National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation (HST)

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Genetic Alliance UK	This will be only the third gene therapy treatment to be authorised by the EMA, and the second to be appraised by NICE (talimogene laherparepvec is expected to be published in July 2016). It also works through a different mechanism of action from that treatment, through gene therapy of autologous ex-vivo stem cells. We consider that the HST appraisal route (limited to three evaluations per year) should be reserved for novel products that do not match accepted paradigms of treatment, and GSK2696273 falls into this category.	Comment noted.
	GlaxoSmithKline	*Would it be appropriate to refer this topic to NICE for evaluation?* Yes	Comment noted.
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?*		
	Genetic Alliance UK	Yes	Comment noted.

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	GlaxoSmithKline	Yes	Comment noted.
Timing Issues	Genetic Alliance UK	GSK2696273 does not yet have marketing authorisation in Europe, though the application was accepted for evaluation in May 2015. Thus the timing of this proposed HST evaluation is appropriate.	Comment noted.
	GlaxoSmithKline	There is an urgent unmet need to provide an alternative for ADA-SCID patients for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available. Survival after hematopoietic stem cell transplantation (HSCT) falls as HLA matching decreases: 86%, 67%, 43%, and 29%, respectively, for matched sibling, matched unrelated, haploidentical, and mismatched unrelated donors (Hassan et al Blood 2012:120:3615-3624.).	Comment noted.

Comment 2: the draft scope

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Background information	Genetic Alliance UK	The text does not make clear whther this treatment is being considered for all patients with immunodeficiency due to adenosine deaminase deficiency. The background information refers to ADA-SCID diagnosed within the first few months of life, which appears to exclude the 10-15% of ADA deficiency cases, where onset of immune deficiency is delayed to between 6 and 24 months of age (delayed onset) or in an even smaller percentage even until adulthood (late onset). However, this could be made clearer, if this interpretation is the case. Immune deficiency in these later-onset cases tends to be less severe. The background information also does not give an indication of what proportion of patients with ADA-SCID no suitable HLA-matched related stem	Comment noted. Attendees at the scoping workshop highlighted that SCID is defined as having an onset in the first 12 months of life. Strimvelis will be evaluated within its marketing authorisation. Attendees at the

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		cell donor is available for. Our reading suggests that this is the case for some 70-80% of patients with ADA-SCID.	scoping workshop noted that an HLA-matched related donor is unavailable for about half of people with ADA-SCID; the background section has been amended accordingly.
	GlaxoSmithKline	We have provided a revised version of the background information. Please see attached document.	Comment noted. The background section has been revised.
The technology/ intervention	*Is the description of the technology or technologies accurate?*		
	Genetic Alliance UK	Yes	Comment noted.
	GlaxoSmithKline	Yes, however, slightly modified wording is proposed via the attached document.	Comment noted. No changes to the description are needed.
Population	*Is the population defined appropriately?*		
	Genetic Alliance UK	The population is accurately and appropriately defined. However, in contrast to other HST scoping we have engaged with, we note that the population section does not attempt to identify the approximate number of individuals in the population, which is surely relevant to the allocative efficiency of the medicine. As discussed elsewhere in the scoping document, if possible it would be appropriate to consider the subgroup based on previous treatment with	Comment noted. The estimated number of people with ADA-SCID in England has been added to the background section.

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		enzyme replacement therapy separately.	Attendees at the scoping workshop stated that almost all people with ADA-SCID in the UK have treatment with enzyme replacement therapy, so this subgroup was not expected to be needed.
	GlaxoSmithKline	No, please amend as follows. Patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available	Comment noted. The wording of the population has been amended.
Comparators	*Is this (are these) the standard treatment(s) currently used with which the technology should be compared?*		
	Genetic Alliance UK	Yes	Comment noted. Attendees at the scoping workshop agreed that bone marrow transplant is the most appropriate comparator.
	GlaxoSmithKline	Yes Please note, a series of 106 ADA-SCID patients treated with bone marrow transplant (BMT) has been published. We believe that BMT is the most relevant comparator and this published data to be the most comprehensive	Comment noted. Attendees at the scoping workshop agreed that bone marrow transplant is the

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		source of comparator data (Hassan et al. Blood 2012:120:3615-3624).	most appropriate comparator.
Outcomes	Genetic Alliance UK	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes	Comment noted. Attendees at the scoping workshop discussed additional outcomes relating to immune function, non-immunological aspects of ADA-SCID and the need for hospitalisation; the scope has been amended accordingly.
	GlaxoSmithKline	We agree with the outcomes listed. As part of health-related quality of life, descriptive measures including school attendance and Lansky index can be considered. The following outcomes are also available: • IVIG use post gene-therapy • Vaccination responses • Presence of gene modified cells • Lymphocyte ADA activity	Comment noted. Attendees at the scoping workshop discussed additional outcomes relating to immune function, non-immunological aspects of ADA-SCID and the need for hospitalisation; the scope has been amended accordingly. If relevant, descriptive measures of quality of life may be considered.

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Equality and Diversity	Genetic Alliance UK	*NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims.* No	Comment noted.
	GlaxoSmithKline	In the UK, ADA-SCID patients have come primarily from the North Indian, Pakistani, Somalian and Irish-traveller communities. Published data on ADA-SCID are limited and assessing impact on these populations specifically would not be possible. GSK suggest additional consultees are included for comment on the remit and scope.	Comment noted. Additional consultees have been added to the matrix.
Innovation	Genetic Alliance UK	This is an innovative treatment in terms of its mode of action.	Comment noted.
	GlaxoSmithKline	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Yes GSK2696273 is the first ex-vivo gene therapy to be considered for EU centralised approval. GSK2696273 is a step-change in the management of ADA-SCID, because it corrects the underlying cause of the disease using the patients' own cells circumventing the need for a stem cell donor search and the risk of immune rejection (GvHD). In ADA-SCID patients with no suitable matched related bone marrow donor, GSK2696273 can offer improved survival rates over bone marrow transplant, when compared indirectly.	Comment noted.
Other	GlaxoSmithKline	We believe that, because of the rarity of the condition and the subsequent	Comment noted.

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considerations		small number of patients requiring treatment, sub group analyses (e.g. examining the effect of prior ERT, prior transplant exposure etc) would not be meaningful. Please include the following under “Nature of the Condition”: • Disease related mortality • Broader effect on family and carers Please note that due to the fact that ADA-SCID is an ultra-rare disease, published data is not available on the impact of disease on carer’s quality of life, however, descriptive information can be provided.	Attendees at the scoping workshop stated that almost all people with ADA-SCID in the UK have treatment with enzyme replacement therapy, so this subgroup was not expected to be needed. Attendees highlighted that consideration should be given to subgroups based on the degree of HLA matching for HSCT (that is, people for whom matched unrelated or haploidentical HSCT is available). Overall survival and effects on the quality of life of carers are included in the outcomes section.
Questions for consultation	GlaxoSmithKline	In England, while a paediatrician or a GP may raise the suspicion of a primary immunodeficiency, patients are subsequently referred to a paediatric immunologist for diagnosis. Our understanding is that there are 15-20 transplant centres in the UK with a specialisation in primary immune	Comment noted.

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		deficiencies. Following diagnosis, the vast majority of cases are referred for treatment to the Great Ormond Street Hospital and Newcastle-Upon Tyne Hospital where a decision is made on the appropriate treatment option.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health