NICE National Institute for Health and Care Excellence

NICE guidance

Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency

Highly specialised technologies guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendation

1.1 Strimvelis is recommended, within its marketing authorisation, as an option for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID) when no suitable human leukocyte antigen-matched related stem cell donor is available.

Why the committee made this recommendation

ADA–SCID is a rare and serious condition that is fatal if untreated, and which severely affects the quality of life of people with the condition and their families. Treatment for ADA–SCID includes haematopoietic stem cell transplants (HSCTs). Clinical trial evidence shows that Strimvelis is effective in treating ADA–SCID. Compared with HSCTs, results suggest the main benefits are that more people live after Strimvelis than after a transplant and fewer people develop graft-versus-host disease. However, the exact size of the clinical benefits are uncertain because the trials have been small and uncontrolled, and the evidence for HSCTs is limited.

There are also several important uncertainties in the cost-effectiveness results associated with Strimvelis. However, there are health-related and wider benefits not included in the economic analysis but which are important to consider. Taking these into account, and considering the additional weight that can be assigned to the benefits when the estimated health gain is large, the plausible cost-effectiveness estimates for Strimvelis are within the range that NICE normally considers acceptable for highly specialised technologies.

The cost of Strimvelis is high and there are some uncertainties in the evidence. However, Strimvelis is likely to provide important benefits for people with ADA–SCID, at a cost that provides value for money in the context of a highly specialised service.

2 The condition

2.1 Adenosine deaminase (ADA) deficiency leads to build up of toxic metabolites that causes severe combined immunodeficiency (SCID) and a systemic metabolic defect. ADA–SCID is an ultra-rare condition caused by inheritance of a faulty gene from both parents, which impairs production of the enzyme ADA. The main features of SCID are due to a lack of lymphocytes resulting in a compromised immune system.

2.2 Signs and symptoms of ADA–SCID typically occur in the first year of life (although about 10% to 15% of people with ADA–SCID have a later onset). Immunodeficiency has the greatest effect on morbidity and mortality, and leads to a high risk of serious and life-threatening recurrent infections. The systemic metabolic defect also causes non-immunological manifestations, including insufficient weight and height gain, cognitive and behavioural problems, and deafness. ADA–SCID has a profound effect on health-related quality of life and, if left untreated, infants die before school age. Quality of life is affected by developmental delay, chronic diarrhoea, failure to thrive, recurrent infections and neurological impairments. People whose condition is untreated must be isolated to reduce the risk of infection. The patient experts highlighted that isolation has a profound effect on both patient and carer quality of life.

2.3 ADA–SCID accounts for about 10% to 15% of all diagnoses of severe combined immunodeficiency. The overall annual incidence is estimated to be between 1 in 200,000 and 1 in 1,000,000 live births, although the incidence varies widely between populations. In England, it is most common in people with Irish traveller and Somalian family origins. The company estimated that 3 people a year would be diagnosed with ADA–SCID in England.

2.4 ADA–SCID is currently treated with haematopoietic stem cell transplants (HSCTs), which can restore the immune system if successful. There is a risk of the transplanted cells rejecting the new host (graft-versus-host disease), so donors are chosen based on how close a human leukocyte antigen (HLA) match they are. The first choice HSCT is from an HLA-matched related donor (MRD). If an MRD is not available, an HLA-matched unrelated donor (MUD) would be considered, or a haploidentical donor (who can be a parent) if a MUD is not available. Immediately after diagnosis, people have enzyme replacement therapy with polyethylene glycol-modified adenosine deaminase every week. This is intended to stabilise the condition and provide a 'bridge' to an HSCT, but is not currently licensed in England. In England, 2 highly specialist centres, at Great Ormond Street Hospital and Great North Children's Hospital diagnose, assess and treat ADA–SCID.

3 The technology

3.1 Strimvelis (GlaxoSmithKline) is an ex vivo gene therapy treatment. A patient's bone marrow-derived cells (CD34+ cells) are collected and modified so that they produce functional adenosine deaminase (ADA) enzyme. The modified cells are infused back into the patient, where they engraft in the bone marrow and repopulate the haematopoietic system with cells that produce active levels of the ADA enzyme. Treatment with Strimvelis is suitable if enough CD34+ cells can be harvested, and a bone marrow biopsy can show whether this is feasible. Strimvelis treatment is a single-dose treatment, and the effects are thought to be lifelong. It has a marketing authorisation in the UK for people 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'.

3.2 The only approved manufacturing centre for Strimvelis is in Milan, Italy. Because of the 6-hour shelf life of Strimvelis, the treatment is currently only available at Hospital San Raffaele Telethon Institute for Gene Therapy in Milan. People from England would need to travel to this hospital for treatment with Strimvelis. Arrangements for NHS funding for travel and accommodation costs for people having Strimvelis and their families will be confirmed by NHS England.

3.3 The adverse reactions listed in the summary of product characteristics for Strimvelis include: anaemia, asthma, autoimmunity, atopic dermatitis, eczema, hypertension, hypothyroidism, neutropenia, pyrexia and allergic rhinitis. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 The price for Strimvelis is €594,000 (excluding VAT; company's evidence submission; at an exchange rate of €1 to £0.85, this equates to £505,000).

