pre-PBAC Response stated that as an ultra-rare disease, the available population limits trial size and statistical power making anchor-based MCID analyses infeasible due to a lack of data. The Pre-PBAC response reiterated the MCIDs were derived using baseline data from the rhLAMAN-05 trial.
- There was an imbalance at baseline between the arms in terms of 3MSCT, 6MWT, FVC (% predicted) and CHAQ-DI score, with more compromised patients randomised to the velmanase alfa arm. The direction of bias was unclear, as these patients may have greater potential for improvement, or may have experienced increased irreversible decline. The PSCR agreed that the potential direction of the bias was difficult to quantify but, noting the progressive and irreversible nature of AM, patients with advanced or more severe disease accumulate damage that limits their capacity for improvement. As a result, it is unlikely that patients with more severe disease would experience greater benefits from treatment compared to those with milder forms of the condition.

6.51 The Sub-Committees considered that the claim of inferior safety to BSC was reasonable and adequately supported by the data.

6.52 The PBAC considered that the claim of superior comparative effectiveness, in terms of biochemical effectiveness, was reasonable. However, the PBAC considered the nature and magnitude of clinical benefit was uncertain based on the available data.

6.53 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.54 The submission presented a cost-utility analysis comparing velmanase alfa plus BSC to BSC alone for the treatment of patients with AM. Table 12 presents a summary of the model structure and rationale.

Table 12: Key components of the economic evaluation

Component	Description	Justification/comments
Treatment	Velmanase alfa and BSC vs BSC	-
Time horizon	Lifetime (until death) in the base-case in the model base case versus 4 years (48 month) in the rhLAMAN-10 trial	The time horizon in the base case exceeded the average life expectancy for patients with AM of 40 years. The ICER was highly sensitive to shorter time horizons
Outcomes	LYs gained, QALYs gained	This was appropriate.
Methods used to generate results	Markov model	This was appropriate.
Health states	Five mutually exclusive health states: Normal walking, Occasional walking aid/wheelchair use; Frequent walking aid/wheelchair use; Wheelchair dependence; and Death Transition probabilities were based on the rhLAMAN-10 trial data and a structured expert elicitation panel. Infections were modelled as an independent event associated with each model health state	While this was reasonable; AM is a multi-systemic disease, characterised by hearing impairment, intellectual disability, facial and skeletal abnormalities, reduced lung function, and immunodeficiency, among other manifestations. The current model structure does not fully capture all clinically relevant aspects of the condition.
Cycle length	Annual (1 year)	This was appropriate.
Transition probabilities	Primary data sources for velmanase alfa arm: • rhLAMAN-10 clinical trial • Structured expert elicitation panel report (Attachment 15 to the submission)	Transition probabilities for most of the health states and BSC arm were based on inputs from a structured expert elicitation panel. The elicitation exercise has limitations as described in paragraph 6.58.
Health-related quality of life	Utility values were based on EQ-5D-5L scores from rhLAMAN-10 and Adam et al. (2019). A utility gain of 0.18 was applied to all patients treated with velmanase alfa (based on the FVC outcome in the rhLAMAN-10 trial).	The utilisation of the same health utility values for 'Occasional walking aid/wheelchair use' and 'Frequent walking aid/wheelchair use' was not appropriate. Additionally, using improvement in FVC to estimate the utility benefit with velmanase alfa may result in double counting as EQ-5D captures overall HRQoL.
Age at model entry	Six years for the under 18 population; 18 years for the over 18 population	Although the assumption of treatment initiation at six years is conservative in Australia, Chin and Fuller (2022) reported a median age at diagnosis of 1.3 years (range: 1.2 to 8.6).
Resource use	Costs included in the model in the base analysis from a payer's perspective: • Drug acquisition and administration cost of the velmanase alfa therapy • Pre-treatment cost for velmanase alfa • HCRU related to disease management • Mortality costs • AEs management Additionally, cost of patient and caregiver productivity loss, and the costs of professional homecare services included in a scenario analysis from a societal perspective.	This was reasonable; however, the frequency and proportion of resource utilisation were derived based on inputs from structured expert elicitation.

Source: Table 3.1-1, pp141-142 of the submission.

AE = Adverse events; AM = alpha-mannosidosis; BSC = best supportive care; EQ-5D-5L, EuroQol-5 Dimension-5 Level questionnaire; FVC = Forced vital capacity; LYs = life-years; HCRU = health care resource use; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years.

6.55 The model structure presented in the submission was consistent with that used by Stevenson et al. (2024), which was an update to the Markov model used for the NICE

evaluation of velmanase alfa in 2023 (NICE HST29).[2] The Markov model assessed the following five mutually exclusive health states: Normal walking, Occasional walking aid/wheelchair use, Frequent walking aid/wheelchair use, Wheelchair dependence, and Death. In the base case, the model allowed backward transition, but only from 'Occasional walking aid/wheelchair use' to 'Normal walking' and only for those receiving velmanase alfa. Infections were modelled as independent events within each health state.

6.56 AM is a multi-systemic disease, characterised by hearing impairment, intellectual disability, facial and skeletal abnormalities, reduced lung function, and immunodeficiency, among other manifestations. The evaluators noted that the model structure did not fully capture all clinically relevant aspects of the condition. Key opinion leaders identified pain as a significant symptom with a substantial impact on QoL and recommended its inclusion in the model, while noting that infection was not a high priority for adults. The NICE evaluation concluded that while other measures of disease progression, such as lung function, could be an option for defining the model structure, the overall model structure was adequate for decision-making. The Sub-Committees considered that although the specified health states were categorised using mobility as the main criteria, they were likely to represent the progression and severity of disease in a reasonable way, so long as the health state utilities applied to each state sufficiently captured the heterogeneity of the symptoms being experienced (on average). The Sub-Committees noted that additional granularity of health state occupation could potentially be added to the model; however, given the paucity of available evidence it would likely unnecessarily increase the complexity of the model and decrease confidence in the results.

