NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency [ID926]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - **GlaxoSmithKline**
   - **Primary Immunodeficiency UK**
   - **NHS England**
   - **Welsh Health Specialised Services Committee**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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.

Comments received from consultees

Consultee	Comment	Response
GlaxoSmithKline	GSK welcomes the draft positive NICE guidance for Strimvelis outlined in the ECD and the recognition that Strimvelis is an innovative technology that is likely to provide important clinical benefits for people with ADA–SCID at a cost that is manageable and value for money. Generally, GSK believes that the summaries of clinical effectiveness and value for money as expressed in the current ECD are reasonable interpretations of the evidence, and that the provisional recommendations represent a sound and a suitable basis for guidance to NHS England. Attached are some specific comments on the ECD in addition to any minor factual inaccuracies identified in the document. Where applicable, we suggest possible amendments and the respective justification. In particular, we request that the committee considers 1.5% as the appropriate level of discounting to use in the base case modelling for this appraisal, in order to identify the most plausible ICER. We believe there is a strong case to support a discounting level of 1.5% for this novel gene therapy procedure, where there is a high upfront cost followed by expected significant lifetime benefits. Assuming a lower discounting rate allows cell and gene therapies to be appraised fairly, relative to chronic treatments. Further, this choice would ensure consistency with how the methods guide section on discounting has been applied within other NICE published guidance, for which there are parallels with Strimvelis.	Comments noted
GlaxoSmithKline	In the *Why the committee made these recommendations* section (Page 3) it is noted that '… the plausible cost-effectiveness estimates for Strimvelis are lower than what NICE normally considers acceptable for highly specialised technologies'. This wording may create some confusion to the general	Comment noted. The FED has been amended to reflect the comment. See section 'Why the committee made these recommendations' section of the Final Evaluation Determination

Consultee	Comment	Response
	public, given that the ICERs were lower than the threshold for acceptability, rather than cost-effectiveness itself. Suggest re-wording to note '… the plausible cost-effectiveness estimates for Strimvelis are within what NICE normally considers acceptable for highly specialised technologies'	(FED).
GlaxoSmithKline	In paragraph 4.8 (Page 10) it is stated that the Committee '… 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 licence to people who are expected to produce enough CD34+ cells • the expertise gained in administering Strimvelis during the 15-year timeframe of the trials. ' GSK would like to clarify that, although it is not expected that patients with low cellularity will receive Strimvelis, as correctly stated by the clinical experts and GSK representatives at the meeting, the licenced therapeutic indication does not explicitly restrict the use. However, it is stated in Section 4.2 of the SmPC (Posology and method of administration) that patients must be able to donate adequate CD34+ cells. For the sake of accuracy, we suggest re-wording the text to note '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 use of Strimvelis only in people who are expected to donate enough CD34+ cells • the expertise gained in administering Strimvelis during the 15-year timeframe of the trials. '	Comment noted. The FED has been amended to reflect the comment. See section 4.8 of the FED.
GlaxoSmithKline	**Pre-procedure PEG-ADA duration** In paragraph 4.23 (Page 19) it is noted that 'The committee considered that	Comment noted. The committee considered that for many people the PEG-ADA duration

Consultee	Comment	Response
	the ERG's preferred assumption that pre-treatment PEG-ADA durations were equal between HSCTs and Strimvelis was plausible'. GSK acknowledges that there may be some uncertainty on whether a potential difference across treatments on the duration of PEG-ADA before treatment will be fully materialised in clinical practice. However, during the first Appraisal Committee meeting, clinical experts confirmed that there is a considerable difference in terms of the process involved in searching for a donor (i.e. that Strimvelis would be used after performing a simple database search, but before the time-consuming process of contacting and testing potential donors). In addition, as per the Kohn 2017 paper and clinical advice received by the ERG, the recommendation is to continue PEG-ADA up to the point of HSCT or for 1 month after if using (lentivirus) gene therapy, whilst for Strimvelis PEG-ADA is stopped 10-22 days beforehand. On top of the potential for optimisation of the clinical schedule for treatment with Strimvelis, this does suggest that time on PEG-ADA for Strimvelis is likely to be considerably less than that observed for HSCT. Thus, GSK still believes that the rationale to justify a shorter duration on PEG-ADA is well established and should warrant a differential time on pre-treatment PEG-ADA to be considered as part of the base case, which would improve even further the cost-effectiveness of Strimvelis. GSK believes that the use in the analyses of a shorter duration of PEG-ADA for Strimvelis prior to initial procedure is warranted and well justified. Even if the Appraisal Committee decided not to agree with using a differential time on PEG-ADA in the base case, we suggest the wording in the ECD around this point to be reflective of the views put forward by the clinical experts and the related discussion at the (open section of) Appraisal Committee meeting.	would be determined by whether their condition were stable. It noted that the PEG-ADA durations in the Strimvelis trials were substantially longer than those estimated in the model. The committee recognised that the duration of pre-treatment PEG-ADA in practice was uncertain, but considered that there was no new evidence that would change its conclusion that the assumption that the durations were equal between HSCTs and Strimvelis was plausible. See section 4.23 of the FED for more information.
	Expected Type of Rescue HSCT In paragraph 4.24 (Page 19) it is noted that '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	Comment noted. The FED has been amended to acknowledge that a matched sibling donor would be the first choice if available. See section 4.24 of the FED.