4 Consideration of the evidence

The evaluation committee (section 6) considered evidence submitted by GlaxoSmithKline, the views of people with the condition, those who represent them, clinical experts and NHS England, and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendation, the committee took into account the full range of factors that might affect its decision including, in particular, the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

4.1 The committee understood that adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID) is a rare and serious condition that is fatal if untreated. It heard that signs and symptoms of ADA–SCID typically occur within the first year of life, the main ones being severe dysfunction of the immune system because of a lack of lymphocytes, and the resulting recurrent infections and failure to thrive. The committee understood this severely affects the quality of life of people with the condition. It heard that, because of the systemic metabolic defect, people can also have non-immunological manifestations of the condition, most commonly cognitive, behavioural and neurosensory deficits. Current treatment options do not improve these abnormalities, so people who have successful treatment may still have lifelong impairments.

Impact of the condition on patients and their families

4.2 The committee heard from patient experts that all aspects of life for both the patient and their family are affected by the condition. The experts highlighted that diagnosis can be delayed because the rarity of the condition can lead to it not immediately being recognised. This can cause profound anxiety to the family as they watch their child suffer recurrent infections without knowing why. The patient experts highlighted that anxiety remains after diagnosis because of the strain of having to think about what lies ahead, including life changes such as isolation to manage the condition before treatment, the possibility of needing to stop work to be a full-time carer and the possibility of embarking on a treatment that carries a mortality risk. The committee concluded that ADA–SCID is a rare, serious, life-threatening and debilitating condition that also severely affects the lives of families and carers.

Diagnosis and management

4.3 The committee heard from clinical experts that, when ADA–SCID is suspected, people will be referred to 1 of the 2 expert centres in England, where a diagnosis will be confirmed by gene testing. The experts explained that the current first-line treatment option for people with ADA–SCID is a haematopoietic stem cell transplant (HSCT) from a human leukocyte antigen (HLA)-matched related donor (MRD) but that for most people, there would not be one available. If an MRD is not available, the next option is an HSCT from an HLA-matched unrelated donor (MUD). To establish whether a MUD is available, a database search for a donor would be started. This is quick, and gives an indication if one might potentially be available. Then, further high-resolution tissue typing and donor availability are confirmed to establish if a transplant is possible. The committee noted the evidence submissions indicated that current clinical practice when a MUD is not available is to enrol people in clinical trials. It noted that, if these trials were unavailable, the next option would be an HSCT from a haploidentical donor. It heard from clinical experts that this option has not been used in clinical practice for a long time but is used for other related conditions, and would be used if clinical trials were unavailable.

4.4 The committee heard that people diagnosed with ADA–SCID at the 2 expert centres are immediately started on enzyme replacement therapy with polyethylene glycol-modified adenosine deaminase (PEG-ADA). The committee was aware that, in England, PEG-ADA is used as a 'bridge' to stabilise the patient's condition before an HSCT. The clinical experts stated that the duration of PEG-ADA as a bridging therapy is highly variable, depending on the patient's condition and the availability of an HSCT.

4.5 The committee heard from clinical experts that the success of current treatment and the severity of lifelong impairment due to the systemic metabolic defect is probably improved by early diagnosis and treatment of the condition. The clinical experts and patient groups noted that, in other countries such as the US, a newborn screening programme identifies people with ADA–SCID at birth. NHS England highlighted that, in England, a consultation is currently in place to determine whether a pilot newborn screening programme for ADA–SCID should be started. The clinical experts considered that starting such a programme could potentially improve the success of treatment and reduce the proportion of people with lifelong impairments.

Impact of the new technology

4.6 The committee discussed the clinical evidence submitted by the company. It was aware that there were several clinical trials that had investigated Strimvelis, the first of which started over 15 years ago. It highlighted that the company preferred to report the results of the clinical trials together, as an 'integrated population', with results from the Named Patient Programme (NPP) presented alongside as supportive evidence. The company stated that it did not include the NPP data in the integrated population because the population of the NPP was substantially different to the population in the other trials, and that it could not access all the patient-level data because the NPP was a clinician-initiated process. Because of the nature of the NPP, the results are confidential and cannot be reported here. The clinical trials reported outcomes consistent with the final decision problem and the company compared outcomes with HSCT treatment. The company identified Hassan et al. (2012), the largest data source on outcomes for patients with ADA–SCID having an HSCT, as the most relevant data source for comparison for most outcomes. However, the company highlighted that often the small patient numbers and differences in reported outcomes made comparisons between Strimvelis and HSCTs difficult. The committee concluded that the approach taken by the company was appropriate for decision-making.

Overall survival

4.7 The committee noted that no deaths have occurred in people with ADA–SCID who have had Strimvelis in the clinical trials. It also heard from the clinical experts that there have been no deaths in people who have had Strimvelis in clinical practice. The committee considered the overall survival to be extremely positive, although it acknowledged that the small patient numbers made the results uncertain. In comparison, overall survival was 67% (10/15) for patients who had an HSCT from a MUD between 1995 and 2009), and was 71% (5/7) for patients who had an HSCT from a haploidentical donor. Results for HSCTs from haploidentical donors were based only on data from 2000–2009 because the company noted substantial improvements in effectiveness over time. The committee heard from the clinical experts that an HSCT from a haploidentical donor is generally expected to be less effective than an HSCT from a MUD, and considered that the higher survival reported in Hassan et al. (2012) for HSCTs from haploidentical donors was unlikely to be borne out in the long term. The committee noted that the figures for overall survival with an HSCT from a MUD have accrued over a long time period. It heard from the clinical experts that they would expect the current overall survival to be higher than reported because of advances in clinical practice over time. The clinical experts noted that they do not have any data on the current overall survival for ADA–SCID treated with an HSCT from a MUD but estimated it could currently be up to 70% to 75%. The committee concluded that Strimvelis improves overall survival compared with HSCT.