6.57 The base case used a lifetime time horizon (i.e., until age 100 or death) to capture the potential long-term benefits of velmanase alfa. The submission noted that the use of a lifetime model was consistent with the March 2022 PBAC consideration of sebelipase alfa, which was listed on the Life Saving Drugs Program in April 2023 for the treatment of infantile onset lysosomal acid lipase deficiency. The model assumed survival until the age of 100 years, which may not be clinically plausible in this population as the average life expectancy for patients with AM is approximately 40 to 50 years. The model inputs were derived from the rhLAMAN-10 trial, which had median follow up of four years (48 months), and as stated in paragraph 6.50, the long-term effectiveness and safety of velmanase alfa was uncertain. Additionally, the model was sensitive to the time horizon; reducing the time horizon to 20 years increased the incremental cost effectiveness ratio (ICER) by % and assuming a time horizon of 30 years increased the ICER by %. The PSCR stated that a 20-year time horizon would be too short given the limited data available in the literature on AM-related mortality and stated that as the average life expectancy for patients with

[2] National Institute for Health and Care Excellence (NICE), Velmanase alfa for treating alpha-mannosidosis Highly specialised technologies guidance Reference number:HST29, December 2023, Accessed: April 2025, https://www.nice.org.uk/guidance/hst29

AM is between 40 and 50 years, a 40-year time horizon might be more appropriate. The PSCR noted that a 40-year horizon increased the ICER by %. The Sub-Committees considered that a time horizon of 30-40 years might be appropriate for both the paediatric and adult populations as greater life expectancy gains may be expected (but not necessarily realised) for patients diagnosed as adults who generally have a milder, more attenuated disease course.

6.58 Health state transition probabilities for progression (forward transition probabilities) and improvement (backward transition probabilities) were based on the rhLAMAN-10 trial data and a structured expert elicitation panel. The Sub-Committees noted that the transition probabilities between normal walking and occasional walking aid/wheelchair use (both forwards and backwards) were based on small numbers from the rhLAMAN-10 trial and it was therefore difficult to assess the effect of the probabilities applied apart from 'include' and 'exclude'. Excluding the backward transition probabilities for velmanase alfa increased the ICER by % to > $1,055,000.

6.59 As limited data was available from rhLAMAN studies, transition probabilities between other health states and for BSC patients were derived using a structured expert elicitation exercise as described in Hemming et al. (2017; IDEA protocol). While the use of expert elicitation was reasonable in the absence of empirical data, the methods followed had some limitations, including the lack of expert interaction, cognitive bias among experts, no guidance on fitting distributions or aggregating responses, and the absence of a formal validation process. The PSCR agreed that there were limitations with the expert elicitation exercise but noted that given the ultra-rare nature of AM, there is a significant lack of published data to inform key model parameters. Further, important clinical aspects such as the incidence of severe infections and the need for surgical interventions were not captured in the rhLAMAN trials and could not be derived from trial data. The PSCR stated that the structured expert elicitation panel report remains the best evidence to inform the model inputs.

6.60 Infections were modelled as independent events that could have economic, HRQoL, and survival consequences. In the absence of available data from rhLAMAN-10 or the literature, rates of acute and recurrent infections in paediatric and adult patients were derived from the structured expert elicitation panel report.

6.61 The submission applied an annual discontinuation rate of 13.3% in Year 1, based on a multi-domain responder analysis where two of 15 patients were non-responders over 12 months. A 10% discontinuation rate was applied in subsequent years to reflect potential factors such as infusion-related reactions, non-compliance, patient preference, and the development of other life-limiting conditions (e.g., cancer). These discontinuation rates were applied uniformly across both paediatric and adult subgroups. Notably, the requested restriction did not include any stopping or continuation criteria, and patients may remain on treatment for life. The Sub-Committees noted that there was a lack of transparency in the submission detailing the transition probabilities in the velmanase alfa arm following

discontinuation of treatment. The Sub-Committees noted that it appeared, from the model, that BSC transitions were applied to these patients.

6.62 Based on the structured expert elicitation panel and published literature, acute infections requiring hospitalisation were considered the primary drivers of mortality, while recurrent infections were assumed not to contribute to increased mortality risk.

6.63 Anaphylaxis and severe hypersensitivity reactions requiring medical treatment were considered in the model. The risk of adverse events and mean exposure to velmanase alfa were sourced from the FDA label. Reported probabilities of adverse events and mean treatment duration were used to calculate the per-cycle probability of experiencing each event. Patients receiving BSC were assumed not to experience any adverse events.

6.64 Health state utilities in the base case for Normal walking, Occasional walking aid/wheelchair use, Frequent walking aid/wheelchair use health states were derived from using the baseline EQ-5D-5L scores collected in the rhLAMAN-10 study (see Table 13). Within the base case, utility values were 0.65 for Normal walking, 0.58 for Occasional walking aid/wheelchair use as well as Frequent walking aid/wheelchair use. As the states reflect disease progression, the use of the same utility value for both the Occasional walking aid/wheelchair use and Frequent walking aid/wheelchair use was not reasonable and may overestimate the actual benefit. The PSCR acknowledged the limitation of applying the same utility value to both the 'Occasional walking aid/wheelchair use' and 'Frequent walking aid/wheelchair use' health states but stated that this was a conservative assumption as more patients in the BSC arm will be in the more severe 'Frequent walking aid/wheelchair use' health state compared to velmanase alfa patients. The PSCR noted that the application of a lower utility value for the 'Frequent walking aid/wheelchair use' health state resulted in a [redacted]% decrease in the ICER.

6.65 As no patients in rhLAMAN-10 were Wheelchair dependent at baseline, utility values for this health state were not estimated from trial data. Instead, they were sourced from Adam et al. (2019), which reported a value of 0.10.

6.66 Additionally, for the velmanase alfa arm, the submission applied a utility gain of 0.18 to each health state to reflect the benefit of treatment and delayed progression with velmanase alfa. The utility gain of 0.18 was based on a +0.9 L improvement in FVC observed among 17 children in the rhLAMAN-10 trial, and the application of a utility gain of 0.2 per +1 L increase in FVC in the NICE evaluation of elosulfase alfa for treating mucopolysaccharidosis type IV A (NICE HST19)[3].