Consultee	Comment	Response
	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…'. Although GSK accepts that MUD may be used more often, if a MSD/MRD is available, as was the case for two patients in the Strimvelis clinical trial programme requiring a rescue, it will always be used in preference to other types of donors. There is the belief that rescue transplants from a younger MSD are likely to become more prevalent as new IVF techniques allow selecting the embryo before birth to ensure the child is born with no genetic predisposition for ADA-SCID. The perception that an eventual rescue transplant will always come from a MUD is inconsistent with the available data and information. Although it is acknowledged there is some uncertainty around the type of transplant received for a rescue, we believe that at least a proportion of rescue transplants should be assumed to be from a MSD, which would improve the cost effectiveness of Strimvelis versus MUD even further. GSK believes that the proportion of type of donor for rescue transplant should reflect that in practice some transplants are indeed expected to be from a MSD. Even if the Appraisal Committee decided not to agree with using a proportion of MSD:MUD (e.g. 25:75) in the base case, we suggest the wording in the ECD around this point to be reflective of the views put forward by the clinical experts and the related discussion at the (open section of) Appraisal Committee meeting.	
	In paragraph 4.24 (Page 20) it is noted that 'The ERG and company highlighted inaccuracies in the modelling of rescue transplants because: • … • … • a patient excluded from analysis has now been confirmed to have met the criteria for intervention-free survival.' The economic model considered only rescue transplant. The investigator confirmed that a patient previously excluded in the cost effectiveness	Comment noted. The FED has been amended to reflect the comment. See section 4.24 of the FED.

Consultee	Comment	Response
	analysis due to lack of continuous follow up had not received a rescue transplant or is receiving ongoing long-term PEG-ADA. It is therefore more appropriate to model and report the patient as not having received a rescue transplant. For clarity, we suggest re-wording the text to note 'The ERG and company highlighted inaccuracies in the modelling of rescue transplants because: • … • … • the investigator confirmed that a patient previously excluded in the cost effectiveness analysis – due to lack of continuous follow-up – had not received a rescue transplant.'	
	Long-term Impairment on Quality of Life With regards to the potential impact of any long-term impairment on the quality of life of surviving patients, in paragraph 4.25 (Page 20) it is noted that 'The company preferred to reflect uncertainty over specific utility values by exploring sensitivity analyses that reduced the utilities by up to 20%, rather than including specific utility values'. Firstly, whilst it is correct the original submission included sensitivity analyses around this input by applying an utility decrement from 5% to a maximum of 20%, we would like to note that it is normal to test model assumptions using extreme values. By exploring a decrement as high as 20% GSK was in no way accepting that would be the most adequate value to be used in the base case. By applying an extreme 20% decrement we were in fact testing what we believed to be the very worst case scenario. Secondly, whilst we do not disagree there may be some morbidity associated with the disease in the long term for some patients, there is great uncertainty on how those will manifest in patients receiving Strimvelis, particularly in very young infants. In our response to the ERG report, GSK explained why we believe the sources and approach used by the ERG to estimate a potential impact on	Comments noted. The FED has been amended to reflect that the 20% value used by the company was an extreme value. See section 4.25 of the FED.

Consultee	Comment	Response
	patients' quality of life were not appropriate. Overall, GSK still believes it not ideal to include estimates in a base case which are not aligned in terms of frequency, duration, and severity of impairment with what was observed in the Strimvelis clinical trial programme. Particularly when, as patient representatives noted at the Appraisal Committee meeting, children with hearing impairment appear to live a normal life. The estimates selected by the ERG appear to considerably overestimate the potential health-related quality of life decrement associated with hearing impairment after the use of Strimvelis and, if amended, this would improve further the estimated cost-effectiveness of Strimvelis.	The committee noted that the long-term morbidity after Strimvelis or HSCT was discussed thoroughly during the evaluation. The committee considered that there was no new evidence that would change its conclusion that the specific utility values were highly uncertain but that the ERG's assumptions were sufficient for decision-making. See section 4.25 of the FED for more information.
	Discount Rate In paragraph 4.28 (Page 23) it is noted that 'The Committee acknowledged that Strimvelis has a high one-off cost, whereas the benefits are accrued over the life time 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 life-long 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.' As noted in the ECD, the Methods Guide does allow for the exception of using a lower discount rate and the NICE Appraisal Committee in the past has accepted justification for using a 1.5% discount rate in other appraisals, such as that of eculizumab for treating atypical haemolytic uraemic syndrome (HST1) and mifamurtide for the treatment of osteosarcoma (TA235). In addition, a 1.5% discount rate is commonly used when assessing interventions where a significant amount of the benefit accrues long after the intervention occurs, such as for public health programmes. Not allowing for this adjustment would put one-off cell and gene therapies with an expected long -term benefit at a disadvantage relative to chronic treatments.	Comment noted. The committee noted that the discounting rate was discussed thoroughly during the evaluation. The committee considered that there was no new evidence that would change its conclusion that both discounting rates should be considered during its decision-making. See section 4.28 of the FED for more information.

