National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation (HST)

Velmanase alfa for treating alpha-mannosidosis
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	MPS Society	Appropriate	Thank you for your comment which has been noted.
	Chiesi	Yes. This referral is both appropriate, relevant and timely. For affected individuals and their families living with alpha-mannosidosis, a chronic, progressive and severely debilitating condition for which there is currently no formal treatment, the potential to benefit from a new enzyme replacement therapy that corrects the underlying metabolic defect is of huge significance. This referral should also be considered a priority given that the condition is progressive, reduces life-expectancy and accrued pathology may be irreversible, creating an urgency for access to this technology for eligible patients. In addition, given the small patient pool (UK maximum of 30 patients1) that could potentially be eligible for treatment with this technology, which will be delivered via a limited number of specialist treatment centres, there is a consequent requirement for national commissioning. We therefore agree that appraisal via the HST process is most appropriate.	Thank you for your comment which has been noted.

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Wording	MPS Society	No comment	Thank you for your comment which has been noted.
	Chiesi	To evaluate the benefits and costs of velmanase alfa within its licensed indication for treating alpha-mannosidosis for national commissioning by NHS England.	Thank you for your comment; the scope has been amended accordingly.
Timing Issues	MPS Society	It is important that this technology is evaluated in parallel to the application for Licensing to prevent any delays in access.	Thank you for your comment which has been noted.
	Chiesi	Other than supportive care there is currently no treatment widely available for patients with alpha-mannosidosis within the NHS and no satisfactory disease-modifying treatment for this condition currently exists. Allogeneic haematopoietic stem cell transplantation (HSCT) from a compatible HLA-matched donor is a potential option for selected patients, but not all patients are eligible for allogeneic HSCT and for eligible patients, compatible donors are not always readily available. Allogeneic HSCT also carries a significant morbidity and mortality risk. Given that alpha-mannosidosis is a life-long inherited genetic condition characterised by progressive and significant disability and early mortality, there is a serious and life-threatening unmet medical need driving the urgency to evaluate velmanase alfa for national commissioning by NHS England. This will ensure that recommendations as to the potential use of this technology within the NHS in England are in place as soon as possible after the grant of the Marketing Authorisation.	Thank you for your comments which were discussed at the scoping workshop. It was noted that some attendees considered allogeneic haematopoietic stem cell transplantation would be a relevant comparator for some people.
	MPS Society	No additional comments	Noted.

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Additional comments on the draft remit	Chiesi	• All reference to recombinant human alpha-mannosidase should be corrected to velmanase alfa. • All reference to Lamazym should be corrected to Lamzede.	Thank you for your comment; the scope has been amended accordingly.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MPS Society	The MPD Society is aware of 12 patients who may fit the criteria for treatment. Onset and severity of symptoms in Alpha Mannosidosis varies widely. Most individuals will experience some level of neurological involvement resulting in mild to moderate learning disabilities. Progressive bone disease is a feature of the disease. HSCT has been performed in some patients. This appears to be clinician / patient led and not based on a treatment protocol.	Thank you for your comments which informed discussion at the scoping workshop. The scope has been altered to reflect the fact that alpha-mannosidosis is a variable condition and that those affected should be considered as individuals on a clinical spectrum. It was noted that some attendees considered allogeneic haematopoietic stem cell transplantation would be a relevant

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			comparator for some people.
	Chiesi	Three sub-types of alpha-mannosidosis have been suggested: a mild form (type 1) clinically recognized after 10 years of age with myopathy, slow progression, and absence of skeletal abnormalities; a moderate form (type 2) clinically recognized before 10 years of age, with myopathy, slow progression, and skeletal abnormalities; and a severe form (type 3) with early death from central nervous system involvement or infection.2,3 While the intent of this sub-typing was to provide patients with prognostic information, the definitions of these phenotypes as distinct have several scientific and practical flaws: 1. No pathophysiological basis has been found to support the existence of distinct phenotypes rather than a continuous spectrum of disease. Indeed, no clear genotype-phenotype or biochemical-clinical correlations have been identified. 2. Phenotypes are impractical for use in clinical studies in such a rare disease. 3. The three phenotypes described above do not provide a clear and full description of the disease. For example, a patient with mild clinical manifestations and without skeletal abnormalities presenting in his first years of life may be identified through genetic testing but could not be classified using the three-type system. The same would be true for a patient with skeletal abnormalities not diagnosed until the teenage years. These limitations are also clear from published case reports4,5 where the authors concluded that there is no correlation between the types of mutations and the clinical manifestations nor are there correlation of the phenotypes and enzyme activity in vitro.	Thank you for your comment which was discussed at the scoping workshop. The scope has been altered to reflect the fact that alpha-mannosidosis is a variable condition and that those affected considered as individuals on a clinical spectrum.