[3] NICE, Elosulfase alfa for treating mucopolysaccharidosis type 4A Highly specialised technologies guidance Reference number:HST19, April 2022, Accessed: April 2025, https://www.nice.org.uk/guidance/hst19

Table 13: Utility values applied in the submission

Health State	VA - on treatment	VA - off treatment	BSC	Source
Base case				
Normal walking	0.83	0.65	0.65	rh-LAMAN-10; NICE committee paper-2; Table 22; Page 61
Occasional walking aid/wheelchair use	0.76	0.58	0.58	
Frequent walking aid/wheelchair use	0.76	0.58	0.58	
Wheelchair-dependent	0.28	0.10	0.10	Adam et al. 2019; Figure 1; Page 4; NICE HST29

Source: Table 3.5-2, p166, Table 3.5-3, p166 and Table 3.5-4, p167 of the submission.
BSC = best supportive care; NICE = National Institute for Health and Care Excellence; VA = velmanase alfa

6.67 The utility gain of 0.18 was applied to both paediatric and adult patients, resulting in identical utility values being assumed for both cohorts. This assumption may not be reasonable given that the *post hoc* subgroup analyses by age demonstrated a larger benefit for FVC (L) in the paediatric (+0.88 L) patient cohort compared to the adult (+0.15 L) patient cohort in rhLAMAN-10. Consequently, this may overestimate the utility benefit in the adult population. Excluding the utility benefit increased the ICER by %. The PSCR agreed that applying the same utility gain to paediatric and adult patients may not be reasonable but stated that the utility gain in the paediatric population would be higher than the 0.18 applied in the submission as the rhLAMAN-11 trial demonstrated a mean FVC improvement of +1.274 L at last observation, which corresponded to a utility gain of 0.255 (1.274 × 0.2). The PSCR presented a scenario analysis which assumed 0.255 and 0.0 utility gains for velmanase alfa patients in the paediatric and adult populations, respectively. This resulted in a % increase in the base case ICER. The Sub-Committees noted that the utility gains (change from baseline in EQ-5D-5L scores up to month 48) for paediatric patients treated with velmanase alfa in the rhLAMAN-10 study was 0.08. The Sub-Committees therefore considered that the applied utility gain of 0.18 lacked face validity and meant that the on-treatment utility value for patients in the Normal walking state was 0.83, which is almost comparable with the general population in Australia.

6.68 Patients who discontinued velmanase alfa received utility values equal to those applied to the BSC arm (i.e. without the 0.18 gain).

6.69 Healthcare resource used in the model appropriately included costs for drug acquisition, administration, pre-treatment for velmanase alfa, disease management and monitoring, and AE management. Notably, the frequency and utilisation of healthcare resource use, except for adverse events, was based on structured expert elicitation panel instead of empirical data from rhLAMAN studies.

6.70 Additionally, costs of patient and caregiver productivity losses, and the costs of professional homecare services were also included in a scenario analysis from a societal perspective. From a societal perspective, the ICER decreased by % compared to health care payer perspective.

6.71 A summary of the key drivers of the model is presented in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact Base case: [redacted][1]/QALY gained
Time horizon	The time horizon in the base case (lifetime, up to 100 years) exceeded the average life expectancy for patients with AM of 40-50 years.	High, favours velmanase alfa Use of 20-year time horizon increased the ICER by [redacted]% to [redacted][1]/QALY gained.
Backwards transition	The model allowed backwards transition for velmanase alfa patients from Occasional walking aid/wheelchair use to Normal walking.	High, favours velmanase alfa Excluding backward transition for velmanase alfa patients increased the ICER by [redacted]% to [redacted][1]/QALY gained.
Utility gain for velmanase alfa patients	The model applied a utility gain of 0.18 to reflect the benefit of treatment with velmanase alfa based on improvement in FVC.	High, favours velmanase alfa Removing the utility gain of 0.18 for patients treated with velmanase alfa increased the ICER by [redacted]% to [redacted][1]/QALY gained.

Source: Source: Table 3.9-2, p190 of the submission.
FVC = forced vital capacity; ICER = Incremental Cost-Effectiveness Ratio; QALYs = Quality-Adjusted Life Year.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*

6.72 Table 15 presents the results of the stepped economic evaluation.

Table 15: Results of the stepped economic evaluation

Step and component	Velmanase alfa	BSC	Increment
Step 1: Trial-based economic evaluation			
Costs	$[redacted]	$0	$[redacted]
LY	3.88	3.83	0.05
Incremental cost/extra LY gained			$[redacted][1]
Step 2: Model-based analysis modelled over a lifetime time horizon			
Costs	$[redacted]	$0	$[redacted]
LY	33.90	24.34	9.56
Incremental cost/extra LY gained			$[redacted][2]
Step 3: Model-based analysis from Step 2 adding discounting of cost and effectiveness outcomes at 5%			
Costs	$[redacted]	$0	$[redacted]
LY	14.07	11.99	2.08
Incremental cost/extra LY gained			$[redacted][1]
Step 4: Model-based analysis from Step 3 adding calculation of QALYs based on time spent in each health state			
Costs	$[redacted]	$0	$[redacted]
QALY	8.67	5.99	2.68
Incremental cost/extra LY gained			$[redacted][1]
Step 5: Model-based analysis from Step 4 adding the cost of HCRU, AE, and mortality and disutility associated with acute infections			
Costs	$[redacted]	$338,594	$[redacted]
QALY	8.17	5.34	2.84
Incremental cost/extra QALY gained			**$**[redacted][1]

Source: Table 3.8-1, p186 of the submission.
AE = adverse event; BSC = best supportive care; HCRU = healthcare resource utilisation; LY = life-years; QALY = quality-adjusted life-years.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*
[2] *$455,000 to < $555,000*

6.73 Overall, the ICER was extremely high in all steps of the economic evaluation. The base case ICER presented by the submission was > $1,055,000 per QALY gained. The Pre-PBAC Response acknowledged the ICER was very high; however, stated that this should be considered in the context of alpha-mannosidosis being an ultra-rare

disease, the high unmet clinical need and as ICER in the paediatric population was lower $955,000 to < $1,055,000 versus > $1,055,000 per QALY in the adult population.