Consultee	Comment	Response
	GSK's original submission did apply a discount rate of 1.5% to both costs and outcomes on this basis and the ERG's base case ICERs also used a 1.5% discount rate. Even though historically some ADA-SCID patients may have experienced some form of long term impairment, this, as heard from patient experts at the Appraisal Committee meeting, does not prevent patients from living a near normal life. In fact, the patient perspective was what was referred to justify that patients receiving mifamurtide would live a near normal life despite increased incidence of hearing loss and hence the acceptance of a 1.5% discount rate to be applied to the base case. Furthermore, for the Strimvelis case it is acknowledged in Paragraph 4.14 of the ECD that '… 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'. It seems therefore apparent that patients treated with Strimvelis are reasonably expected to have a long and sustained benefit and regain normal life expectancy. Overall, although we understand the need for the Committee's discussion around which discount rate to use, GSK believes that the assessment of Strimvelis truly reflects the case for which the use of an alternative discount rate was established, i.e. high upfront cost with significant long term benefit accruing over a patient's lifetime. Thus, we consider that the Strimvelis cost effectiveness estimates using a 1.5% discount rate remain the most appropriate to be used as the base case figures to inform decision making. GSK believes applying a 1.5% discount rate is the most appropriate option given the nature of the intervention and the expected lifelong benefits. Therefore, we would welcome the ECD to reflect the ICERs derived from a 1.5% base case to be the primary figures used for decision-making by the Appraisal Committee and be used to identify the most plausible ICER.	
	Rescue Transplant Rates In paragraph 4.31 (Page 25) it is noted that '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'. GSK welcomes the rationale which, supported by the opinion expressed by	Comment noted. The FED has been amended to reflect that the committee was reassured that the potential QALY weighting would be higher if rates of rescue transplant were equal across all the treatment arms. See section

Consultee	Comment	Response
	the clinical experts at the Appraisal Committee meeting, suggests that the rate of rescue transplant could be assumed to be similar across treatments. This would further improve the cost-effectiveness of Strimvelis versus HSCT from a MUD and we believe this should in fact be considered in the base case used to inform the Appraisal Committee decision making. GSK would also like to note that, if that were the case, the estimated undiscounted QALY gain would be 15.43. This would result in a higher adjusted acceptability threshold of £154,000/QALY gained, which would increase further the probability of Strimvelis being considered cost-effective. GSK believes that, based on the discussion at the (open section of) the Appraisal Committee meeting the most plausible ICER used for decision making should reflect the assumption of a similar rate of rescue transplant across treatments. Not only will this directly improve the cost-effectiveness estimates, but the higher undiscounted QALY gain would also allow a higher weight of 1.54 to be applied to the adjusted acceptability threshold when Strimvelis is compared to HSCT from a MUD, increasing the probability of Strimvelis being considered cost-effective.	4.32 of the FED.
NHS England	There had been a suggestion in the documentation that NHS England should pay for the non-drug costs for treatment via the 'S2' funding route. However, in England, the budget for 'S2' referrals is not held by the NHS but rather by the Department of Health. This funding route is therefore not available for NHS England. NHS England would anticipate putting in place a contracting arrangement directly with the treating hospital in Milan with the expectation that the NHS would pay the same rates as for statutory Italian patients (there was a suggestion during previous discussions with the drug company that there would be a different, higher rate for some aspects of the treatment package). The plan to contract directly with the hospital in Milan is because (a) NHS	Comments noted. The FED has been amended to incorporate the committee's considerations on the implementation and commissioning in England. See sections 4.27, 4.34 and 5.2 of the FED.

Consultee	Comment	Response
	England does not have access to the S2 funding route and (b) NHS England would wish to assure themselves that the hospital is offering NHS patients a high quality service (in the same as they would for all treatments available to NHS patients. There is no expectation on the part of NHS England that a direct contract with Milan would mean discounted compared to that paid for statutory Italian patients. NHS England confirms that it would develop a travel and accommodation policy building on the experience of contracting with centres outside of the UK for proton beam therapy and where patients and their families have to spend protracted periods away from home. NHS England confirms that it would be able to implement these arrangements by the end of April 2018.	
Primary Immunodeficiency UK	**Overall comment:** PID UK welcomes that NICE view Strimvelis as an important development in the treatment of ADA-SCID and supports the decision by NICE to provisionally recommend it as a treatment option for ADA-SCID when a suitable HLA stem cell donor is not available. As our patient survey showed, treatment by gene therapy has a transformational impact on the health of the child and on the quality of life of the family unit. Furthermore our findings showed that families would consider the option of travelling abroad to access Strimvelis treatment so we hope full approval will be given. PID UK agrees that all the relevant evidence has been taken into account in a fair way. We were particularly pleased that the patient evidence provided at the committee meeting was carefully considered and played an important part in the decision making process. PID UK agrees that the summaries of the criteria and clinical and economic considerations have been interpreted in a reasonable way. PID UK agrees that the provisional recommendations are sound in the context of national commissioning by NHS England. **Section 3.2**: **Costs to patient to access therapy**	Comments noted. NHS England confirmed that, as part of the commissioning process, it would develop a