Intervention-free survival

4.8 The committee noted that intervention-free survival after Strimvelis (defined in the Strimvelis clinical trials as survival without post-gene therapy PEG-ADA used continuously for 3 months or more, a further HSCT or death) was reported as 82% (14/17). However, it heard from the company that a patient excluded from the analysis because of missing data had since been confirmed as meeting the criteria for intervention-free survival; including these data gives an intervention-free survival of 83% (15/18). It also heard from the clinical experts that they would expect the intervention-free survival of Strimvelis to be greater in clinical practice than reported in the clinical trials because of:

- the restriction of the use of Strimvelis to only people who are expected to produce enough CD34+ cells
- the expertise gained in administering Strimvelis during the 15-year timeframe of the trials.

Looking at the evidence for intervention-free survival after an HSCT, the committee noted that reintroduction of PEG-ADA was not reported systematically for the whole population in Hassan et al. (2012). However, there was evidence that 1 person of the 15 who had had an HSCT from a MUD then had a second HSCT. Of the 7 people who had had an HSCT from a haploidentical donor, 2 did not engraft; 1 of them subsequently had gene therapy and 1 of them had 2 rescue HSCTs and then died. The committee recalled that overall survival with an HSCT is likely to have improved since Hassan et al. (2012; see section 4.7). However, the company argued that, if overall survival increases, it is possible that intervention-free survival would decrease because people who historically would have died may survive but need more interventions to manage their condition. The committee concluded that intervention-free survival was an important measure of Strimvelis's efficacy but, because of differences in reporting, it was difficult to make a comparison with HSCTs.

Immune function

4.9 The committee was aware that the company had collected several measures of immune function in the clinical trials. The committee heard from clinical experts that these measures correlate strongly with clinical outcomes, and are used in clinical practice to inform treatment decisions. It noted that treatment with Strimvelis was broadly shown to lead to immune reconstitution, and considered this was likely to translate into long-term clinical improvement. The committee recalled that recurrent infections because of the lack of lymphocytes are one of the main features of ADA–SCID (see section 2.1). In the Strimvelis clinical trials, severe infections were defined as infections that led to or prolonged hospitalisation, and the estimated rates of infection were 1.17 pre-treatment, 0.26 at 4 months to 3 years post-treatment, and 0.07 at 4 years to 8 years post-treatment. Severe infections had not been clearly reported in the available literature for HSCTs, so rates of severe infection could not be calculated nor compared with those for Strimvelis. However, the committee heard from clinical experts that they would not expect the rate of severe infection to be different between successful treatment with Strimvelis or an HSCT. The committee concluded that the severe infection rate is likely to be similar for Strimvelis and HSCT, and that the rate estimated in the Strimvelis clinical trials represented the best available evidence for decision-making.

Non-immunological aspects of ADA–SCID

4.10 The committee noted that non-immunological events were reported by all but 1 patient after Strimvelis treatment, with the most common being hearing impairment. The committee heard from clinical experts that Strimvelis treatment is also unlikely to improve these aspects of ADA–SCID. However, there is hope that early diagnosis and treatment might limit these symptoms. The committee recalled that treatment with an HSCT does not alleviate the non-immunological aspects of ADA–SCID (see section 4.1). The reporting of these aspects in trials in people who have had an HSCT has been limited. However, the committee noted evidence highlighting that people treated with an HSCT have a mean IQ of more than 2 standard deviations below the general population mean and had a greater risk of behavioural problems. The committee heard from the clinical experts that, in clinical practice, they would expect some people to present with no learning difficulties and a few to present with moderate learning difficulties. It heard from patient experts that they consider the potential neurological abnormalities to be relatively minor in comparison with the importance of a treatment being life-saving. However, the committee concluded that neither Strimvelis nor HSCTs improve the non-immunological aspects of ADA–SCID, and that a substantial proportion of people who have successful treatment will have lifelong impairments.

Adverse events

4.11 The committee was aware that busulfan conditioning is needed to suppress a person's immune system before either an HSCT or Strimvelis, and that this may cause adverse effects. It heard that reduced-dose busulfan protocols are now used when doing an HSCT from a MUD, and that the busulfan dose used before Strimvelis is even lower. The committee accepted that adverse events due to busulfan conditioning are dose dependent, and so conditioning before Strimvelis treatment would be likely to cause fewer adverse events than conditioning before an HSCT. The experts also highlighted that, in infants, the conditioning is known to cause fertility problems in later life and that reduced doses of busulfan are expected to lead to a lower incidence of these; the committee understood that there is no evidence for this reduction yet because people who have had Strimvelis in clinical trials have yet to reach child-bearing age. The committee concluded that Strimvelis treatment is expected to cause fewer adverse events during treatment because of the lower busulfan conditioning needed.

4.12 The committee was aware that graft-versus-host disease (GvHD), in which donor immune cells reject the new host, is an adverse event that can lead to ongoing morbidity or mortality after an HSCT. It noted that no one who has had Strimvelis has developed GvHD, which is to be expected because it is a treatment that uses the patient's own cells. The committee heard from the company, patient experts and clinical experts that they consider the lack of GvHD to be a key benefit of using Strimvelis compared with HSCTs. The clinical experts noted that GvHD is a substantial factor in post-treatment mortality and morbidity after HSCT, and that there is an inverse correlation between how closely matched the HSCT donor is and the risk of GvHD. However, they noted that, even with an HSCT from an MRD, there remains a risk of GvHD. The committee concluded that the lack of GvHD is a valuable benefit of Strimvelis.