6.74 Based the presented model, the median life expectancy for paediatric patients receiving velmanase alfa was 37 years and 27 years for those receiving BSC. Less than 10% of the paediatric population were receiving treatment by the age of 25. For adults, the median life expectancy for velmanase alfa patients was 51 years and 40 years for those receiving BSC. Less than 10% of the population were still on treatment by the age of 37.

6.75 The results of key univariate sensitivity analyses were summarised in Table 16.

Table 16: Sensitivity analyses

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change from base case
Base case		2.84	[redacted][1]	-
Discount rate (base case: 5% costs and outcomes)				
• 0% costs and outcomes		6.57	[redacted][2]	[redacted]%
• 3.5% costs and outcomes		3.50	[redacted][1]	[redacted]%
Time horizon (base case: 100 years)				
• 20 years		2.18	[redacted][1]	[redacted]%
• 30 years		2.61	[redacted][1]	[redacted]%
Utility source (base case: rhLAMAN-10 /NICE HST29)				
• rhLAMAN-10/NICE HST29 and SEEP		2.82	[redacted][1]	[redacted]%
• MPS Society Survey/NICE HST29		3.60	[redacted][3]	[redacted]%
Population (base case: both <18 and ≥18 years)				
• <18 years		2.81	[redacted][1]	[redacted]%
• ≥18 years		2.88	[redacted][1]	[redacted]%
Backwards transition for velmanase alfa (base case: include)	[redacted]			
• Exclude		2.17	[redacted][1]	[redacted]%
Perspective (base case: payer)	[redacted]			
• Societal		2.71	[redacted][1]	[redacted]%
Utility gain with velmanase alfa treatment (base case: include)	[redacted]			
• Exclude		1.84	[redacted][1]	[redacted]%
Utility value for Frequent walking aid/wheelchair health state (base case: the same as Occasional walking aid/wheelchair health state, i.e., 0.76 for velmanase alfa – on treatment and 0.58 for velmanase alfa)				
• Using a lower utility value of 0.66 for velmanase alfa – on treatment and 0.47 for velmanase alfa – off treatment and BSC[a]		2.92	[redacted][1]	[redacted]%

Source: Table 3.9-2, p190 of the submission.

BSC = best supportive care; HST = highly specialised technology; ICER = Incremental Cost-Effectiveness Ratio; MPS = mucopolysaccharidosis; NICE = National Institute of Care and Excellence; QALYs = Quality-Adjusted Life Year; SEEP = Structured Expert Elicitation Panel.

[a] The lower utility value of 0.66 and 0.58 for Frequent walking aid/wheelchair health state was based on the Structured Expert Elicitation Panel conducted by the submission as presented in Table 3.5-3, p166 of the submission.

The redacted values correspond to the following ranges:

[1] *> $1,055,000*

[2] *$755,000 to < $855,000*

[3] $955,000 to < $1,055,000

Cost/patient/year

6.76 Table 17 summarises the cost per patient per year with velmanase alfa.

Table 17: Cost per patient per year

	Trial dose and duration	Model	Financial estimates
Mean dose	Velmanase alfa 1 mg/kg of body weight administered once a week by IV infusion plus BSC		
Mean weight at baseline/entry	60.2 kg[a]	Paediatrics: 24 - 73 kg Adults: 70.9 kg	Paediatrics: 47.4 kg Adults: 70.9 kg
Cost/patient/year	$[redacted][b]	Paediatrics: $[redacted] - $[redacted] Adults: $[redacted]	$[redacted][c]

Source: Prepared during evaluation.
[a] Average weight of paediatric and adult patients based on the rhLAMAN-05 trial.
[b] The cost per patient per year in the trial was calculated using cost per vial required based on average weight of 60.2 kg.
[c] The financial estimates include 75% adult patients (5) and 25% paediatric patients (2). An assumption of 100% compliance based on the Attachment 23 – Lamzede AM Financial Model to the submission

6.77 Treatment with velmanase alfa is expected to be life-long. Based on the trial, the cost per year of treatment for a 60.2 kg patient (average of paediatric and adult patients combined) was $[redacted].

6.78 The economic evaluation estimated an average cost per patient per year of $[redacted] for a 71 kg adult. The average weight of a paediatric patient was not able to be incorporated into the model, but weights of 24 kg and 73 kg resulted in a cost per year of $[redacted] to $[redacted] respectively.

6.79 The financial estimates applied an average weight for paediatric patients of 47.4 kg and 70.9 kg for adults. The estimates assumed that 75% of patients were adult, resulting in an average cost per patient per year of $[redacted].

Estimated PBS usage & financial implications

6.80 This submission was considered by DUSC at a joint meeting of ESC and DUSC. The submission used an epidemiological approach to estimate the financial impact of listing velmanase alfa for the treatment of patients with AM.

6.81 Table 18 summarises the key inputs and data sources to estimate the utilisation of velmanase alfa.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Commentary on the submission	Sub-Committees' comments
Prevalent patients with AM	[redacted][1] patients in Year 1; population adjusted prevalence based on UK prevalence reported in NICE HST29	There is limited data relating to epidemiology of AM in Australia. Chin and Fuller (2022) reported a prevalence of AM of 0.08 per 100,000 in Australia, corresponding to 22 prevalent cases in Year 1; however, this may include patients eligible for HSCT. This higher prevalence was tested in the sensitivity analyses.	The Sub-Committees noted clinician advice that there are currently 7[1] known patients with AM in Australia and therefore, considered this parameter to be overestimated.

