NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technologies Evaluation

OTL-101 for treating adenosine deaminase deficiency–severe combined immunodeficiency

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of OTL-101 within its marketing authorisation for treating adenosine deaminase deficiency–severe combined immunodeficiency caused by for national commissioning by NHS England.

Background

Immunodeficiency is caused by failure of a component of the immune system and results in increased susceptibility to infections. Severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID) is a disease in which the body cannot make functional lymphocytes (a type of white blood cell) and, as a result, patients have a severely impaired immune system. A faulty gene inherited from both parents impairs production of an essential protein called adenosine deaminase, which is particularly important for the formation of lymphocytes and a functioning immune system. This deficiency usually results in the onset of serious infections within the first few months of life. The symptoms of ADA-SCID include an increased susceptibility to infections and failure to thrive; ADA-SCID also has non-immunological manifestations, including neurological and developmental effects. ADA-SCID is chronically debilitating and life-threatening.

ADA-SCID accounts for about 10–15% of all diagnoses of severe combined immunodeficiency[1]. The overall annual incidence is estimated to be between 1 in 200,000 and 1 in 1,000,000 live births[1], although the incidence varies widely between populations; it is estimated that approximately 3 people are born with ADA-SCID per year in England.

Diagnosis of ADA-SCID includes lymphocyte count, immunoglobulin testing and biochemical and genetic testing. Initial management includes treatment with antibiotics, antiviral and antifungal medicines, intravenous immunoglobulins and prophylaxis for *Pneumocystis jiroveci* (a type of fungal pneumonia), but most people with ADA-SCID ultimately require a bone marrow transplant. Treatment is based on allogeneic haematological stem cell transplantation (HSCT), ideally from a human leukocyte antigen (HLA)-matched related stem-cell donor. However, for about half of people with ADA-SCID, an HLA-matched related donor cannot be found, and other treatment options are considered. These include Strimvelis (an ex vivo gene therapy treatment using a retroviral vector) and HSCT from an HLA-matched unrelated donor, an HLA haploidentical donor (usually a parent), or umbilical cord derived stem cells). Enzyme replacement therapy with pegylated adenosine deaminase enzyme (does not currently have a marketing

authorisation in the UK) is often considered in clinical practice as a short-term option before a bone marrow transplant.

The technology

OTL-101 (brand name unknown, Orchard Therapeutics) is a gene therapy containing autologous $CD34^+$ cells transduced ex vivo with lentiviral vector encoding for the human ADA gene in the DNA sequence. The patient's haematopoietic progenitor and stem cells are harvested from the bone marrow and purified. These are then modified using a lentiviral vector to insert one or more copies of the ADA gene into the cells. When sufficient transduced cells are produced, the patient has pre-treatment with busulfan and the transduced cells are reintroduced into the patient. OTL-101 is administered intravenously.

OTL-101 does not currently have a marketing authorisation in the UK for treating severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID). It has been studied for treating this condition in people for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Intervention(s)	OTL-101 (lentiviral-transduced autologous CD34+ cells)
Population(s)	People with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available
Comparators	• Bone marrow transplant (including HSCT from an HLA-matched unrelated donor or HSCT from an HLA-haploidentical donor) • Strimvelis
Outcomes	The outcome measures to be considered include: • overall survival • intervention-free survival • immune function (including rate of severe infection, lymphocyte counts, thymopoiesis, use of intravenous immunoglobulin, vaccination response) • non-immunological aspects of ADA-SCID (including neurological and developmental effects) • need for and duration of in-patient treatment • adverse effects of treatment • health-related quality of life (for patients and

	carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.

Other considerations	If the evidence allows, subgroups based on the degree of HLA matching for HSCT (that is, people for whom matched unrelated or haploidentical HSCT is available) will be considered. The analysis will include consideration of the duration of enzyme replacement therapy with pegylated adenosine deaminase in people treated with the intervention or comparator, and should include any relevant differences in costs or outcomes associated with this. • Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements.
Related NICE recommendations and NICE Pathways	Related Guidelines: 'Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency' (2018). NICE Highly specialised technologies guidance 7. Review date February 2021. Related NICE Pathways: Immune system conditions (2018) NICE pathway; Metabolic conditions (2018) NICE pathway http://pathways.nice.org.uk/
Related National Policy	NHS England (2017) Manual for prescribed specialised services 2017/18. Chapter 100: Severe combined immunodeficiency and related disorders service (children) NHS England (2013) NHS standard contract for severe immunodeficiency and related disorders service (children) Department of Health (2016) NHS Outcomes Framework 2017-2018. Domains 1, 2, 4 and 5.

Questions for consultation

Have all relevant comparators for OTL-101 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for adenosine deaminase deficiency–severe combined immunodeficiency (ADA-SCID)?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

Would OTL-101 be considered only for people with no HLA-matched related donor, or all people with ADA-SCID?

Would any changes to the delivery of the highly specialised service for ADA-SCID be needed if OTL-101 were made available?

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. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eteplirsen will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

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)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.

References

1. Orphanet (2012) Severe combined immunodeficiency due to adenosine deaminase deficiency. Accessed May 2018.