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		We do not therefore consider it appropriate, or even feasible, to apply the proposed three-phenotype classification when investigating treatment for alpha-mannosidosis. Furthermore, it is now recognised that the disease can best be described as a continuum of clinical findings from a perinatal-lethal form to one that is not diagnosed until adulthood. In general, distinct phenotypes of patients with alpha-mannosidosis are not “clearly distinguishable” and the clinical course of the disease for any individual patient is challenging and unpredictable.	
The technology/ intervention	MPS Society	Appropriate	Thank you for your comment which has been noted.
	Chiesi	The technology is called velmanase alfa, which is the agreed INN. This technology will be marketed under the brand name Lamzede.	Thank you for your comment; the scope has been amended accordingly.
Population	MPS Society	Appropriate	Thank you for your comment which has been noted.
	Chiesi	The target population is adults, adolescents and children aged 6 years and older with alpha-mannosidosis. There are three subgroups that should be considered separately; children aged 6-11 years (at the time of treatment initiation), adolescents aged 12-17 years (at the time of treatment initiation) and adults aged 18 years and over (at the time of treatment initiation). These different age groups may gain differential clinical benefit from treatment and differential cost-effectiveness may be seen in these subgroups.	Thank you for your comment the scope has been altered to indicate that where evidence allows consideration will be given to subgroups based on age.

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Comparators	MPS Society	The Society is aware of 5 patients who have received a HSCT. It is unclear whether this can be viewed as an alternative care option.	Thank you for your comment which was discussed at the scoping workshop. It was noted that some attendees considered allogeneic haematopoietic stem cell transplantation would be a relevant comparator for some people.
	Chiesi	We question whether allogeneic HSCT is an appropriate comparator for this technology appraisal. Allogeneic HSCT is typically reserved for cases of alpha-mannosidosis with extensive disease presenting in early infancy, which is often lethal soon thereafter. Given the target indication for Marketing Authorisation for velmanase alfa, i.e. adults, adolescents and children aged 6 years and older, we do not believe that patients who are eligible for treatment with velmanase alfa would also be suitable candidates for allogeneic HSCT and suggest that this comparator is removed from the scope as this comparison would not be clinically meaningful.	Thank you for your comment which was discussed at the scoping workshop. It was noted that some attendees considered allogeneic haematopoietic stem cell transplantation would be a relevant comparator for some people.
Outcomes	MPS Society	Appropriate	Thank you for your comment.

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	Chiesi	In order to capture the most important health related benefits, the relevant outcome measures to be considered should be: • Change in serum oligosaccharides • Change in serum IgG immunoglobulins • Change in locomotor endurance • Change in motor development • Change in respiratory function • Change in cognition • Change in hearing • Mortality • Adverse effects of treatment • Health-related quality of life If required for scoping, greatest weighting or emphasis should be given to change in locomotor endurance, motor development and respiratory function as these outcome measures are key drivers of change in health-related quality of life.	Thank you for your comment; the scope has been amended to include outcomes discussed at the scoping workshop.
Equality and Diversity	MPS Society	Appropriate	Thank you for your comment.
	Chiesi	We have not identified any equality issues relating to this technology appraisal. According to available epidemiological data, alpha-mannosidosis does not disproportionately affect any of the protected groups as defined in the Equality Act 2010.	Thank you for your comment.

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Other considerations	MPS Society	N/A	Noted.
Innovation	MPS Society	This is the only treatment currently being trialled for patients with a confirmed diagnosis of alpha mannosidosis. The technology has only been trialled in patients 5 -35 years. Reported outcomes have shown positive effects on some aspects of the disease.	Thank you for your comments which have been noted.
	Chiesi	Alpha-mannosidosis is one of a group of lysosomal storage diseases heralding a new era in the treatment of genetic diseases. Velmanase alfa moves the treatment of this disorder from symptomatic management to therapeutic intervention. Whilst velmanase alfa is not a cure for this disorder, it can significantly modify or attenuate the phenotype and represents a 'step-change' in the management of alpha-mannosidosis delivering real and valuable benefits in health related quality of life to affected individuals. Given the significant morbidity, mortality and unmet clinical need in this condition, coupled with the lack of other available treatments for this rare condition, velmanase alfa was granted orphan medicinal product designation by the EU Committee for Orphan Medicinal Products in January 2005 (EU/3/04/260).	Thank you for your comments which have been noted.
Questions for consultation	MPS Society	The MPD Society is aware of 23 patients in the UK with a confirmed diagnosis of alpha mannosidosis. 5 have received a HSCT so would not be eligible for treatment. 6 are over the age of 35 years so outside of the treatment age criteria.	Thank you for your comments which have been noted and informed discussion at the scoping workshop. It was noted that the HST process can only evaluate the technology