Parameter	Value applied and source	Commentary on the submission	Sub-Committees' comments
Prevalent patients eligible for treatment with VA	[redacted][1] patients; based on Australian clinical expert opinion, 57% of patients were considered eligible for treatment with velmanase alfa ([redacted][1] of the [redacted][1] had previously undergone HSCT and were therefore ineligible for velmanase alfa treatment).	-	The Sub-Committees noted clinician advice and considered there would likely be [redacted][1]-[redacted][1] eligible prevalent patients.
Proportion of prevalent patients (<18 years and (≥18 years)	<18 years: 25% ([redacted][1] paediatric patients) ≥18 years: 75% ([redacted][1] adult patients); assumption based on Australian clinical expert opinion.	While this was conservative; the higher proportion of adult patients was inconsistent with the median age of diagnosis of 1.3 years reported by Chin and Fuller (2022).	The Sub-Committees considered in the later years of listing, the financial estimates would be overestimated given the size of the paediatric population. The Sub-Committees noted the financial estimates were sensitive to this parameter.
Incidence patients with AM	1 case every two years, based on retrospective data from the National Referral Laboratory for LSDs – Australia (Chin and Fuller, 2022) reporting 1 case every three to four years. The submission further assumed that all incident cases would be paediatric, given the median age at diagnosis reported by Chin and Fuller (2022) was 1.3 years.	The submission noted that velmanase alfa is currently underdiagnosed due to rarity of the disease, gradual onset and lack of treatment options. Availability of velmanase alfa may increase diagnosis rate, supporting the assumption of [redacted][1] new case every two years instead of 3 to 4 years. Lower incidence of was tested in the sensitivity analyses.	The Sub-Committees commented although the availability of VA may increase awareness of AM, the Sub-Committees considered the incidence estimate to be overestimated and would likely be [redacted][1] case every 3-4 years. The Sub-Committees noted the PSCR noted, "the expected incidence of AM is [redacted][1] new patient every 3-4 years."
Uptake rate	[redacted]%; Sponsor's assumption	-	The Sub-Committees noted clinician advice and considered treatment uptake rate to be overestimated given the frequency and mode of administration. The Pre-PBAC Response stated that given the rarity of AM and the lack of alternative options, all or nearly all eligible patients would be offered and accept velmanase alfa treatment in practice.

Parameter	Value applied and source	Commentary on the submission	Sub-Committees' comments
Treatment discontinuation per year	10%; based on NICE HST29 and clinical expert opinion	While the treatment discontinuation of 10% was consistent with that applied from Year 2 onwards in the economic model, the submission did not directly apply the treatment discontinuation rate. Instead, it assumed that each patient would take 90% of the medication annually. Given the small patient population this approach was not precise.	The Sub-Committees noted based on the approach used, the submission assumed there was no discontinuation. The Sub-Committees considered this assumption to be reasonable given VA is a lifelong treatment.
Treatment compliance	100%; Sponsor's assumption	This aligns with the rhLAMAN-05 trial, where treatment compliance exceeded 90%.	The Sub-Committees noted based on the approach used, the submission assumed 90% compliance. The Sub-Committees commented that trial conditions may not reflect real world practice and considered this parameter may be overestimated given the frequency and mode of administration.
Dose (1mg/kg weekly IV infusion)	Mean body weight of paediatrics 47.4kg (dosing rounded to 50kg) derived from the average body weight of 6–17-year-old children from the Australian Bureau of Statistics. Mean body weight of adults 70.9kg (dosing rounded to 80kg) used based on the mean weight of ≥18 years old patients from the rhLAMAN-10 trial	Although this aligns with the economic model, the weight of patients with AM may differ from that of the general population.	The Sub-Committees noted the submission did not account for the change in weight distribution in children as they become older, however commented that this estimate may be reasonable given weight was overestimated in newly diagnosed infants.
IV administration	MBS Item code 13950 $123.05	-	The Sub-Committees noted this parameter assumed that all administration would occur in the public hospital and considered it reasonable for initiating treatment, however considered patients may transition to home infusions which would incur additional costs.

Source: Table 4.1-1, p193, Table 4.2-3, p198, Table 4.5-1, p203, Table 4.5-2, p203 of the submission.
AM = Alpha-mannosidosis; DUSC = Drug Utilisation Sub Committee; HSCT = haemopoietic stem cell transplant; HST = highly specialised technology; IV = intra venous; Kg = kilogram; LSD = lysosomal storage disease; MBS = Medicare Benefits Schedule; mg = milligram, NICE = National Institute of Care and Excellence; PBS = Pharmaceutical Benefits Scheme; TGA = Therapeutic Goods Administration; VA = velmanase alfa.
The redacted values correspond to the following ranges:
[1] < 500

6.82 Table 19 and Table 20 present the estimated utilisation and financial implications of listing of velmanase alfa.

Table 19: Estimated use and financial implications of velmanase alfa

			Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Estimated number of patients with AM		[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
B	Estimated number of patients eligible for the requested restriction		[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
C	Number of treated paediatric (<18 years) patients		[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
D	Number of treated adult (≥18 years) patients		[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
E	Number of patient-years of treatment paediatric (<18 years) patients	C x 0.9	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
F	Number of patient-years of treatment adult (≥18 years) patients	D x 0.9	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
G	# of 10mg VA vials required per year treatment paediatric (<18 years) patient	260[b] x E	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
H	# of 10mg VA vials required per year treatment adult (≥18 years) patient	416[c] x F	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
J	Number of 1x10mg pack (max qty =4) VA scripts	H x 0.4 /4[d]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
K	Number of 5x10mg pack (max qty =4) VA scripts	G /20[e]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
L	Number of 10x10mg pack (max qty =4) VA scripts	H x 0.6/40[f]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
M	Total VA script numbers	J+K+L	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]

Source: Table 4.2-2, p197; Table 4.2-5, p199; Table 4.2-6, p199 of the submission

AM = Alpha-mannosidosis, VA = Velmanase alfa, Qty = quantity, max = maximum; mg = milligrams

[a] Number of patient-years calculated by the product of number of patients and (1- treatment discontinuation rate)

[b] Based on the weight-dosing each paediatric patient year of treatment requires 260 vials

[c] Based on the weight-dosing each adult patient year of treatment requires 416 vials

[d] To minimise the number of scripts required, the submission assumed optimal prescribing for adult patients is to prescribe 40% of required units as the 1x10mg pack. Each script provides a maximum of 4 units.