4.13 The committee was aware that the use of gene therapy treatment for conditions other than ADA–SCID has been associated with cancer, and that the European Medicines Agency concluded that the long-term carcinogenic potential of Strimvelis could not be determined at the time of assessment. The committee heard from the company that, since 2000, 40 people with ADA–SCID have had treatment with gamma retroviral vectors, including Strimvelis, and that there have been no reports of leukaemia. It heard from the clinical experts that there are theoretical reasons why gene therapy for ADA–SCID is less likely to cause cancer than in other conditions, but that the risk cannot be entirely ruled out. The clinical experts noted that, in other conditions, people who develop cancer present with signs and symptoms relatively soon after treatment, and the company highlighted the median follow-up for Strimvelis in the clinical trials was 6.9 years. The company stated that, as part of its regulatory commitments, it is running a long-term patient registry that will identify and investigate any cases of cancer. NHS England also stated that, as part of the commissioning process, it would produce a patient pathway that would detail the long-term follow-up needed for people in England who have Strimvelis. The committee acknowledged that the risk of cancer, although probably small, could not be excluded. It was reassured that the company and NHS England have measures in place to identify the risks of cancer associated with the treatment in general, and to follow individual patients over time to provide care and treatment if it occurs.

Generalisability of the clinical evidence

4.14 The committee discussed the generalisability of the clinical evidence to people who would have Strimvelis in clinical practice in England. It noted that the median age of people in the clinical trials was 1.7 years, but that the oldest were up to 6 years. The committee recalled that, for most people, signs and symptoms of ADA–SCID begin within the first year of life (see section 2.2). It heard from the clinical experts that they would expect people who have Strimvelis in clinical practice to be younger than those in the clinical trial. The committee heard that it is plausible that, because of this, Strimvelis would be more effective in clinical practice than in the clinical trials. This is because a younger population would be expected to produce a greater harvest of CD34+ cells needed for Strimvelis manufacture, and may have fewer non-immunological aspects of the condition. The committee concluded that the age of the population who would have Strimvelis in clinical practice may be lower than that in the clinical trial, and that this could lead to greater clinical benefit.

Impact of Strimvelis on patients and their families

4.15 The committee heard from patient experts that they considered having the option of Strimvelis would be life changing for patients with ADA–SCID. They highlighted that, because treatment with Strimvelis carried less risk of post-treatment mortality and GvHD than an HSCT from a MUD or haploidentical donor, anxiety for family and carers would be reduced before treatment. They also highlighted that the busulfan conditioning needed for Strimvelis treatment was less harsh than for HSCT, and that this would make a substantial difference to the patients' and carers' quality of life during treatment. The patient experts discussed the upheaval of travelling to Milan for treatment and noted that, although this may be difficult for some people, evidence from a survey of parents suggested that all respondents would be willing to travel for the benefits offered by treatments like this. The committee also heard from 1 patient expert that they expected the financial impact, and impact on family and work, might be similar to currently available treatments because of the need for pre-treatment isolation and travel to 1 of the 2 expert centres in England for HSCTs. The committee recognised that treatment abroad with Strimvelis is potentially a major upheaval for some people. However, it concluded that, on balance, people considered Strimvelis to have a substantial benefit over HSCTs because of the expectation of lower risk of mortality and adverse events.

Cost to the NHS and value for money

4.16 The committee was aware that Strimvelis is administered once at a single specialist centre in Italy, and the price of the technology is €594,000 per person. It highlighted that the cost to the NHS would be in pounds sterling, and noted that the company assumed an exchange rate of €1 to £0.85. The committee was aware that there are other costs that will be incurred in Italy because of the need for hospitalisation during the treatment; these are commercial in confidence and cannot be reported here. The ERG highlighted that there are uncertainties associated with making payments in Euros (because of the fluctuating foreign exchange rate), and with any additional costs incurred by a patient during their stay (for example, if hospitalisation is extended). NHS England stated that it would expect, as part of any contract with the company and the Italian healthcare provider, that the uncertainty associated with cross-border commissioning would be minimised. The committee acknowledged that uncertainties remain over the specific costs that would be incurred by the NHS at the time of the evaluation, but was reassured that NHS England would take steps to minimise these during commissioning.

Number of people who would have Strimvelis

4.17 The committee was aware that the company and NHS England expected 3 people to be diagnosed with ADA–SCID in England per year, but noted that the submission from the patient group stated that it expected 6 to 10 people to be diagnosed per year. The committee heard from the clinical experts and NHS England that this higher estimate relates to the number of people who had treatment in the expert centres each year, which includes people who travel from other European countries. The company estimated that, of the 3 people diagnosed each year, 1 will have an MRD and 1 will choose not to have Strimvelis because of the need to travel to Italy. The committee heard evidence from the clinical experts that about 20% to 25% of people have an MRD. It recalled that the patient experts expected travelling to Italy would be an upheaval, but that families had reported that they would be willing to travel for treatment if necessary (see section 4.15). The committee concluded that the company's estimated patient numbers were reasonable but noted the apparent greater willingness to travel for treatment expressed by the patient experts. It accepted that, because ADA–SCID is a very rare condition, the number of people who would have Strimvelis each year would vary.

5-year budget impact of Strimvelis

4.18 The committee was aware that the company assumed 1 person a year would have Strimvelis treatment. It noted that the total net 5-year budget impact was £2.35 million and £0.93 million for Strimvelis compared with an HSCT from a MUD and a haploidentical donor respectively. The committee noted that the results were highly sensitive to the number of patients having treatment. It concluded that the assumptions made by the company in the budget impact analysis were reasonable.