Consultee	Comment	Response
	Once full approval has been given we would welcome details from NHS England about NHS funding for travel and accommodation for people having Strimvelis. **Section 4.13**: **Risk of oncogenic events** It is essential that long-term follow up be done for patients who access gene therapy through clinical trials and commercially approved medicines. NICE guidance should give details of what requirements need to be met and who is responsible. **Section 4.20: Model of decision making** PID UK agrees with the model of decision making for patients to access Strimvelis. **Section 4.26 and 4.33: Impact on carer quality of life post treatment** PID UK understands that a monetary value cannot be attributed but is reassured that NICE accepts the qualitative impact that GT can have on a carer's QoL and that it will be taken into consideration for decision-making. **Section 4.27: Cost of travel** PID UK agrees that cost of travel to access treatment should be taken into consideration in the model. **Section 4.34: Ensuring patient choice** If full approval is given specialist centres should be obliged as part of their commissioned services to offer Strimvelis as a treatment option for patients where appropriate even if clinical trials using other gene therapy vectors are on-going at their centre. **Section 4.37: Equality issues** Reducing the disparity between different ethnic groups is an important issue and PID UK agrees that this should absolutely be taken into account. **Section 5: Implementation** PID UK would welcome information on the timelines for full implementation if NICE approval is given i.e. when will the guidance be published? This is an important step forward for the families who helped with our patient survey and we want to keep them informed of the process and timescale to this	travel and accommodation policy. See section 4.34 of the FED for more information. The committee discussed the long-term follow up for people who have Strimvelis, and were 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. See section 4.13 of the FED for more information. When NICE recommends a treatment ‘as an option’, 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 recommendations. See section 5.3 of the FED for more information. When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within 3 months. See section 5.3 of the FED for more information.

Consultee	Comment	Response
	treatment being offered to patients. **Section 5.2: Implementation - NHS Wales** PID UK hopes that arrangements within NHS Wales will be confirmed swiftly such that they do not unduly delay the publication and implementation of final guidance. **Section 5.3: Implementation by the NHS within 3 months of final published** **guidance** PID UK trusts that the NHS will keep to this mandate and not put in place any stumbling blocks to delay access to Strimvelis.	NHS England confirmed in its response to consultation that implementation would be within the standard implementation timeline in England, that is within 3 months of publication of the final guidance. WHSSC anticipates implementing the recommendations in this evaluation from April 2018 (that is, 3 months after its anticipated date of publication). See sections 5.2 and 5.3 of the FED for more information.

Comments received from clinical specialists and patient experts

No comments received

Comments received from commentators

Commentator	Comment	Response
Welsh Health Specialised Services Committee (WHSSC)	The Welsh Health Specialised Services Committee (WHSSC) is responsible for the joint planning of Specialised and Tertiary Services on behalf of Local Health Boards in Wales. Consequently we are responsible for the commissioning of all interventions used in the treatment of ADA–SCID including haematopoietic stem cell transplantation (HSCTs). We are aware that ADA-SCID is an ultra rare condition and the use of Strimvelis is only intended when a stem cell transplant cannot be undertaken usually because no suitable human leukocyte antigen-matched related stem cell donor is available At present 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 Wales (and their family members/carers) would need to travel to this hospital for treatment.	Comment noted. The FED has been amended to incorporate the information on implementation in Wales. See section 5.2 of the FED.

Commentator	Comment	Response
	We know that colleagues in Highly Specialised Services (NHS England) have already started to plan for the implementation of this treatment. Given the rarity of this condition and highly specialised nature of the treatment pathway (and to avoid unnecessary duplication of effort) WHSSC has contacted NHS England to suggest a collaboration in order to develop a common referral pathway and protocol. It may also include agreeing and defining suitable gate-keeping arrangements. This collaboration has been agreed in principle and further discussion is planned for early in 2018. It is anticipated that WHSSC will be invited to attend meetings with the two specialist centres in England who diagnose, assess and treat ADA-SCID (Great Ormond Street Hospital and Great North Children's Hospital) and contribute to the development of referral pathways, protocols and a commissioning policy. It is anticipated that the arrangements for NHS funding of travel and accommodation costs for people in Wales having Strimvelis and their families will be assessed using a similar model to that already in use for Proton Beam Therapy. The Welsh Government launched the New Treatment Fund (NTF) in January 2017. This is a key commitment within the programme for Government – Taking Wales Forward. The fund will provide an additional £16 million annually for Health Boards and Trusts in Wales to support the faster introduction of new medicines recommended by NICE and the All Wales Medicines Strategy Group. For NICE recommendations, a medicine should be available no later than 60 calendar days after the first publication of the Final Evaluation Determination for Highly Specialised Technologies. However setting up the service to deliver Strimvelis will take time and implementation is likely to exceed this 60-day timeframe. In exceptional circumstances, where the scale of service planning necessary to make a health care intervention available will take longer than two months, this can be amended. WHSSC will be writing to the Welsh Government Minister requesting such an extension with our reasons clearly set out. Given the scale of planning and implementation required we are not	