[e] To minimise the number of scripts required, the optimal prescribing for paediatric patients is to prescribe the 5x10mg pack. Each script provides a maximum of 20 units

[f] To minimise the number of scripts required, the submission assumed optimal prescribing for adult patients is to prescribe 60% of required units as the 10x10mg pack. Each script provides a maximum of 40 units.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$0 to < $10 million*

Table 20: Estimated financial impact of listing velmanase alfa

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost to PBS less copayments	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Net financial implications						
Net cost to PBS	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**
Net cost to MBS	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Net cost to PBS and MBS	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]

Source: Table 4.4-1, p202 and Table 4.5-3, p204 of the submission
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme
The redacted values correspond to the following ranges:
1 $0 to < $10 million

6.83 The total cost to the PBS of listing velmanase alfa was estimated to be $0 to < $10 million in Year 6, and a total of $30 million to < $40 million in the first 6 years of listing.

6.84 The main sources of uncertainty relating to the estimated use of velmanase alfa were:

- The number of prevalent patients in Australia was uncertain. Using UK data from NICE HST29, which reported 25 AM cases in England, and assuming similar prevalence while adjusting for population size (England ~57.1M; Australia ~27.6M in 2024), the submission estimated < 500 prevalent AM patients in Australia for Year 1. Chin and Fuller (2022) reported a prevalence of AM of 0.08 per 100,000 in Australia, corresponding to 22 prevalent cases in Year 1. However, this prevalent population may include patients eligible for HSCT, though the exact number remains uncertain. The Sub-Committee's noted that there are currently < 500 patients in Australia with AM, and considered, based on clinician advice, that < 500 to < 500 would be eligible for treatment with velmanase alfa. The Sub-Committee's considered that the number of incident patients, i.e. <500 every 3 to 4 years, was reasonable.
- The drug cost per patient varies significantly with body weight and age. As more patients begin treatment and existing patients grow older, the average cost per patient is expected to increase due to weight gain over time.

6.85 Sensitivity analyses of the financial estimates were presented in the submission, as summarised in Table 21.

Table 21: Sensitivity analysis

Net cost to PBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	% changes in total cost over 6 years from base case
Base case	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	-
Decreased prevalence of [redacted][1] patients ([redacted][1] eligible) (BC = [redacted][1] patients, [redacted][1] eligible) ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	-[redacted]%
Increased incidence of 1 new case per year (BC = 1 new case per 2 years) ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	+[redacted]%
Incident cases – all adult patients (BC = all paediatric patients) ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	+[redacted]%
Treatment discontinuation rate of 0% (BC = 10%) ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	+[redacted]%
Decreased uptake rate of [redacted]% (BC = 100%) ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	-[redacted]%
Alternative split in script dispensing in paediatric (<18 years) patients [a] ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted]%
Alternative split in script dispensing in adult (≥18 years) patients [b] ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted]%

Source: Table 4.6-2, p206 of the submission, and Attachment 23 – Lamzede AM Financial Model – Revised, "Inputs and results"
BC = base case; PBS = Pharmaceutical Benefits Scheme; VA = Velmanase alfa.
[a] Assuming scripts in the paediatric population are distributed in a 0/0/100 split across the 1x10mg/5x10mg/10x10mg packs instead of a 0/100/0 split as assumed in the submission.
[b] Assuming scripts in the adult population are distributed in a 6/0/94 split across the 1x10mg/5x10mg/10x10mg packs instead of a 40/0/60 split as assumed in the submission.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *$0 to < $10 million*

6.86 The financial estimates were highly sensitive to varying prevalence and incidence rates of AM, and assuming no discontinuation. The Pre-PBAC Response acknowledged the financial estimates were sensitive to these parameters and noted the inputs preferred by the Sub-Committees (see Table 18) would result in a lower PBS expenditure on velmanase alfa than the submission model.

Quality Use of Medicines

6.87 The submission stated that the Quality Use of Medicines (QUM) was implemented through packaging in accordance with the approved PI and TGA requirements. Additionally, a QR code on the packaging directs patients to the Consumer Medicine Information (CMI). The submission also stated that the presentation of educational material and activities complies with the Medicines Australia Code of Conduct.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of velmanase alfa for the treatment of non-neurological manifestations of alpha-mannosidosis (AM), to allow for further discussion to better clarify the benefits of treatment and associated cost-effectiveness, and to further develop the restriction. The Committee acknowledged AM is an extremely rare and devastating genetic condition arising from an improperly functioning AM enzyme, leading to excess mannose-rich oligosaccharides throughout the body with multi-systemic effects on patients, and that no effective pharmacological therapies for this disease are currently available. However, the PBAC considered that whilst the clinical data demonstrated that velmanase alfa is biochemically effective for reducing serum oligosaccharides, further information from the Sponsor regarding the clinical and patient-relevant benefits of treatment would be informative. The PBAC considered that the proposed cost of velmanase alfa was very high and uncertain as it was dependent on weight-based dosing and the duration of therapy. The PBAC considered that the economic model was not sufficiently reliable for decision-making due to the uncertainty in the clinical data. However, the PBAC considered that velmanase alfa was not cost effective, noting the cost per patient per year was substantially higher than that for previously recommended treatments for ultra-rare diseases funded on the PBS with benefits which are likely similar in terms of clinical impact. The PBAC noted that the estimated utilisation of velmanase alfa was likely overestimated by the submission and considered that a risk sharing arrangement (RSA) would be an appropriate way to manage potential use outside the restrictions and higher than predicted average doses (as dosing is weight based).