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		12 are aged between 5-35 years, have not been treated with HSCT and may be eligible for treatment. We are aware of 2 of these patients who have participated in the clinical trial for this technology. Current understanding of using ERT in other LSD conditions is that the earlier you treat the better the outcomes are likely to be. We are unclear as to whether the technology will be available to children under 5 years, or if the treatment will be extended past 35 years. The technology may be limited in its effects for individuals who have progressive neurological decline, due to ERT not being able to cross the blood brain barrier.	in accordance with its marketing authorisation.
	Chiesi	How is a diagnosis of alpha-mannosidosis confirmed? Diagnosis of alpha-mannosidosis is based on increased levels of mannose-rich oligosaccharides in urine or serum, reduced activity of alpha-mannosidase in leukocytes or fibroblasts, and the finding of at least two pathogenic mutations in the MAN2B1 gene. How is alpha-mannosidosis disease severity defined and categorised? See above. How many patients with alpha-mannosidosis are expected to be treated in NHS specialists centres annually? The MPSSociety, which co-ordinates the MPS Registry for MPS and related diseases, knows of 30 affected individuals with alpha-mannosidosis in the UK.1 This represents the UK prevalent population, although it is possible that not all affected individuals will be suitable candidates for treatment. Given the	Thank you for your comments which have been noted and informed discussion at the scoping workshop. The scope has been amended to reflect comments on the population age range and the variability of the condition. It was noted that some attendees considered allogeneic haematopoietic stem cell transplantation

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		rarity of the condition (1 in 500,000 to 1 in 1,000,000) the incident population is expected to be no more than one new patient born per year. Would velmanase alfa be expected to be used in children younger than 6 years? Not at this stage. The target indication for this technology is adults, adolescents and children aged 6 years and older with alpha-mannosidosis. There are also currently no data for use of velmanase alfa in patients aged <6 years. As per the approved EU paediatric investigation plan, study rhLAMAN-08 (an open-label 2 year study of the pharmacology, efficacy and safety of velmanase alfa) is planned. This study will include at least 3 patients aged <6 years at the time of study enrolment. Results will not be available for this study until 2020. Are the comparators for velmanase alfa defined appropriately in the scope? See above. What is considered standard treatment without velmanase alfa in the NHS? Supportive care, which is aimed at managing symptoms, treating infections, delaying disease progression and improving quality of life. As the expression of the disease is complex and highly variable, supportive care is typically multifactorial and tailored to the needs of the individual, i.e. is not a standardised package of care. Describe which patients with alpha-mannosidosis would be considered for allogeneic haematopoietic stem cell transplantation? Due to the rarity of the disease, there are no guidelines on allogeneic HSCT in alpha-mannosidosis. The published literature is limited and describes only very few case reports of patients with alpha-mannosidosis undergoing allogeneic HSCT. Potential candidates would typically include patients with extensive disease presenting in early infancy. The availability of an HLA-	would be a relevant comparator for some people.

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		matched live related donor ensuring a high level of HLA compatibility appears to be a key factor for successful outcome. Are there any subgroups of people in whom alpha-mannosidase is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately? See above. Are the outcome measures listed in the scope appropriate? Is there any other relevant outcome measure that should be included? See above.	
Additional comments on the draft scope	MPS Society	N/A	Noted.
	Chiesi	• All reference to recombinant human alpha-mannosidase should be corrected to velmanase alfa. • All reference to Lamazym should be corrected to Lamzede. • Velmanase alfa has been studied in patients aged 6 years and over, not 5 years as currently written in the draft scope. Reference to the lower age of patients studied should be corrected throughout. Please be aware that this value refers to the age of the patient at enrolment into the studies/treatment initiation. • We note that as per the requirements of the highly specialised technologies process that is proposed for this technology appraisal, velmanase alfa will be appraised taking into account technical, productive and allocative efficiency. However, it is not obvious what this means in practice and how these parameters are expected to be measured or what is meant by “value for money” either in general terms or in the context of alpha-mannosidosis. We would value any additional feedback or clarification that NICE can offer on these points.	Thank you for your comments; the scope has been amended to reflect the correct drug name and the relevant population.