Commentator	Comment	Response
	expected to have this work completed until at least April 2018.	

Comments received from members of the public

No comments received

The following consultees/commentators indicated that they had no comments on the Evaluation Consultation Document

Department of Health

Genetic Alliance UK

GlaxoSmithKline
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TW8 9GS
United Kingdom

FAO Jo Ekeledo
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
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M1 4BT

13 November 2017

Dear Jo,

Reference: Evaluation Consultation Document (ECD) for Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID)

GSK welcomes the draft positive NICE guidance for Strimvelis outlined in the ECD and the recognition that Strimvelis is an innovative technology that is likely to provide important clinical benefits for people with ADA–SCID at a cost that is manageable and value for money.

Generally, GSK believes that the summaries of clinical effectiveness and value for money as expressed in the current ECD are reasonable interpretations of the evidence, and that the provisional recommendations represent a sound and a suitable basis for guidance to NHS England. Attached are some specific comments on the ECD in addition to any minor factual inaccuracies identified in the document. Where applicable, we suggest possible amendments and the respective justification.

In particular, we request that the committee considers 1.5% as the appropriate level of discounting to use in the base case modelling for this appraisal, in order to identify the most plausible ICER. We believe there is a strong case to support a discounting level of 1.5% for this novel gene therapy procedure, where there is a high upfront cost followed by expected significant lifetime benefits. Assuming a lower discounting rate allows cell and gene therapies to be appraised fairly, relative to chronic treatments. Further, this choice would ensure consistency with how the methods guide section on discounting has been applied within other NICE published guidance, for which there are parallels with Strimvelis.

Should you have any further queries please do not hesitate to contact [redacted] ([redacted]).

Yours sincerely,

[redacted]

GSK, Value Evidence and Outcomes

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID)

Response to consultation on ECD

Issue	Suggested Amendment
In the *Why the committee made these recommendations* section (Page 3) it is noted that '… the plausible cost-effectiveness estimates for Strimvelis are lower than what NICE normally considers acceptable for highly specialised technologies'. This wording may create some confusion to the general public, given that the ICERs were lower than the threshold for acceptability, rather than cost-effectiveness itself.	Suggest re-wording to note '… the plausible cost-effectiveness estimates for Strimvelis are within what NICE normally considers acceptable for highly specialised technologies'
In paragraph 4.8 (Page 10) it is stated that the Committee '… 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 licence to people who are expected to produce enough CD34+ cells • the expertise gained in administering Strimvelis during the 15-year timeframe of the trials. ' GSK would like to clarify that, although it is not expected that patients with low cellularity will receive Strimvelis, as correctly stated by the clinical experts and GSK representatives at the meeting, the licenced therapeutic indication does not explicitly restrict the use. However, it is stated in Section 4.2 of the SmPC (Posology and method of administration) that patients must be able to donate adequate CD34+ cells.	For the sake of accuracy, we suggest re-wording the text to note '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 use of Strimvelis only in people who are expected to donate enough CD34+ cells • the expertise gained in administering Strimvelis during the 15-year timeframe of the trials. '

Issue	Suggested Amendment
Pre-procedure PEG-ADA duration In paragraph 4.23 (Page 19) it is noted that 'The committee considered that the ERG's preferred assumption that pre-treatment PEG-ADA durations were equal between HSCTs and Strimvelis was plausible'. GSK acknowledges that there may be some uncertainty on whether a potential difference across treatments on the duration of PEG-ADA before treatment will be fully materialised in clinical practice. However, during the first Appraisal Committee meeting, clinical experts confirmed that there is a considerable difference in terms of the process involved in searching for a donor (i.e. that Strimvelis would be used after performing a simple database search, but before the time-consuming process of contacting and testing potential donors). In addition, as per the Kohn 2017 paper and clinical advice received by the ERG, the recommendation is to continue PEG-ADA up to the point of HSCT or for 1 month after if using (lentivirus) gene therapy, whilst for Strimvelis PEG-ADA is stopped 10-22 days beforehand. On top of the potential for optimisation of the clinical schedule for treatment with Strimvelis, this does suggest that time on PEG-ADA for Strimvelis is likely to be considerably less than that observed for HSCT. Thus, GSK still believes that the rationale to justify a shorter duration on PEG-ADA is well established and should warrant a differential time on pre-treatment PEG-ADA to be considered as part of the base case, which would improve even further the cost-effectiveness of Strimvelis.	GSK believes that the use in the analyses of a shorter duration of PEG-ADA for Strimvelis prior to initial procedure is warranted and well justified. Even if the Appraisal Committee decided not to agree with using a differential time on PEG-ADA in the base case, we suggest the wording in the ECD around this point to be reflective of the views put forward by the clinical experts and the related discussion at the (open section of) Appraisal Committee meeting.