7.2 The PBAC recognised the high and urgent clinical need for treatments for AM, for which there are currently no available pharmacological treatments. The PBAC noted that AM is an ultra-rare disease with very substantial impacts on quality of life (QoL) for patients and their carers. The PBAC noted that the age of diagnosis of AM is variable and can range from early infancy in patients with more severe forms of disease up to early adulthood for less severe forms of disease. The PBAC noted the sponsor hearing and the consumer input descriptions of the disease progression in individuals with AM, including skeletal development issues and loss of mobility, increased risk of infections and organ damage as well as developmental delay and psychiatric disturbance. Noting that velmanase alfa is indicated as a treatment of non-neurological manifestations of AM, the PBAC considered that delaying the loss of mobility, by even a small amount, and improving other clinical symptoms is highly valued by patients and their carers. The PBAC acknowledged that there is also a high financial burden for families and carers of people with AM.

7.3 The PBAC noted velmanase alfa is a first-generation enzyme replacement therapy (ERT) for AM, and accepted it is effective at reducing serum oligosaccharides.

However, the PBAC considered that it was challenging to assess the clinical outcomes reported in the trials due to the rarity of disease, selection of measured outcomes, how the disease manifests, individual variation in symptoms and given most of the patient population were children.

7.4 The PBAC considered that the nomination of best supportive care (BSC; defined as symptomatic and supportive care) as the comparator was reasonable. The PBAC acknowledged there was a high clinical need for effective therapies for AM, as treatment is largely limited to symptomatic management in practice. The Committee noted haematopoietic stem cell transplant (HSCT) is a treatment option for this condition and may be considered in some young patients; however, this option carries a high mortality risk and in practice is likely reserved for patients where the benefits are expected to outweigh the high risk of mortality. The PBAC considered the possibility that velmanase alfa may be used as a 'bridge' to HSCT could not be excluded, despite the lack of evidence supporting use for this purpose.

7.5 The PBAC noted that the proposed restriction did not include an explicit stopping rule for patients who were not receiving a clinical benefit whilst on treatment. The Committee noted that the burden of treatment was substantial, with weekly infusions (typically as a hospital outpatient), and in practice it was possible that patients not receiving a clinical benefit would discontinue treatment without an explicit stopping rule. However, the PBAC also noted that the cost of treatment per patient was very high and therefore considered that it would be reasonable to include a stopping rule in the restriction to reinforce that velmanase alfa treatment would only be considered acceptably cost effective if a patient was receiving a clinical benefit (i.e. not just a biochemical one). Additionally, the PBAC noted that:

- It is not appropriate to list the same pharmaceutical item (i.e. the same drug, form and strength) with different maximum quantity units for the same circumstances (restrictions), therefore, the maximum quantity should be amended to 1 (rather than 1, 5 and 10) with a Prescriber Instruction stating that the appropriate number of vials required for 4 weeks treatment should be requested;
- treatment eligibility should be confirmed, with a Prescriber Instruction stating that applicable diagnostic reports must be documented;
- the proposed restriction should align with the rhLAMAN-05 trial and require an alpha-mannosidase activity of < 10% of normal activity in blood leukocytes; and
- the restriction should be age agnostic.

7.6 The PBAC considered there was likely a clinical place for velmanase alfa for the treatment of non-neurological manifestations of AM, but the nature of the clinical benefits of treatment remained uncertain based on the information presented in the submission.

7.7 The PBAC noted the submission was supported by information from four clinical studies, comprising two primary studies (rhLAMAN-05 (Phase III) and rhLAMAN-08

(paediatric Phase II)), pooled data analyses (rhLAMAN-10) and a longer-term follow-up study (rhLAMAN-11) (see Table 3 and Table 4). The Committee also noted supporting information from four observational studies (see Table 3). The PBAC noted the clinical studies nominated serum oligosaccharide levels as the primary outcome, with clinical outcomes such as 3-minute stair climb test (3MSCT), 6-minute walk test (6MWT), forced vital capacity (FVC) percentage and QoL outcomes as secondary outcomes (see Table 4). The Committee also noted the challenges of undertaking a double-blinded, randomised controlled trial (rhLAMAN-05) in such a rare condition in a largely paediatric population and acknowledged the efforts of the Sponsor to undertake such a trial under these conditions. Further, the PBAC considered the clinical outcomes collected, which were focused on mobility and lung capacity, were unlikely to capture the full potential range of clinically relevant benefits patients may experience from an effective treatment for AM, and that it may be difficult to collect robust data for these types of outcomes in a very small and largely paediatric population.

7.8 With respect to comparative effectiveness, the PBAC accepted velmanase alfa is biochemically effective at reducing serum oligosaccharide. The PBAC noted that statistically significant reductions for patients receiving velmanase alfa were reported at 12 months in rhLAMAN-05 (adjusted mean relative change -70.47% versus BSC, see Table 6), with similar reductions in the paediatric rhLAMAN-08 study, and that these reductions appeared to be maintained over longer periods (as reported in rhLAMAN-08, -10 and -11, see Table 8 and paragraph 6.40). However, the PBAC noted the results for the clinical outcomes of 3MSCT, 6MWT and change in FVC, whilst trending towards a numerical benefit for velmanase alfa in rhLAMAN-05, did not achieve statistical significance or exceed the nominated minimum clinically important differences (MCIDs; see Table 6). The PBAC noted the paediatric rhLAMAN-08 study observed improvements in 3/6 patients for 6MWT and 2/6 for 3MSCT. In addition, the Committee noted the results for the follow-up studies rhLAMAN-10 and -11 found a statistically significant improvement in 3MSCT from baseline to last observation and a modest effect for FVC, but not for 6MWT (see Table 8) and that some patients became independent of mobility assistance, but the patient numbers in these longer-term follow-up studies were very small. With respect to QoL outcomes, the PBAC noted there were typically small changes in CHAQ domain scores and EQ-5D-5L outcomes; and caregivers in the paediatric rhLAMAN-08 study reported improvements in all domains including self-care, mobility and social function.