Company's economic model

4.19 The committee was aware that the model was based on a decision tree to establish the proportion of patients whose initial treatment was successful, with long-term survival extrapolated over a lifetime time horizon using a Markov modelling approach. The company noted that people entered the model aged 1 year, which is younger than reflected in the clinical evidence. It was aware that a younger age affects drug costs because of weight-dependent doses, especially for costs associated with PEG-ADA. The committee recalled that the age of people in the clinical trials was higher than in clinical practice (see section 4.14), and heard from the clinical experts that the starting age of people in the model was more reflective of people with newly diagnosed ADA–SCID who would be identified in clinical practice. The committee concluded that the model structure was suitable for decision-making.

4.20 The committee was aware that the ERG highlighted alternative treatment pathways to initial and rescue transplant after treatment failure. The ERG also highlighted that people who choose Strimvelis may do so after searching for a MUD. The committee recalled that the time-limiting factor when searching for an HSCT donor is contacting and testing potential donors (see section 4.3). It heard from the clinical experts that, if Strimvelis were to be recommended, they would discuss the choice of treatment after doing a database search, but before contacting and testing potential donors. The ERG suggested that, after treatment failure, people who have not had Strimvelis may choose to have it as a rescue therapy. However, the committee heard from the clinical experts that this is not possible because people who have already had busulfan conditioning would be unable to donate sufficient CD34+ cells for the treatment. The committee concluded that the treatment pathway used in the company model was appropriate for decision-making.

Clinical evidence in the model

4.21 The committee noted that the company's model was based on evidence from the 'integrated population' of the Strimvelis clinical trials, but excluded the evidence from the NPP. The ERG considered that the NPP evidence should have been included because of low patient numbers in the evidence. The results of the NPP are confidential and cannot be reported here. However, the committee was aware that the ERG had also identified issues with the generalisability of the NPP evidence. The committee heard from the clinical experts that the patient characteristics of the NPP population were distinctly different from those seen in clinical practice. It recalled that, based on the marketing authorisation of Strimvelis, treatment is only suitable if enough CD34+ cells can be harvested for Strimvelis production, and this can be detected by a bone marrow biopsy (see section 3.1). The committee considered that the population of the NPP was not similar to what would be expected in clinical practice. It also considered that people similar to the NPP population would likely be ineligible for Strimvelis because the treatment is restricted to people in whom sufficient CD34+ cells can be harvested. The committee therefore concluded that the NPP evidence could be excluded from the model.

Uncertainty of model inputs

4.22 The committee recognised that survival after an HSCT or Strimvelis was one of the most influential factors affecting the model results. It was aware that values in the model were based on survival as reported in the Strimvelis clinical trials and Hassan et al. (2012), but that these estimates were highly uncertain because of the limited evidence. The committee recalled that it had considered that the overall survival values reported for an HSCT from a MUD in Hassan et al. were an underestimate because of improvements in outcomes with HSCTs over time (see section 4.7). The clinical experts, when pressed, suggested that current overall survival mortality would be around 70% to 75%. The committee considered that the exact survival rate after an HSCT from MUD was uncertain but considered that a more conservative assumption than used by the company or ERG would be appropriate. It concluded that a value of 72.5% would be reasonable to inform decision-making.

4.23 The company assumed that people having Strimvelis would have 10 weeks less PEG-ADA therapy than people having an HSCT because of the need to search the registry for a donor. The ERG highlighted that the duration of PEG-ADA in practice is uncertain, and that the lengths of time it was given in the Strimvelis trial were substantially longer than those estimated in the model. The ERG stated that it preferred to use equal pre-treatment durations for Strimvelis and HSCTs. The committee heard from the clinical experts that the duration of PEG-ADA in the clinical trial was extended because of the trial inclusion criteria and protocol. It accepted that this was not representative of clinical practice in England. However, it recalled that, in clinical practice, people would not proceed to an HSCT or Strimvelis therapy if their condition was not stable, and would remain on PEG-ADA (see section 2.4). The committee recognised that the duration of pre-treatment PEG-ADA in practice was uncertain, but considered that the ERG's preferred assumption that the durations were equal between HSCTs and Strimvelis was plausible.

4.24 The committee was aware the company assumed that if treatment failure occurred the person would have a rescue HSCT from a newly born matched sibling donor, and that this subsequent treatment would always be successful and would carry no risk of post-treatment adverse events. The committee heard from the clinical experts that, in clinical practice, most people who have a subsequent HSCT would have it from a MUD, and that the success rate of this subsequent transplant would be similar or perhaps slightly lower than for people who were having a first transplant. After consultation, the committee acknowledged that a matched sibling donor would be the first choice if available, although it recalled that a MUD transplant would be more common. The company used the intervention-free survival clinical evidence to inform the rates of rescue transplant in the model, whereas the committee heard from the clinical experts that they expect rescue rates to be equal across the different treatments. The ERG and company highlighted inaccuracies in the modelling of rescue transplants because:

- the rates were not conditional on survival of the initial transplant
- rescue was assumed to occur a year before chronic GvHD had resolved
- a patient previously excluded from analysis because of incomplete data had now been confirmed to have not had a rescue transplant.