Issue	Suggested Amendment
Expected Type of Rescue HSCT In paragraph 4.24 (Page 19) it is noted that '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…'. Although GSK accepts that MUD may be used more often, if a MSD/MRD is available, as was the case for two patients in the Strimvelis clinical trial programme requiring a rescue, it will always be used in preference to other types of donors. There is the belief that rescue transplants from a younger MSD are likely to become more prevalent as new IVF techniques allow selecting the embryo before birth to ensure the child is born with no genetic predisposition for ADA-SCID. The perception that an eventual rescue transplant will always come from a MUD is inconsistent with the available data and information. Although it is acknowledged there is some uncertainty around the type of transplant received for a rescue, we believe that at least a proportion of rescue transplants should be assumed to be from a MSD, which would improve the cost effectiveness of Strimvelis versus MUD even further.	GSK believes that the proportion of type of donor for rescue transplant should reflect that in practice some transplants are indeed expected to be from a MSD. Even if the Appraisal Committee decided not to agree with using a proportion of MSD:MUD (e.g. 25:75) in the base case, we suggest the wording in the ECD around this point to be reflective of the views put forward by the clinical experts and the related discussion at the (open section of) Appraisal Committee meeting.
In paragraph 4.24 (Page 20) it is noted that 'The ERG and company highlighted inaccuracies in the modelling of rescue transplants because: • … • …	For clarity, we suggest re-wording the text to note 'The ERG and company highlighted inaccuracies in the modelling of rescue transplants because: • … • …

Issue	Suggested Amendment
• a patient excluded from analysis has now been confirmed to have met the criteria for intervention-free survival.' The economic model considered only rescue transplant. The investigator confirmed that a patient previously excluded in the cost effectiveness analysis due to lack of continuous follow up had not received a rescue transplant or is receiving ongoing long-term PEG-ADA. It is therefore more appropriate to model and report the patient as not having received a rescue transplant.	• the investigator confirmed that a patient previously excluded in the cost effectiveness analysis – due to lack of continuous follow-up – had not received a rescue transplant.'
Long-term Impairment on Quality of Life With regards to the potential impact of any long-term impairment on the quality of life of surviving patients, in paragraph 4.25 (Page 20) it is noted that 'The company preferred to reflect uncertainty over specific utility values by exploring sensitivity analyses that reduced the utilities by up to 20%, rather than including specific utility values'. Firstly, whilst it is correct the original submission included sensitivity analyses around this input by applying an utility decrement from 5% to a maximum of 20%, we would like to note that it is normal to test model assumptions using extreme values. By exploring a decrement as high as 20% GSK was in no way accepting that would be the most adequate value to be used in the base case. By applying an extreme 20% decrement we were in fact testing what we believed to be the very worst case scenario. Secondly, whilst we do not disagree there may be some morbidity associated with the disease in the long term for some patients, there is great uncertainty on how those will manifest in patients receiving Strimvelis, particularly in very young infants.	Not applicable.

Issue	Suggested Amendment
In our response to the ERG report, GSK explained why we believe the sources and approach used by the ERG to estimate a potential impact on patients' quality of life were not appropriate. Overall, GSK still believes it not ideal to include estimates in a base case which are not aligned in terms of frequency, duration, and severity of impairment with what was observed in the Strimvelis clinical trial programme. Particularly when, as patient representatives noted at the Appraisal Committee meeting, children with hearing impairment appear to live a normal life. The estimates selected by the ERG appear to considerably overestimate the potential health-related quality of life decrement associated with hearing impairment after the use of Strimvelis and, if amended, this would improve further the estimated cost-effectiveness of Strimvelis.	
Discount Rate In paragraph 4.28 (Page 23) it is noted that 'The Committee acknowledged that Strimvelis has a high one-off cost, whereas the benefits are accrued over the life time 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 life-long 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.' As noted in the ECD, the Methods Guide does allow for the exception of using a lower discount rate and the NICE Appraisal Committee in	GSK believes applying a 1.5% discount rate is the most appropriate option given the nature of the intervention and the expected lifelong benefits. Therefore, we would welcome the ECD to reflect the ICERs derived from a 1.5% base case to be the primary figures used for decision-making by the Appraisal Committee and be used to identify the most plausible ICER.