7.9 Although there was a lack of statistically significant improvements in clinical outcomes in the trial and studies presented, the PBAC noted the input from the sponsor hearing and consumers that highlighted a range of benefits were likely to be seen that were not captured in the trials, such as stabilisation of clinical features, improvements in immune system function and preventing further accumulation of organ damage caused by the presence of excess oligosaccharides.

7.10 The PBAC acknowledged some patients appeared to benefit from treatment and considered it would be helpful if the Sponsor could provide more information to

further describe the potential benefits of treatment. Noting the complex and heterogenous nature of AM, the PBAC considered that the multi-domain responder analysis presented by the submission, the Global Treatment Response (GTR) model, was informative. The PBAC noted that single measures in the trial did not indicate significant improvements in clinical outcomes (see paragraph 7.8); however, the GTR model appeared to indicate clinically meaningful improvements associated with velmanase alfa based on data from the randomised rhLAMAN-05 trial. A GTR (defined by response to at least two of the following domains: pharmacodynamic, functional and QoL) was achieved by 87% of patients in the velmanase alfa arm, compared to 30% in the BSC arm after 12 months (see paragraph 6.36). The PBAC considered it would be informative for the Sponsor to provide further discussion regarding the patient relevant impacts of achieving a treatment response as defined by the GTR.

7.11 Overall, the PBAC found the clinical effectiveness data difficult to interpret. The PBAC considered that velmanase alfa was superior compared to placebo in terms of biochemical effectiveness, i.e. reduction in serum oligosaccharide. However, the impact on the clinical outcomes, i.e. 3MSC, 6MWT, FEV, was uncertain, with substantial individual variation in clinical manifestations of disease and observed clinical responses to treatment over the considerably long durations of follow up in the extension studies. Noting the challenges of obtaining robust data and the clinically important improvements achieved by some patients whilst on treatment (such as becoming independent of mobility assistance), the PBAC considered it was reasonable to conclude that velmanase alfa likely provides some clinical benefit.

7.12 With respect to comparative safety, the PBAC noted that velmanase alfa was associated with higher rates of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), with almost all patients in rhLAMAN-05 and -10 treated with velmanase alfa reporting TEAEs (see Table 11). Overall, the PBAC considered the claim of inferior comparative safety to BSC was appropriate.

7.13 The PBAC considered that while the structure of the economic model was generally acceptable, the inputs to the model, especially given the paucity of clinical data and uncertainty in the clinical outcomes, meant the economic evaluation presented was not sufficiently robust for decision-making. The Committee agreed with the Sub-Committee's that the health states defined in the model, while based on mobility, were likely adequately representative of progression and severity of disease. However, the PBAC noted that inputs to the model were uncertain (some transition probabilities were based on a structured expert elicitation panel and there were very limited data to inform other probabilities, uncertainties in utilities, and a lack of longer term data; see paragraphs 6.57, 6.58, 6.59, 6.64, 6.66 and 6.67). The PBAC considered that the uncertain inputs combined with the impact of the very high treatment cost culminated in the resultant ICER (base case > $1,055,000 per QALY) likely not being reliable. The PBAC considered that the value proposition was difficult to assess with a traditional ICER due to the limited clinical data and lack of patient-relevant outcomes to inform the model, the small number of patients included in the studies, and the

individualised nature of AM progression. The PBAC considered that the uncertainty in the ICER is unlikely to be adequately resolved with further revision to the model structure.

7.14 Noting the high and urgent clinical need for effective pharmacological treatments for AM and the importance of even small clinical gains in mobility and other clinical symptoms, the PBAC compared the range of the benefits, number of patients expected to be treated, and the treatment cost per patient per year for velmanase alfa at the proposed price, with other high-cost treatments for rare diseases funded on the PBS. The PBAC noted that the cost of treatment per year, for an average patient in the rhLAMAN-05 trial, exceeded $ per year (see Table 17) and considered that a substantial reduction in the cost of velmanase alfa would be required for it to be considered cost-effective.

7.15 The PBAC noted that the AM patient population was uncertain but generally accepted to be very low. Further, the PBAC noted that the use of velmanase alfa in practice would likely be affected by individual variation in symptoms and variable response to treatment. Thus, the PBAC considered that some patients will not elect to receive treatment or may elect to discontinue treatment if not receiving an adequate benefit. The PBAC considered that the incidence of disease meant a new case would likely emerge only every 3 to 4 years in the Australian population (see Table 18). The PBAC agreed with the Sub-Committees that the likely number of eligible prevalent patients electing treatment with velmanase alfa was overestimated. Overall, the PBAC considered that there would be a maximum of 5 patients eligible for treatment over the 6 years of financial impact estimates.

7.16 The PBAC considered an RSA would be required for velmanase alfa, to manage potential use outcomes of the restriction, such as in patients who have had an unsuccessful HSCT, and higher than predicted average doses (as dosing is weight based).

7.17 The PBAC considered that the Sponsor should provide the following to assist with its deliberations following the deferral of this item:

- Additional information clarifying the clinical and patient-relevant impact of velmanase alfa treatment on patients treated. Acknowledging the rarity of disease and paucity of available data, the PBAC advised that the sponsor should present all available clinical data for velmanase alfa, including any real-world data and any further information relating to the GTR (see paragraph 7.10) or other similar outcomes;
- A pricing proposal which results in a substantial reduction to the cost of treatment per year (see paragraph 7.14);
- Revised financial estimates, which include reduced patient estimates and the reduced pricing (see paragraph 7.15);
- A proposed RSA (see paragraph 7.16); and

- A revised restriction that includes a stopping rule for patients who are not receiving benefit from treatment and the other suggested changes (see paragraph 7.5).

Outcome:
Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The Sponsor welcomes the Committee's recognition of the high and urgent clinical need for treatments for Alpha-Mannosidosis, for which there are currently no available pharmacological treatments available in Australia. The Sponsor remains committed to ensuring timely and equitable access to velmanase alf for this underserved and vulnerable group of Australians.