The committee was also aware that the model assumed that all rescue transplants occur 2 years after the initial transplant. However, it noted that, in clinical practice, rescue therapy could be done sooner for people treated with Strimvelis compared with HSCTs because Strimvelis does not cause GvHD, and that this would reduce the duration of PEG-ADA needed as a bridge to transplant. The committee concluded that it was more appropriate to assume rescue transplant from a MUD and that the identified inaccuracies should be corrected. However, it considered that the rates were very uncertain because of limitations in the intervention-free survival data. The committee concluded that it was reasonable to consider the scenario in which the rescue rates were equal across the treatment arms in its decision-making.

Utilities

4.25 The committee was aware that the Strimvelis clinical trials collected some quality-of-life data but these had not been included in the model because they were limited; the company instead used utilities from the literature. The ERG highlighted that, in the company model, no disutility was considered for people having intravenous immunoglobulin (IVIG) or for those who had severe infections; after year 8, people were assumed to have regained full health and to have utilities equal to the general population. The committee heard from the company that the assumptions used in the model were for simplicity because no specific long-term utilities for ADA–SCID were identified. The impact of these assumptions was explored in sensitivity and scenario analyses. The ERG preferred to incorporate the company's scenario analysis in which a utility weight of 0.75 was applied to people who had IVIG. The committee heard from clinical experts that people who need IVIG are likely to be sicker than people who do not need it. So, it considered that applying a disutility for these people was reasonable. Moreover, the committee considered it implausible that people would return to full health because it recalled that a substantial proportion of people who have successful treatment will have lifelong impairments (see section 4.10). The committee was aware that the ERG preferred to include costs and utilities associated with bilateral deafness, which has been identified as a common aspect of the condition that would be unaffected by treatment (see section 4.10). The committee heard from the company that these costs and utility values were derived from people with congenital hearing loss and may not reflect people with ADA–SCID whose hearing loss is acquired during infancy. The company preferred to reflect uncertainty over specific utility values by exploring sensitivity analyses that reduced the utilities by up to an extreme value of 20%, rather than including specific utility values. The committee considered it appropriate that restoration to a lower utility than that seen in the general population should be used. However, it was unclear whether specific costs associated with lifelong impairments should be included because these costs are not associated with the treatment. It agreed that the specific utility values were highly uncertain, but noted that quality-of-life gains were similar between the ERG's preferred approach and the company's sensitivity analysis. The committee concluded that, because the ERG's preferred assumptions were based on available evidence, they were preferable for decision-making.

4.26 The committee was aware that the company included a scenario analysis in which an additional disutility was associated with bereavement after the death of a child. The committee considered that this would not fully reflect the quality-of-life benefit to carers after successful treatment. The committee recalled that the patient experts stated that caring for someone who has ADA–SCID affects all aspects of life for a carer (see section 4.2). It heard from the patient experts that improvements to the quality of life of the carer occurred immediately after a successful treatment. The committee heard from the company and ERG that there were no specific carer-related utilities that could be identified to reflect the benefit in quality of life after successful treatment. The committee considered that improvements in carer-related quality of life were an important aspect of successful treatment, but acknowledged that a specific value could not be identified. It concluded that improvements to carer-related quality of life should be qualitatively taken into consideration in the committee's decision-making.

Costs of treating ADA–SCID

4.27 The committee was aware that, at clarification, the company submitted an alternative 'secondary' analysis that included updated unit costs for PEG-ADA and IVIG, costs to the NHS for providing travel to Milan, and ambulance costs to and from the airports. NHS England stated that a policy for NHS funding of travel and accommodation will be developed, building on its experience of commissioning proton beam therapy. It also stated that the cost of travel to Milan for patients and families would be one of the key additional costs to the NHS associated with Strimvelis treatment. The committee therefore considered that these costs should have been included in the model. The ERG also highlighted further alternative unit costs in its critique, which were included in its preferred analysis. These included alternative costs for an HSCT, admission to hospital for GvHD and costs incurred for testing people ineligible for Strimvelis treatment. The committee considered the alternative costs identified by the ERG to be reasonable. It concluded that it was reasonable to include the updated costs in the company's secondary analysis and the ERG's analysis.

Discounting rate for costs and health effects

4.28 The committee was aware that NICE's guide to the methods of technology appraisal (2013) and NICE's interim process and methods of the highly specialised technologies programme (2017) specify that the reference case discounting rate is 3.5%. However, it also states that a non-reference-case rate of 1.5% may be used when treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives, if it is highly likely that there will be long-term benefits, and if the treatment does not commit the NHS to significant irrecoverable costs. The committee heard from the company that it considered a discount rate of 1.5% to be most appropriate because Strimvelis restores people who would otherwise die or have a very severely impaired life to full or near-full health, and sustains gains over a very long period. The committee acknowledged that Strimvelis has a high one-off cost, whereas the benefits are accrued over the lifetime of the patient. It considered that it was likely that the alternative 1.5% discounting rate was intended to cover situations similar to this – that is, when costs are incurred up-front but benefits are accrued over a longer period. The committee acknowledged that the technology was transformative for people who, without treatment, would otherwise die. However, it recalled that people who have successful treatment often have lifelong impairments (see section 4.10). The committee was highly uncertain about whether people treated with Strimvelis would be considered to have 'normal or near-normal health'. The committee was reassured by the clinical experts that the immune reconstitution seen with Strimvelis was expected to translate to long-term immune competence. However, it also recognised that there were uncertainties in whether the long-term benefits of treatment would be achieved because of the limited evidence. The committee concluded that it was uncertain about whether Strimvelis fully met the criteria to use a discounting rate of 1.5%, and that both discount rates should be considered by the committee during its decision-making.