Issue	Suggested Amendment
the past has accepted justification for using a 1.5% discount rate in other appraisals, such as that of eculizumab for treating atypical haemolytic uraemic syndrome (HST1) and mifamurtide for the treatment of osteosarcoma (TA235). In addition, a 1.5% discount rate is commonly used when assessing interventions where a significant amount of the benefit accrues long after the intervention occurs, such as for public health programmes. Not allowing for this adjustment would put one-off cell and gene therapies with an expected long - term benefit at a disadvantage relative to chronic treatments. GSK's original submission did apply a discount rate of 1.5% to both costs and outcomes on this basis and the ERG's base case ICERs also used a 1.5% discount rate. Even though historically some ADA-SCID patients may have experienced some form of long term impairment, this, as heard from patient experts at the Appraisal Committee meeting, does not prevent patients from living a near normal life. In fact, the patient perspective was what was referred to justify that patients receiving mifamurtide would live a near normal life despite increased incidence of hearing loss and hence the acceptance of a 1.5% discount rate to be applied to the base case. Furthermore, for the Strimvelis case it is acknowledged in Paragraph 4.14 of the ECD that '… 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'. It seems therefore apparent that patients treated with Strimvelis are reasonably expected to have a long and sustained benefit and regain normal life expectancy. Overall, although we understand the need for the Committee's discussion around which discount rate to use, GSK believes that the	

Issue	Suggested Amendment
assessment of Strimvelis truly reflects the case for which the use of an alternative discount rate was established, i.e. high upfront cost with significant long term benefit accruing over a patient's lifetime. Thus, we consider that the Strimvelis cost effectiveness estimates using a 1.5% discount rate remain the most appropriate to be used as the base case figures to inform decision making.	
Rescue Transplant Rates In paragraph 4.31 (Page 25) it is noted that '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'. GSK welcomes the rationale which, supported by the opinion expressed by the clinical experts at the Appraisal Committee meeting, suggests that the rate of rescue transplant could be assumed to be similar across treatments. This would further improve the cost-effectiveness of Strimvelis versus HSCT from a MUD and we believe this should in fact be considered in the base case used to inform the Appraisal Committee decision making. GSK would also like to note that, if that were the case, the estimated undiscounted QALY gain would be 15.43. This would result in a higher adjusted acceptability threshold of £154,000/QALY gained, which would increase further the probability of Strimvelis being considered cost-effective.	GSK believes that, based on the discussion at the (open section of) the Appraisal Committee meeting the most plausible ICER used for decision making should reflect the assumption of a similar rate of rescue transplant across treatments. Not only will this directly improve the cost-effectiveness estimates, but the higher undiscounted QALY gain would also allow a higher weight of 1.54 to be applied to the adjusted acceptability threshold when Strimvelis is compared to HSCT from a MUD, increasing the probability of Strimvelis being considered cost-effective.

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PID UK response to ECD: Strimvelis for ADA-SCID (ID 926)

Overall comment:

PID UK welcomes that NICE view Strimvelis as an important development in the treatment of ADA-SCID and supports the decision by NICE to provisionally recommend it as a treatment option for ADA-SCID when a suitable HLA stem cell donor is not available.

As our patient survey showed, treatment by gene therapy has a transformational impact on the health of the child and on the quality of life of the family unit. Furthermore our findings showed that families would consider the option of travelling abroad to access Strimvelis treatment so we hope full approval will be given.

PID UK agrees that all the relevant evidence has been taken into account in a fair way. We were particularly pleased that the patient evidence provided at the committee meeting was carefully considered and played an important part in the decision making process.

PID UK agrees that the summaries of the criteria and clinical and economic considerations have been interpreted in a reasonable way.

PID UK agrees that the provisional recommendations are sound in the context of national commissioning by NHS England.

Section 3.2: **Costs to patient to access therapy**

Once full approval has been given we would welcome details from NHS England about NHS funding for travel and accommodation for people having Strimvelis.

Section 4.13: **Risk of oncogenic events**

It is essential that long-term follow up be done for patients who access gene therapy through clinical trials and commercially approved medicines. NICE guidance should give details of what requirements need to be met and who is responsible.

Section 4.20: Model of decision making

PID UK agrees with the model of decision making for patients to access Strimvelis.

Section 4.26 and 4.33: Impact on carer quality of life post treatment

PID UK understands that a monetary value cannot be attributed but is reassured that NICE accepts the qualitative impact that GT can have on a carer's QoL and that it will be taken into consideration for decision-making.

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Part of Genetic Disorders UK

Section 4.27: Cost of travel
PID UK agrees that cost of travel to access treatment should be taken into consideration in the model.

Section 4.34: Ensuring patient choice
If full approval is given specialist centres should be obliged as part of their commissioned services to offer Strimvelis as a treatment option for patients where appropriate even if clinical trials using other gene therapy vectors are on-going at their centre.

Section 4.37: Equality issues
Reducing the disparity between different ethnic groups is an important issue and PID UK agrees that this should absolutely be taken into account.

Section 5: Implementation
PID UK would welcome information on the timelines for full implementation if NICE approval is given i.e. when will the guidance be published? This is an important step forward for the families who helped with our patient survey and we want to keep them informed of the process and timescale to this treatment being offered to patients.

Section 5.2: Implementation - NHS Wales
PID UK hopes that arrangements within NHS Wales will be confirmed swiftly such that they do not unduly delay the publication and implementation of final guidance.

Section 5.3: Implementation by the NHS within 3 months of final published guidance
PID UK trusts that the NHS will keep to this mandate and not put in place any stumbling blocks to delay access to Strimvelis.

NHS ENGLAND COMMENTS ON THE CONSULTATION ON STRIMVELIS FOR TREATING SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY ADENOSINE DEAMINASE DEFICIENCY [ID926]

Background

NICE asked NHS England to provide some additional information about the commissioning of a service for patients who require Strimvelis for the treatment of severe combined immunodeficiency caused by adenosine deaminase deficiency.

NHS England comments

There had been a suggestion in the documentation that NHS England should pay for the non-drug costs for treatment via the 'S2' funding route.

However, in England, the budget for 'S2' referrals is not held by the NHS but rather by the Department of Health. This funding route is therefore not available for NHS England.

NHS England would anticipate putting in place a contracting arrangement directly with the treating hospital in Milan with the expectation that the NHS would pay the same rates as for statutory Italian patients (there was a suggestion during previous discussions with the drug company that there would be a different, higher rate for some aspects of the treatment package).

The plan to contract directly with the hospital in Milan is because (a) NHS England does not have access to the S2 funding route and (b) NHS England would wish to assure themselves that the hospital is offering NHS patients a high quality service (in the same as they would for all treatments available to NHS patients. There is no expectation on the part of NHS England that a direct contract with Milan would mean discounted compared to that paid for statutory Italian patients.

NHS England confirms that it would develop a travel and accommodation policy building on the experience of contracting with centres outside of the UK for proton beam therapy and where patients and their families have to spend protracted periods away from home.

NHS England confirms that it would be able to implement these arrangements by the end of April 2018.

[redacted]

November 2017

Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)
Welsh Health Specialised Services Committee (WHSSC)

Your ref/eich cyf:
Our ref/ein cyf:
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Jo Ekeledo
Project Manager, Technology Appraisals and HST
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Dear Jo

Re: Severe combined immunodeficiency (adenosine deaminase deficiency - Strimvelis [NICE HST ID926]

I would be grateful if the following information could be considered and recorded by NICE as part of their consultation on the above Highly Specialised Technology.

The Welsh Health Specialised Services Committee (WHSSC) is responsible for the joint planning of Specialised and Tertiary Services on behalf of Local Health Boards in Wales. Consequently we are responsible for the commissioning of all interventions used in the treatment of ADA–SCID including haematopoietic stem cell transplantation (HSCTs).

We are aware that ADA-SCID is an ultra rare condition and the use of Strimvelis is only intended when a stem cell transplant cannot be undertaken usually because no suitable human leukocyte antigen-matched related stem cell donor is available

At present 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 Wales (and their family members/carers) would need to travel to this hospital for treatment.

[redacted]

We know that colleagues in Highly Specialised Services (NHS England) have already started to plan for the implementation of this treatment. Given the rarity of this condition and highly specialised nature of the treatment pathway (and to avoid unnecessary duplication of effort) WHSSC has contacted NHS England to suggest a collaboration in order to develop a common referral pathway and protocol. It may also include agreeing and defining suitable gate-keeping arrangements. This collaboration has been agreed in principle and further discussion is planned for early in 2018. It is anticipated that WHSSC will be invited to attend meetings with the two specialist centres in England who diagnose, assess and treat ADA-SCID (Great Ormond Street Hospital and Great North Children's Hospital) and contribute to the development of referral pathways, protocols and a commissioning policy.

It is anticipated that the arrangements for NHS funding of travel and accommodation costs for people in Wales having Strimvelis and their families will be assessed using a similar model to that already in use for Proton Beam Therapy.

The Welsh Government launched the New Treatment Fund (NTF) in January 2017. This is a key commitment within the programme for Government – Taking Wales Forward. The fund will provide an additional £16 million annually for Health Boards and Trusts in Wales to support the faster introduction of new medicines recommended by NICE and the All Wales Medicines Strategy Group.

For NICE recommendations, a medicine should be available no later than 60 calendar days after the first publication of the Final Evaluation Determination for Highly Specialised Technologies. However setting up the service to deliver Strimvelis will take time and implementation is likely to exceed this 60-day timeframe. In exceptional circumstances, where the scale of service planning necessary to make a health care intervention available will take longer than two months, this can be amended. WHSSC will be writing to the Welsh Government Minister requesting such an extension with our reasons clearly set out.

Given the scale of planning and implementation required we are not expected to have this work completed until at least April 2018.

Yours sincerely

[redacted]

cc [redacted], WHSSC

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