Cost-effectiveness estimates

4.29 The committee noted that, in the company's deterministic base case, Strimvelis was associated with incremental cost-effectiveness ratios (ICERs) of £36,360 and £14,645 per quality-adjusted life year (QALY) gained compared with an HSCT from a MUD and a haploidentical donor respectively. The committee highlighted that the costs and QALYs accrued over the lifetime of the model were high; Strimvelis was associated with 13.6 and 11.7 incremental QALYs and £494,255 and £170,668 incremental costs when compared with an HSCT from a MUD and a haploidentical donor respectively.

4.30 The committee recalled that the ERG made several changes to the company's base case. These were:

- inclusion of NPP data (see section 4.21)
- assuming equal wait time and pre-treatment PEG-ADA use across treatment arms (see section 4.23)
- assuming rescue therapy has cost and health outcomes equal to an initial HSCT from a MUD (see section 4.24)
- including ongoing healthcare costs and morbidity associated with bilateral deafness (see section 4.25)
- using alternative assumptions from the company's secondary analysis and inclusion of alternative unit costs (see section 4.27).

The committee noted that applying all of the ERG's changes increased the ICERs, at a discount rate of 1.5% for Strimvelis, to £86,815 and £16,704 per QALY gained compared with an HSCT from a MUD and a haploidentical donor respectively. The committee recalled that it had considered including the NPP data or costs associated with hearing loss to be inappropriate. Furthermore, it considered that the overall survival after an HSCT from a MUD was underestimated and it was reasonable to use a more conservative estimate of 72.5% (see section 4.22), and that there was also uncertainty over the most appropriate discount rate that should be used (see section 4.28). The results of the cost–utility analysis incorporating the committee's preferred assumptions at a 3.5% discounting rate were £120,506 and £12,106 per QALY gained compared with an HSCT from a MUD and a haploidentical donor respectively. At a 1.5% discounting rate, the results of the model were £74,430 per QALY gained compared with an HSCT from a MUD, and Strimvelis was dominant (that is more effective and less costly) compared with an HSCT from a haploidentical donor.

4.31 The committee recalled that there was uncertainty in the rates of rescue treatment used in the model, and that it was plausible that the rates were equal across treatment arms (see section 4.24). The ERG explored the ICERs when the rescue rate was equal across all the treatment arms. In this scenario analysis, incorporating the committee's preferred assumptions and at a 3.5% discounting rate, the ICERs were £91,910 and £84,172 per QALY gained compared with an HSCT from a MUD and a haploidentical donor respectively. At a 1.5% discounting rate, the ICERs were £54,072 and £49,429 per QALY gained compared with an HSCT from a MUD and a haploidentical donor respectively. The committee acknowledged that the rate of rescue was a key driver of the ICER, but was reassured that it was plausible that the ICER for Strimvelis compared with an HSCT from a MUD may be lower than that estimated using the committee's preferred assumptions.

4.32 The committee understood that NICE's interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained. The committee noted that, based on the most plausible assumptions, the undiscounted QALY gains were 14.0 and 19.6 when Strimvelis was compared with an HSCT from a MUD and a haploidentical donor respectively. The committee understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs, and that this would result in a QALY weighting of 1.40 and 1.96 for Strimvelis compared with an HSCT from a MUD and a haploidentical donor respectively. The committee recalled that rates of rescue treatment were uncertain (see section 4.31), and was reassured to note that the potential QALY weighting would be higher if rates of rescue transplant were equal across all the treatment arms. The committee was satisfied that there was sufficient evidence that Strimvelis offers significant QALY gains, and therefore applied this weighting in its consideration of the value for money of Strimvelis.

Impact of the technology beyond direct health benefits and on the delivery of the specialised

service

4.33 The committee considered the potential benefits of Strimvelis treatment beyond direct health benefits. It understood from the patient experts that, before treatment, people who have ADA–SCID must remain in isolation to avoid the risk of infection, and often a parent must stop working to become a full-time carer. Because Strimvelis reconstitutes the immune system, it could enable children with the condition to be educated at school and for carers of people with the condition to return to work. The committee was aware that travelling abroad for treatment would have an impact on families and patients. It also noted that there are substantial carer quality-of-life benefits from using Strimvelis, but that these have not been captured in the QALY and should be considered by the committee qualitatively in its decision-making. On balance, the committee agreed that there would be cost savings and benefits with Strimvelis incurred outside the NHS and personal and social services.

4.34 The committee discussed the impact of Strimvelis on the delivery of specialised services. It was aware that people would need to travel to Italy for treatment with Strimvelis, so no additional infrastructure would be needed at the specialist centres in England to provide the Strimvelis treatment. The committee noted that the submissions received from NHS England indicated that it expected to contract directly with the hospital in Milan to ensure patients get the high standard of care that they would expect to have in England, but that it did not expect any issues with cross-border commissioning or with implementing Strimvelis treatment within 3 months of publication of the final guidance. NHS England confirmed that, as part of the commissioning process, it would develop a travel and accommodation policy, building on the experience of contracting with centres outside of the UK for proton beam therapy. It also confirmed that it would publish a treatment pathway that would define the process of accessing Strimvelis treatment, and detail the subsequent follow-up needed. NHS England did not indicate the need for any additional training or education of staff at the specialist centres in England. The committee was satisfied that no major changes in staffing and infrastructure would be needed if Strimvelis was made available. It was reassured that NHS England had confirmed its plans for commissioning, and that implementation would occur within the usual timelines.

Other factors

4.35 The committee discussed whether any consideration should be made to reflect the fact that the population under consideration for this technology includes children. It was aware that ADA–SCID is a devastating condition that begins in infancy, and that people with the condition as well as their families and carers are affected in all aspects of life. The committee recalled that it considered that there were important uncaptured health-related benefits for carers associated with successfully treating ADA–SCID, and that these should be considered qualitatively in its decision-making (see section 4.26). It considered that the fact that children are affected by the condition is reflected in the clinical evidence and model, and in the committee's understanding of the nature of the condition. The committee concluded that no additional considerations were needed in its decision-making.

4.36 The committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when evaluating Strimvelis. The committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation of Strimvelis. It therefore concluded that the PPRS payment mechanism was not relevant in considering the value for money offered by Strimvelis.

4.37 The committee was aware of the potential equality issue raised that the incidence of ADA–SCID in England is most common in people from Irish traveller and Somalian family origins. The committee heard from the clinical experts that donor availability for an HSCT can differ based on ethnicity. People from non-white backgrounds have a more difficult time finding a suitable donor and have, on average, a longer wait for an available donor. The company highlighted that treatment with Strimvelis would avoid the expected longer wait times for these populations, but that it was unable to explore subgroup analyses by ethnicity because of the small patient numbers. The committee considered that access to Strimvelis may reduce the disparity in wait times for transplant between different ethnic groups, but acknowledged that there were no data on the size of this potential impact. The committee concluded that this potential equality issue should be qualitatively taken into consideration in its decision-making.

4.38 The committee considered the innovative nature of the technology. It noted that, to date, Strimvelis is the only ex vivo gene therapy to gain marketing authorisation from the European Medicines Agency. The company considered that Strimvelis is a step-change in managing ADA–SCID because it corrects the underlying cause of the condition using the patient's own cells, circumventing the need for a stem cell donor search and the risk of immune rejection (GvHD). The committee concluded that Strimvelis was an innovative technology.

4.39 The committee discussed ongoing evidence collection for Strimvelis. It recalled that the company stated that, as part of its regulatory commitments, it was running a patient registry (see section 4.13). The company stated that data collected as part of this process would be made available to inform a review of this guidance. The committee understood that a number of important outcomes (including survival and use of rescue treatments) were being collected in the registry. However, it noted that a process designed as part of the company's regulatory commitments may not collect some outcomes that would be needed to reduce key uncertainties in the economic model, such as health-related quality of life. The company stated that, because the registry was observational, it would be difficult to require the collection of outcomes that are not collected in standard practice, such as health-related quality of life. However, it stated that it would ensure these data were made available if collected. The committee welcomed access to available evidence for any future review of this guidance. It was encouraged that the company would endeavour to collect data that could reduce some uncertainties identified by the committee during the evaluation. The committee reiterated that, because there were several important uncertainties in the economic model, any possible review of the guidance should explicitly take into account whether the uncertain assumptions were supported by the evidence collected.

Conclusion

4.40 The committee considered the possible recommendations for Strimvelis, taking into account the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits. It appreciated that ADA–SCID is a rare, serious, life-threatening and debilitating condition that has severe effects on the lives of people with the condition, as well as their families and carers. After considering all available evidence, and the opinions of the clinical and patient experts, the committee recognised that Strimvelis represents an important development in the treatment of ADA–SCID. The committee recognised that the results of the trials were uncertain because of low patient numbers and limited evidence for the comparator. However, it agreed that Strimvelis is a clinically effective treatment that improves survival and reconstitutes the immune system for people with ADA–SCID. It understood that the key benefits of Strimvelis compared with an HSCT are the lower risk of post-treatment mortality and the lack of GvHD, although the precise size of the clinical benefits was uncertain. The committee discussed in detail the assumptions in the cost–utility model. Although it recognised that there were a number of important uncertainties in the model (in particular the survival benefit associated with Strimvelis), it considered that the model was sufficient for decision-making. The committee noted that the highest plausible ICER was £120,506 per QALY gained for Strimvelis compared with an HSCT from a MUD at a 3.5% discount rate and noted that, in other scenarios (including when the discount rate was 1.5%), the ICERs were lower. The committee was persuaded that there was evidence that Strimvelis offers significant QALY gains of at least 14 QALYs compared with an HSCT from a MUD, and therefore considered that a QALY weighting of 1.4 could be applied for this comparison. It agreed that Strimvelis was associated with a sizeable incremental therapeutic improvement. The committee noted that, when compared with an HSCT from a haploidentical donor, the ICERs for Strimvelis were consistently substantially lower than £100,000 per QALY gained. The committee also noted that there were several health-related benefits and wider benefits of Strimvelis treatment that were not captured in the economic analysis, and recognised that Strimvelis is an innovative technology. The committee concluded that, although Strimvelis was a high-cost technology and uncertainties remained in the clinical evidence, it is likely to provide important clinical benefits for people with ADA–SCID at a cost that is manageable and value for money in the context of a highly specialised service.

5 Implementation

5.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendation in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation determination. The Welsh Health Specialised Services Committee has written to the Welsh minister to request an extension to the implementation period because of the scale of the service planning required for this treatment. It stated that it planned to deliver this technology in collaboration with NHS England, and that it anticipated implementing the recommendation in this evaluation from April 2018 (that is, 3 months after its anticipated date of publication).

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months. This means that, if a patient has adenosine deaminase deficiency–severe combined immunodeficiency and the doctor responsible for their care thinks that Strimvelis is the right treatment, it should be available for use, in line with NICE's recommendation.

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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